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Original Contribution

Association between use of enhanced recovery after surgery protocols and postoperative complications in colorectal surgery in Europe: The EuroPOWER international observational study

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ABSTRACT

Study objective: Assess the relationship between the Enhanced Recovery After Surgery (ERAS®) pathway and routine care and 30-day postoperative outcomes.
Design: Prospective cohort study.
Setting: European centers (185 hospitals) across 21 countries.
Patients: A total of 2841 adult patients undergoing elective colorectal surgery. Each hospital had a 1-month recruitment period between October 2019 and September 2020.
Interventions: Routine perioperative care.
Measurements: Twenty-four components of the ERAS pathway were assessed in all patients regardless of whether they were treated in a formal ERAS pathway. A multivariable and multilevel logistic regression model was used to adjust for baseline risk factors, ERAS elements and country-based differences.
Results: A total of 1835 patients (65%) received perioperative care at a self-declared ERAS center, 474 (16.7%) developed moderate-to-severe postoperative complications, and 63 patients died (2.2%). There was no difference in the primary outcome between patients who were or were not treated in self-declared ERAS centers (17.1% vs. 16%; OR 1.00; 95%CI, 0.79–1.27; $P = 0.986$). Hospital stay was shorter among patients treated in self-declared ERAS centers (6 [5–9] vs. 8 [6–10] days; OR 0.82; 95%CI, 0.78–0.87; $P < 0.001$). Median adherence to 24 ERAS elements was 57% [48%–65%]. Adherence to ERAS-pathway quartiles (≥65% vs. <48%) suggested that patients with the highest adherence rates experienced a lower risk of moderate-to-severe complications (15.9% vs. 17.8%; OR 0.71; 95%CI, 0.53–0.96; $P = 0.027$), lower risk of death (0.3% vs. 2.9%; OR 0.10; 95%CI, 0.02–0.42; $P = 0.002$) and shorter hospital stay (6 [4–8] vs. 7 [5–10] days; OR 0.74; 95%CI, 0.69–0.79; $P < 0.001$).
Conclusions: Treatment in a self-declared ERAS center does not improve outcome after colorectal surgery. Increased adherence to the ERAS pathway is associated with a significant reduction in overall postoperative complications, lower risk of moderate-to-severe complications, shorter length of hospital stay and lower 30-day mortality.

1. Introduction

The Enhanced Recovery After Surgery (ERAS®) Study Group [1] was founded to address variability and lack of standardization in the perioperative care of patients undergoing colorectal surgery [2]. In 2005, the first ERAS Consensus Protocol was published. It included multiple evidence-based interventions covering the entire patient journey from hospital admission through the preoperative, intraoperative and postoperative periods [3]. Based on the work of Kehlet [4], they created a model based on an integrated, multidisciplinary approach in which a "bundle" of evidence-based elements is combined in a synergistic and coordinated way [5]. Although the first ERAS guidelines [6] represented a milestone for evidence-based perioperative care, implementation on a large scale has been slow [7]. Moreover, adopting an ERAS pathway

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does not necessarily lead to improved outcomes [6] unless adequate adherence is achieved consistently [8,9].

The initial implementation program for ERAS started in Sweden. Then, it spread to the Netherlands, United Kingdom and Switzerland, and subsequently to Canada, Australasia, the USA, other European countries and Latin America [7]. Nowadays, many centers worldwide have adopted the ERAS pathway as a standard of care in colorectal surgery, even though many of them are not registered within the ERAS Society and the current standard of reporting is frequently incomplete [10]. This scenario may lead to variability in adherence to the ERAS pathway and, consequently, prevent comparisons of results [11].

We aimed to characterize the perioperative care strategies in patients undergoing elective colorectal surgery in Europe, including centers with and without the established ERAS pathway. We also wished to analyze the association between individual elements of ERAS protocols (as defined by the 2018 ERAS Society guidelines [12]) and postoperative complications. The primary outcome of the study was the incidence of moderate-to-severe complications within 30 days of surgery. Secondary outcomes included overall complications, readmission rates, reoperations, mortality, length of hospital stay (LOS) and adherence to ERAS elements.

2. Methods

2.1. Study design and participants

The Postoperative Outcomes within Enhanced Recovery after Surgery Protocol in Colorectal Surgery in Europe (EuroPOWER) study was a prospective, 1-month, multicenter study involving a European cohort. The study protocol was approved (9 October 2019; Acta No: 17/2019) by the Ethics Committee of the Instituto Aragonés de Ciencias de la Salud (Zaragoza, Spain) and by the Spanish Medical Agency, and was registered prospectively (NCT03814681). The ethics committee or institutional review board of each center in each country approved the study protocol. Written informed consent was obtained from patients to participate in the study if required by the local ethics committees according to the regulations in each participating country. Individual participating centers secured local ethical approval according to national ethical-approval guidelines. Participants and investigators did not receive financial compensation. This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [13] for cohort studies and the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) Checklist [14]. Participation by hospitals and investigators was facilitated through the Spanish Perioperative Audit and Research Network (RedGERM). European hospitals were invited to participate by national coordinators and through announcement of the study on the Internet website of the study and social media, regardless of their characteristics and existence of an ERAS pathway.

2.2. Procedures

All consecutive adult (>18 years) patients scheduled to undergo elective primary colorectal surgery with a planned overnight stay were assessed for inclusion during a single period of 1 month of recruitment at each participating center. Each participating center selected a single month for data collection between October 2019 and September 2020.

Each patient was followed up for 30 days after surgery. Patient information was obtained through the medical records of the hospital and primary-care providers. Data were collected using the Castor EDC [15] platform (www.castoredc.com/) and de-identified before entry into a secure, Internet-based form for electronic case records designed specifically for EuroPOWER. Criteria defining a center with successful implementation of the ERAS pathway in Europe were lacking. Hence, we asked centers that considered themselves to be an "ERAS center" if they had implemented a multidisciplinary ERAS pathway regardless of the perioperative elements that constituted the pathway and whether adherence to the ERAS pathway was audited regularly. Centers were not considered to be an ERAS center merely if they were part of the ERAS Society or another group based on enhanced recovery. Ultimately, centers declared themselves to be an ERAS center or "non-ERAS center".

Individual data on 24 ERAS elements (Supplemental Digital Content 1) were collected prospectively for each patient. The definition of individual ERAS components was based on the ERAS Society guidelines for colorectal surgery published in 2018 [12]. We did not include the item "preoperative fluid and electrolyte therapy" due to the ambiguity in the original definition and the difficulty involved in reporting it. Data included patient characteristics (age, sex, body mass index, smoking status, American Society of Anesthesiologists physical status (ASA), Malnutrition Universal Screening Tool grade (MUST), Rockwood Clinical Frailty Scale score, comorbidities), the procedure undertaken, surgical approach, preoperative laboratory results (levels of hemoglobin, albumin and creatinine), perioperative interventions, ERAS elements, and outcomes (including postoperative complications, hospital readmissions, reoperations, 30-day mortality, LOS, adherence to ERAS elements). Complications 30 days after surgery were predefined and graded as "mild", "moderate" or "severe", as described by the European Perioperative Clinical Outcome (EPCO) definitions [16] (Supplemental Digital Content 2)—except for postoperative delirium due to its complexity and requirement of trained staff. In addition, complications were graded according to the Clavien–Dindo classification [17]. Data were censored 30 days after surgery for patients who remained hospitalized. Data validation was conducted by investigators from each center who were not in charge of the perioperative care of the patients, follow-up, or data collection. We aimed to recruit as many hospitals and countries as possible. Hence, formal calculation of the sample size was not undertaken before study initiation.

2.3. Outcomes

The primary outcome was the incidence of 30-day moderate-to-severe postoperative complications according to EPCO definitions [16], which was compared between ERAS centers versus non-ERAS centers as well as among high- versus low-compliant patients. Secondary outcome measures were overall complications, hospital readmission, reoperation rates, mortality, LOS and adherence to the ERAS items. "Adherence to the ERAS pathway" was defined as the percentage of ERAS items that were applied to each patient over the total number of interventions recommended by the ERAS Society [12].

2.4. Statistical analyses

Results were analyzed according to whether the patient underwent surgery in a self-declared ERAS center or in a non-ERAS center. Discrete variables are described as absolute frequencies and percentages (based on the non-missing sample size) and their differences were analyzed using Fisher's exact test or chi-square test. Continuous variables are presented with median values with their corresponding interquartile ranges (IQR) and statistical differences were calculated using the Wilcoxon rank sum test. Subsequently, the analysis was repeated after we had subdivided the entire sample into four quartiles according to the rate of adherence to ERAS elements for each patient (Q1: highest adherence; Q4: lowest adherence) regardless of whether or not the patients were treated at a self-declared ERAS center. For all clinical outcomes (except LOS) the significant trends across increasing quartiles were estimated by the Cochran–Armitage trend test.

Univariate and multilevel logistic regression with country as a random intercept were used to identify the influence of highest adherence versus lowest adherence for clinical outcomes. Quasi-Poisson regression was employed to identify the influence of the highest adherence versus lowest adherence on prolonged LOS. A univariate regression model to assess the influence of adherence to the ERAS

protocol on clinical outcomes, and a quasi-Poisson regression were used to identify the influence of the rate of ERAS adherence on prolonged LOS. We employed a multilevel mixed-effects model including variables that were significant in the univariate analysis to explore the independent factors associated with postoperative complications using country as a random intercept. Missing data in the original dataset were imputed using the nearest-neighbor method. Comparisons for which $P < 0.05$ were considered significant. Data are the median and IQR unless stated otherwise. Odds ratios (ORs) are shown with their 95% confidence intervals (95%CIs). Statistical analyses were undertaken with R 4.0.5 (R Institute for Statistical Computing, Vienna, Austria). For mixed models, "finalfit", "nlme" and "lmerTest" packages were used. Prescription packages were used to impute missing data.

3. Results

3.1. Participants

Data describing 2841 patients were collected at 185 centers across 21 European countries (Fig. 1). Of these, 1697 (60%) were men; the median age was 68 [IQR, 59–76] years. Other characteristics are shown in Table 1. According to the hospitals in which the procedures were undertaken, 1835 patients (65%) were included in self-declared ERAS centers. Self-declared ERAS and non-ERAS groups showed demographic differences in the number of patients with ASA-I score (138 (8%) vs. 98 (10%), $P = 0.048$), arterial hypertension (887 (48%) vs. 533 (53%), $P = 0.020$) and coronary artery disease (172 (9%) vs. 126 (13%), $P = 0.011$), respectively. The preoperative hemoglobin level differed between the two groups (13 [IQR 11.7–14.3] vs. 12.8 [IQR 11–14] g/dl, $P < 0.001$). More patients in the self-declared ERAS group underwent laparoscopic (1271 (69%) vs. 532 (53%), $P < 0.001$) surgery. In addition, the intraoperative fluid balance was less positive (843 [IQR 444–1293] vs. 1118 [IQR 698–1722] ml, $P < 0.001$) and more patients received adjuvant regional analgesia (896 (49%) vs. 370 (37%), $P < 0.001$) in the self-declared ERAS group. Differences were also documented in postoperative levels of hemoglobin and albumin (Table 1). The number of centers and patients included per country is shown in Supplemental Digital Content 3.

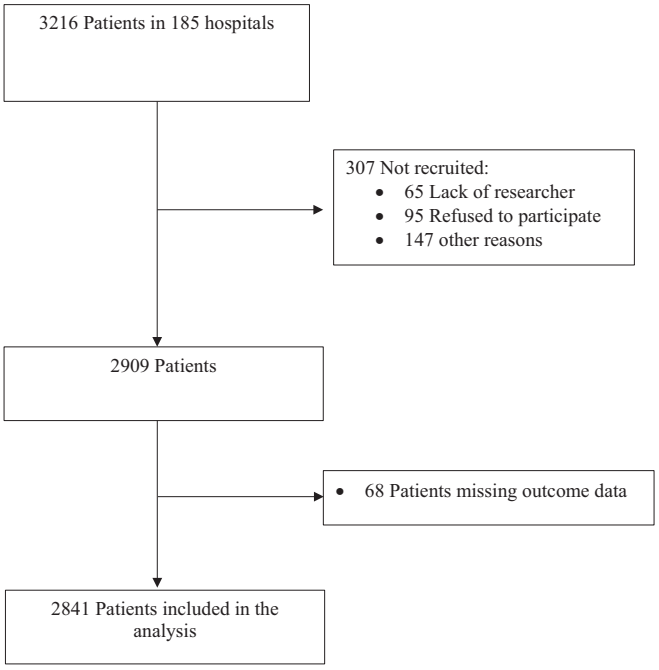

Fig. 1. STROBE flow diagram for included patients.

Table 1
Patient characteristics.

Characteristic	Overall (N = 2841)	Non-ERAS (N = 1006)	Self-declared ERAS (N = 1835)	p.value
Age	68 [59–76]	68 [59–76]	68 [59–76]	0.717
Sex: male	1697 (60%)	600 (60%)	1097 (60%)	0.974
BMI	26.1 [23.4–29.2]	26.2 [23.7–29.1]	25.9 [23.3–29.2]	0.125
ASA				
I	236 (8%)	98 (10%)	138 (8%)	0.048
II	1523 (54%)	515 (51%)	1008 (55%)	0.059
III	1007 (35%)	361 (36%)	646 (35%)	0.756
IV-V	74 (3%)	32 (3%)	42 (2%)	0.193
Smoking-status				
Current	493 (17%)	180 (18%)	313 (17%)	0.615
Smoker No	1622 (57%)	555 (55%)	1067 (58%)	0.130
Previous >1 year	641 (23%)	241 (24%)	400 (22%)	0.208
Previous <1 year	81 (3%)	29 (3%)	52 (3%)	1.000
Malnutrition Universal Screening Tool				
0	2133 (77%)	723 (74%)	1410 (79%)	0.004
1	323 (12%)	128 (13%)	195 (11%)	0.100
2	215 (8%)	79 (8%)	136 (8%)	0.713
3	69 (3%)	37 (4%)	32 (2%)	0.002
4	33 (1%)	15 (2%)	18 (1%)	0.300
5	4 (0.1%)	1 (0.1%)	3 (0.2%)	1.000
6	3 (0.1%)	0 (0.0%)	3 (0.2%)	0.557
Rockwood Clinical Frailty Scale score				
1	204 (7%)	67 (7%)	137 (8%)	0.505
2	955 (34%)	337 (34%)	618 (34%)	0.999
3	1068 (38%)	373 (38%)	695 (38%)	0.820
4	383 (14%)	139 (14%)	244 (13%)	0.683
5	107 (4%)	37 (4%)	70 (4%)	0.967
6	77 (3%)	26 (3%)	51 (3%)	0.879
7–8	30 (1.1%)	16 (1.6%)	14 (0.8%)	0.058
Comorbidities	1998 (70%)	726 (72%)	1272 (69%)	0.122
Hypertension	1420 (50%)	533 (53%)	887 (48%)	0.020
Diabetes mellitus	571 (20%)	220 (22%)	351 (19%)	0.090
Diabetes mellitus with end-organ damage	102 (18%)	48 (22%)	54 (15%)	0.062
Coronary artery disease	298 (11%)	126 (13%)	172 (9%)	0.011
Heart failure	190 (7%)	73 (7%)	117 (6%)	0.412
Cirrhosis	31 (1%)	12 (1%)	19 (1%)	0.843
Stroke	162 (6%)	54 (5%)	108 (6%)	0.628
COPD/asthma	344 (12%)	121 (12%)	223 (12%)	0.970
Chronic kidney disease	191 (7%)	77 (8%)	114 (6%)	0.165
Dementia	62 (2%)	18 (2%)	44 (2%)	0.354
Metastatic solid tumor	185 (7%)	59 (6%)	126 (7%)	0.339
Preoperative hemoglobin (g/dl)	13 [11.5–14.2]	12.8 [11–14]	13 [11.7–14.3]	<0.001
Preoperative creatinine (mg/dl)	0.84 [0.7–1.0]	0.82 [0.7–1.0]	0.85 [0.71–1.01]	0.105
Preoperative albumin (g/dl)	4.1 [3.7–4.4]	4.1 [3.7–4.4]	4.1 [3.7–4.4]	0.341
Glycosylated hemoglobin (%)	5.9 [5.4–6.7]	6.1 [5.5–6.9]	5.9 [5.3–6.5]	0.049
Oncologic surgery	2458 (87%)	876 (87%)	1582 (86%)	0.556
Surgical procedure				
Right hemicolectomy	856 (30%)	315 (31%)	541 (30%)	0.318
Left hemicolectomy	299 (11%)	106 (11%)	193 (11%)	1.000
Transverse colectomy	28 (1%)	8 (1%)	20 (1%)	0.577
Low anterior resection	470 (17%)	171 (17%)	299 (16%)	0.655
High anterior resection	213 (8%)	76 (8%)	137 (8%)	0.983
Extended right hemicolectomy	91 (3%)	30 (3%)	61 (3%)	0.706
Sigmoid colectomy	553 (20%)	186 (19%)	367 (20%)	0.365
Abdominoperineal resection	174 (6%)	58 (6%)	116 (6%)	0.617
Subtotal colectomy	55 (2%)	26 (3%)	29 (2%)	0.085
Total colectomy	58 (2%)	18 (2%)	40 (2%)	0.575

(continued on next page)

Table 1 (*continued*)

Characteristic	Overall (*N* = 2841)	Non-ERAS (*N* = 1006)	Self-declared ERAS (*N* = 1835)	p.value
Total proctocolectomy	41 (1%)	10 (1%)	31 (2%)	0.188
Surgical approach				
Open	747 (26%)	383 (38%)	364 (20%)	<0.001
Laparoscopy	1803 (64%)	532 (53%)	1271 (69%)	<0.001
Laparoscopy assisted	290 (10%)	91 (9%)	199 (11%)	0.146
Conversion to open	177 (9%)	62 (10%)	115 (8%)	0.130
Stoma	688 (24%)	242 (24%)	446 (24%)	0.918
Duration of surgery (minutes)	180 [130–240]	180 [140–230]	180 [128–240]	0.089
Regional anesthesia	1266 (45%)	370 (37%)	896 (49%)	<0.001
Intraoperative fluid balance (ml)	952 [535–1457]	1118 [698–1722]	843 [444–1293]	<0.001
Postoperative hemoglobin (g/dl)	11.6 [10.3–12.8]	11.4 [10.2–12.7]	11.6 [10.4–12.9]	0.013
Postoperative creatinine (mg/dl)	0.81 [0.68–1.01]	0.81 [0.69–1.00]	0.82 [0.68–1.01]	0.890
Postoperative albumin (mg/dl)	3.3 [2.9–3.7]	3.3 [2.9–3.6]	3.3 [2.9–3.7]	0.023

ERAS: Enhanced recovery after surgery; COPD: chronic obstructive pulmonary disease. Percentage reflects over non-missing sample size. Discrete variables n (%). Continuous variables Median[Q1-Q3].

3.2. Outcome data

A total of 770 patients (27.1%) experienced postoperative complications, which were graded as moderate-to-severe in 474 (16.7%). Differences were not found in the number of patients with overall postoperative complications between the self-declared ERAS group and non-ERAS group (495 (27%) vs. 275 (27.3%); OR 0.93; 95%CI, 0.77–1.12; $P = 0.459$), or for moderate-to-severe complications (313 (17.1%) vs. 161 (16%); OR 1; 95%CI, 0.79–1.27; $P = 0.986$). Differences were not found in terms of the rates of readmissions, re-interventions or mortality (Fig. 2). The self-declared ERAS group had shorter median LOS (6 [IQR 5–9] vs. 8 [IQR 6–10] days; OR 0.82; 95%CI, 0.78–0.87; $P < 0.001$). Fewer patients in the self-declared ERAS group had superficial infections at the surgical site (38 (2.1%) vs. 36 (3.6.%); OR 0.56; 95% CI, 0.35–0.89; $P = 0.014$), whereas more patients had pneumonia (41 (2.2%) vs. 9 (0.9%); OR 2.40; 95%CI, 1.14–5.03; $P = 0.021$) (Fig. 2).

3.3. Adherence data

The overall adherence rate to the 24 elements of the ERAS pathway was 57% [IQR 48%–65%], with the rate for self-declared ERAS centers being 61% [IQR 52%–70%] vs. 50% [IQR 42%–57%] at non-ERAS centers ($P < 0.001$). Adherence to most of the ERAS elements was higher in the ERAS cohort. However, adherence to the elements "avoidance of drainage in the peritoneal cavity and in the pelvis" was lower in this group (996 (54.3%) vs. 755 (75.1%), P < 0.001). No differences were observed in use of pre-anesthetic medication or the rate of thromboprophylaxis between groups (Table 2).

Adherence to ERAS elements in the highest adherence quartile (Q1) was ≥65% whereas, in the lowest adherence quartile (Q4), it was <48%. Patients with high adherence (Q1) carried a lower risk of moderate-to-severe complications (OR 0.71; 95%CI, 0.53–0.96; $P = 0.027$), 30-day mortality (OR 0.10; 95%CI, 0.02–0.42; $P = 0.002$), and shorter LOS (OR 0.74; 95%CI, 0.69–0.79; P < 0.001) compared with those in the low-adherence group (Q4), as well as lower risk of acute kidney injury (AKI; OR 0.33; 95%CI, 0.14–0.77, $P = 0.010$), acute respiratory distress syndrome (ARDS; OR 0.10; 95%CI, 0.01–0.79, $P = 0.028$), arrhythmia (OR 0.31; 95%CI, 0.10–0.92, $P = 0.035$), postoperative hemorrhage (OR 0.25; 95%CI, 0.08–0.75; $P = 0.013$) and pulmonary edema (OR 0.09; 95%CI, 0.01–0.67; $P = 0.019$) (Fig. 3). The Cochran–Armitage trend test showed that the relative risks for moderate-to-severe postoperative

Patients With at Least	Total (N=2841)	Self-Declared ERAS (N=1835)	Self-Declared Non-ERAS (N=1006)	Odds Ratio (95% CI)	P Value	Multilevel
Moderate to severe postoperative complications	474 (16.7)	313 (17.1)	161 (16)	1.08(0.88-1.33)	0.473	1.00 (0.79-1.27, p=0.986)
Postoperative complications	770 (27.1)	495 (27)	275 (27.3)	0.98(0.83-1.17)	0.835	0.93 (0.77-1.12, p=0.459)
Readmission	241 (8.5)	163 (8.9)	78 (7.8)	1.15(0.87-1.54)	0.317	1.33 (0.97-1.83, p=0.075)
Reoperation	178 (23.1)	120 (24.2)	58 (21.1)	1.2(0.84-1.71)	0.322	1.19 (0.82-1.72, p=0.364)
Mortality rate	63 (2.2)	30 (1.6)	33 (3.3)	0.49(0.29-0.81)	0.006	0.61 (0.35-1.07, p=0.084)
Length of Stay (days)	7[5-9]	6[5-9]	8[6-10]	0.84(0.8-0.88)	<0.001	0.82 (0.78-0.87, p<0.001)
Number of days in level 2 and 3 critical care	0[0-1]	0[0-1]	0[0-1]	0.82(0.64-1.06)	0.129	0.85 (0.64-1.12, p=0.248)
Acute kidney injury	45 (1.6)	26 (1.4)	19 (1.9)	0.74(0.41-1.38)	0.341	0.69 (0.37-1.26, p=0.227)
Acute respiratory distress syndrome	26 (0.9)	18 (1)	8 (0.8)	1.22(0.54-3.02)	0.638	1.24 (0.54-2.86, p=0.614)
Anastomotic leak	119 (4.2)	77 (4.2)	42 (4.2)	1(0.69-1.49)	0.985	1.00 (0.68-1.46, p=0.980)
Arrhythmia	28 (1)	18 (1)	10 (1)	0.98(0.46-2.23)	0.959	0.99 (0.46-2.15, p=0.980)
Bloodstream infection	33 (1.2)	20 (1.1)	13 (1.3)	0.84(0.42-1.74)	0.627	0.84 (0.42-1.70, p=0.637)
Gastrointestinal bleed	37 (1.3)	20 (1.1)	17 (1.7)	0.64(0.33-1.25)	0.187	0.60 (0.31-1.18, p=0.141)
Myocardial infarction	7 (0.2)	3 (0.2)	4 (0.4)	0.42(0.08-1.99)	0.265	0.42 (0.09-1.98, p=0.272)
Paralytic ileus	170 (6)	120 (6.5)	50 (5)	1.34(0.96-1.89)	0.09	1.07 (0.74-1.55, p=0.704)
Pneumonia	50 (1.8)	41 (2.2)	9 (0.9)	2.5(1.26-5.54)	0.007	2.40 (1.14-5.03, p=0.021)
Postoperative hemorrhage	48 (1.7)	31 (1.7)	17 (1.7)	1(0.55-1.85)	0.988	0.92 (0.49-1.74, p=0.806)
Pulmonary embolism	7 (0.2)	4 (0.2)	3 (0.3)	0.72(0.15-3.92)	0.684	0.73 (0.16-3.28, p=0.684)
Pulmonary edema	21 (0.7)	10 (0.5)	11 (1.1)	0.5(0.2-1.19)	0.116	0.50 (0.21-1.17, p=0.111)
Stroke	3 (0.1)	1 (0.1)	2 (0.2)	0.29(0.01-3.6)	0.332	0.27 (0.02-3.03, p=0.292)
Surgical site infection (deep)	51 (1.8)	32 (1.7)	19 (1.9)	0.92(0.52-1.66)	0.774	0.81 (0.45-1.46, p=0.480)
Surgical site infection (organ/space)	84 (3)	53 (2.9)	31 (3.1)	0.93(0.6-1.48)	0.766	0.85 (0.52-1.37, p=0.506)
Surgical site infection (superficial)	74 (2.6)	38 (2.1)	36 (3.6)	0.57(0.36-0.91)	0.018	0.56 (0.35-0.89, p=0.014)
Urinary tract infection	23 (0.8)	15 (0.8)	8 (0.8)	1.02(0.44-2.57)	0.967	1.03 (0.44-2.44, p=0.944)
Cardiac arrest	22 (0.8)	14 (0.8)	8 (0.8)	0.95(0.4-2.42)	0.911	0.96 (0.40-2.30, p=0.931)

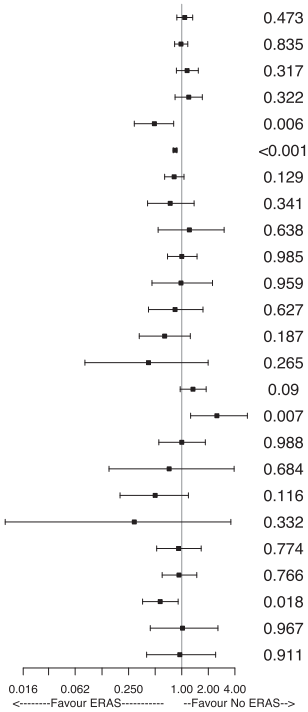

Fig. 2. Postoperative outcomes.
Complications in all included patients and in patients who did or did not receive the Enhanced Recovery After Surgery (ERAS) protocol.
Note. Data are expressed as number (%) or median [Q1-Q3].

Table 2
Adherence to ERAS elements in self-declared ERAS and non-ERAS centers.

Characteristic	Overall	Non-ERAS (N = 1006)	Self-declared ERAS (N = 1835)	p value
ERAS adherence	57 [48–65]	50 [42–57]	61 [52–70]	<0.001
Preadmission information, education and counselling	2308 (81.3%)	675 (67.2%)	1633 (89%)	<0.001
Preoperative optimization	655 (46.8%)	146 (30.2%)	509 (55.6%)	<0.001
Prehabilitation	375 (13.2%)	36 (3.6%)	339 (18.5%)	<0.001
Preoperative nutritional care	136 (42%)	41 (31.1%)	95 (49.5%)	0.001
Management of anemia	409 (27.1%)	114 (20%)	295 (31.4%)	<0.001
Prevention of nausea and vomiting	2476 (87.2%)	745 (74.2%)	1731 (94.4%)	<0.001
Pre-anesthetic medication	1681 (59.2%)	593 (59%)	1088 (59.3%)	0.876
Antimicrobial prophylaxis and skin preparation	2786 (98.1%)	968 (96.2%)	1818 (99.1%)	<0.001
Avoid Bowel Preparation	1788 (63.1%)	743 (74.2%)	1045 (57.1%)	<0.001
Preoperative fasting and carbohydrate loading	890 (31.4%)	108 (10.8%)	782 (42.7%)	<0.001
Standard Anesthetic Protocol	936 (33.3%)	221 (22.1%)	715 (39.5%)	<0.001
Intraoperative fluid and electrolyte therapy	1588 (56%)	512 (51%)	1076 (58.8%)	<0.001
Preventing intraoperative hypothermia	2652 (94.3%)	894 (89.1%)	1758 (97.1%)	<0.001
Surgical access (open and minimally invasive surgery including laparoscopic, robotic and trans-anal approaches)	2075 (73%)	614 (61%)	1461 (79.6%)	<0.001
Avoid drainage in the peritoneal cavity and pelvis	1751 (61.7%)	755 (75.1%)	996 (54.3%)	<0.001
Avoid nasogastric intubation	1073 (37.8%)	480 (47.8%)	593 (32.4%)	<0.001
Postoperative analgesia	1529 (54.1%)	417 (41.6%)	1112 (60.9%)	<0.001
Thromboprophylaxis	2618 (94.1%)	937 (93.1%)	1681 (94.7%)	0.123
Postoperative fluid and electrolyte therapy	1553 (55%)	497 (49.9%)	1056 (57.8%)	<0.001
Urinary drainage	740 (26.1%)	188 (18.7%)	552 (30.1%)	<0.001
Prevention of postoperative ileus	1043 (36.7%)	340 (33.8%)	703 (38.3%)	0.019
Postoperative glycemic control	1959 (69%)	718 (71.4%)	1241 (67.6%)	0.040
Postoperative nutritional care	1231 (43.5%)	258 (25.8%)	973 (53.2%)	<0.001
Early Mobilization	2224 (78.6%)	711 (71%)	1513 (82.8%)	<0.001

ERAS: Enhanced recovery after surgery; COPD: chronic obstructive pulmonary disease. Percentage reflects value over non-missing sample size. Discrete variables n (%). Continuous variables median[Q1-Q3].

complications, survival, AKI, ARDS, arrhythmia, postoperative hemorrhage, pulmonary edema and surgical-site infection increased significantly along with decreasing adherence quartiles (Fig. 4 and Supplemental Digital Content 4). The linear adherence fit showed that with each 1% additional adherence to the ERAS pathway, the odds of moderate-to-severe complications decreased by 1% (OR 0.99, P = 0.017), the odds of AKI decreased by 3% (OR 0.97, P = 0.01), the risk of ARDS decreased by 4% (OR 0.96, P = 0.02), the risk of arrhythmia decreased by 4% (OR 0.96, P = 0.006), the risk of postoperative hemorrhage decreased by 2% (0.98, P = 0.044) and the risk of postoperative pulmonary edema decreased by 7% (OR 0.93, P < 0.001) (Fig. 3).

Multivariable and multilevel analyses of individual ERAS elements showed a significant reduction of moderate-to-severe complications among patients in whom drainage of the abdominal cavity was not employed (OR 1.41; 95%CI, 1.08–1.83; P = 0.011), whereas preoperative management of anemia (OR 1.57; 95%CI, 1.19–2.09; P = 0.002) and postoperative analgesia (OR 1.40; 95%CI, 1.10–1.79; P = 0.007), were associated with an increased risk of moderate-to-severe complications (Supplemental Digital Content 5). Women carried a lower risk of moderate-to-severe postoperative complications (OR 0.65; 95%CI, 0.51–0.82; P < 0.001), whereas patients with a preoperative MUST score of 4 (OR 2.71; 95%CI, 1.20–6.11, P = 0.016), Rockwood Clinical Frailty Scale score of 4–5 and 7–8, asthma or chronic obstructive pulmonary disease had more moderate-to-severe postoperative complications. The likelihood of complications increased with an increased duration of surgical procedure (OR 1.16; 95%CI, 1.06–1.26, P = 0.001) (Supplemental Digital Content 5). The grading of postoperative complications is shown in Supplemental Digital Content 6–7.

4. Discussion

The principal finding of our study is that patients receiving perioperative care in a self-declared ERAS center did not experience improved outcomes after elective colorectal surgery. However, analysis of compliance with the 24 elements of the ERAS pathway suggests that these findings can be explained by low levels of intervention fidelity. Our findings suggest that merely receiving treatment in a self-declared ERAS center is not sufficient to ensure improved treatment outcomes unless staff ensure high levels of compliance with pathway interventions.

In a meta-analysis of 16 randomized, controlled studies, Greco and collaborators showed that complication rates decreased by 40% upon adoption of the ERAS pathway [18]. High adherence to the ERAS pathway is the best indicator to improve postoperative outcomes [11,19,20], but the evidence regarding the relative number and combination of key ERAS elements implemented is insufficient [20]. Our data suggest that high perioperative adherence to the ERAS pathway decreases moderate-to-severe complications, and reduces LOS, which appears to be dose-responsive, as reported by our research team [8] and others [21,22]. However, the group with the highest adherence had an adherence below the minimum 70% that has been set as a requirement to achieve significant improvements in outcome [21], which may signify that the threshold is too ambitious for everyday clinical practice. Conversely, the occurrence of postoperative complications limits adherence to postoperative ERAS items, which reduces overall adherence.

Our findings also highlight the overall limited adherence to the ERAS pathway among self-declared ERAS centers in Europe. This phenomenon might be due to several barriers reported previously, including patient-level characteristics [23] (i.e., malnutrition, comorbidity, age, low socioeconomic status), or institutional factors (i.e., volume of patients, leadership, number of operating rooms) [24]. In addition, adherence rates among European centers were highly heterogeneous, which might have been due to the individual characteristics of healthcare systems, differences in infrastructure, or administrative support from institutions.

In 2018, the ERAS Society [12], as well as the American Society of Colon and Rectal Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons [25], published the guidelines for clinical practice for enhanced recovery pathways in colorectal surgery. Although ERAS Society guidelines summarize evidence-based recommendations [26], recent guidelines included new evidence-based elements and updated the definition of some of the items involving several perioperative measures which could hamper achievement of adherence to individual items. This scenario could explain the low adherence found in our cohort for individual items in self-declared ERAS and non-ERAS centers, and for overall adherence to the ERAS pathway. Clinical-practice guidelines are developed through a process that begins with a review and evaluation of the available scientific literature which, in

Patients With at Least	Adherence >=65% Q1(n=653)	Adherence >=57% but <65% Q2(n=699)	Adherence >=48% but <57% Q3(n=687)	Adherence <48% Q4(n=802)	Q1 vs Q4 Odds Ratio (95% CI)	Q1 vs Q4 P Value	Adherence Regression Fit OR(P Value)	Multilevel
Moderate to severe postoperative complications	104 (15.9)	94 (13.4)	122 (17.8)	122 (17.8)	0.8(0.61-1.05)	0.104	0.99(0.017)	0.71 (0.53-0.96, p=0.027)
Postoperative complications	172 (26.3)	172 (24.6)	193 (28.1)	193 (28.1)	0.87(0.69-1.1)	0.252	1(0.149)	0.84 (0.66-1.08, p=0.171)
Readmission	63 (9.6)	46 (6.6)	61 (8.9)	61 (8.9)	1.1(0.77-1.56)	0.618	1(0.546)	1.18 (0.80-1.72, p=0.403)
Reoperation	33 (19.2)	44 (25.6)	50 (25.9)	50 (25.9)	0.85(0.52-1.38)	0.512	1(0.836)	0.83 (0.50-1.36, p=0.453)
Mortality rate	2 (0.3)	16 (2.3)	20 (2.9)	20 (2.9)	0.1(0.02-0.35)	<0.001	0.97(0.001)	0.10 (0.02-0.42, p=0.002)
Length of Stay (days)	6[4-8]	6[5-9]	7[5-10]	7[5-10]	0.76(0.71-0.81)	<0.001	0.99(<0.001)	0.74 (0.69-0.79, p<0.001)
Number of days in level 2 and 3 critical care	0[0-1]	0[0-0]	0[0-1]	0[0-1]	0.61(0.43-0.84)	0.004	0.98(0.001)	0.61 (0.42-0.87, p=0.007)
Acute kidney injury	7 (1.1)	5 (0.7)	9 (1.3)	9 (1.3)	0.36(0.14-0.8)	0.011	0.97(0.01)	0.33 (0.14-0.77, p=0.010)
Acute respiratory distress syndrome	1 (0.2)	7 (1)	6 (0.9)	6 (0.9)	0.11(0-0.59)	0.005	0.96(0.02)	0.10 (0.01-0.79, p=0.028)
Anastomotic leak	22 (3.4)	27 (3.9)	34 (4.9)	34 (4.9)	0.74(0.43-1.27)	0.281	0.99(0.218)	0.71 (0.41-1.24, p=0.228)
Arrhythmia	4 (0.6)	4 (0.6)	4 (0.6)	4 (0.6)	0.31(0.09-0.86)	0.024	0.96(0.006)	0.31 (0.10-0.92, p=0.035)
Bloodstream infection	4 (0.6)	10 (1.4)	7 (1)	7 (1)	0.42(0.11-1.22)	0.114	0.98(0.229)	0.41 (0.13-1.28, p=0.124)
Gastrointestinal bleed	9 (1.4)	6 (0.9)	11 (1.6)	11 (1.6)	1.01(0.4-2.48)	0.986	1(0.968)	0.92 (0.37-2.33, p=0.867)
Myocardial infarction	2 (0.3)	0 (0)	2 (0.3)	2 (0.3)	0.84(0.1-5.52)	0.853	0.95(0.116)	0.95 (0.15-6.13, p=0.954)
Paralytic ileus	40 (6.1)	33 (4.7)	43 (6.3)	43 (6.3)	0.9(0.59-1.38)	0.643	1(0.589)	0.70 (0.45-1.11, p=0.128)
Pneumonia	17 (2.6)	9 (1.3)	11 (1.6)	11 (1.6)	1.62(0.78-3.44)	0.198	1.02(0.154)	1.45 (0.68-3.09, p=0.332)
Postoperative hemorrhage	4 (0.6)	13 (1.9)	13 (1.9)	13 (1.9)	0.28(0.08-0.75)	0.01	0.98(0.044)	0.25 (0.08-0.75, p=0.013)
Pulmonary embolism	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	0.45(0.02-3.84)	0.485	0.98(0.474)	0.41 (0.04-3.97, p=0.443)
Pulmonary edema	1 (0.2)	1 (0.1)	5 (0.7)	5 (0.7)	0.1(0-0.49)	<0.001	0.93(<0.001)	0.09 (0.01-0.67, p=0.019)
Stroke	0 (0)	1 (0.1)	1 (0.1)	1 (0.1)			0.94(0.231)	
Surgical site infection (deep)	10 (1.5)	15 (2.1)	9 (1.3)	9 (1.3)	0.72(0.31-1.57)	0.419	0.99(0.524)	0.67 (0.29-1.52, p=0.334)
Surgical site infection (organ/space)	18 (2.8)	20 (2.9)	19 (2.8)	19 (2.8)	0.82(0.44-1.49)	0.511	1(0.701)	0.74 (0.36-1.51, p=0.408)
Surgical site infection (superficial)	13 (2)	18 (2.6)	12 (1.7)	12 (1.7)	0.51(0.25-0.96)	0.037	0.98(0.019)	0.46 (0.23-0.92, p=0.028)
Urinary tract infection	4 (0.6)	5 (0.7)	4 (0.6)	4 (0.6)	0.5(0.13-1.53)	0.232	0.98(0.36)	0.49 (0.15-1.58, p=0.233)
Cardiac arrest	2 (0.3)	4 (0.6)	10 (1.5)	10 (1.5)	0.43(0.06-1.93)	0.285	0.97(0.114)	0.44 (0.09-2.26, p=0.324)

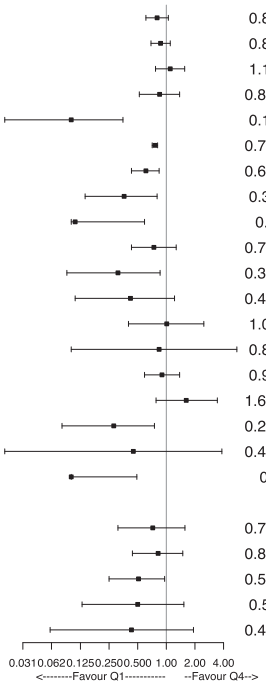

Fig. 3. Postoperative outcomes and Enhanced Recovery After Surgery (ERAS) adherence.
Postoperative complications in all included patients depending on the quartile (Q) of adherence to the ERAS protocol.
Note. Data are expressed as number (%) or median [Q1-Q3].

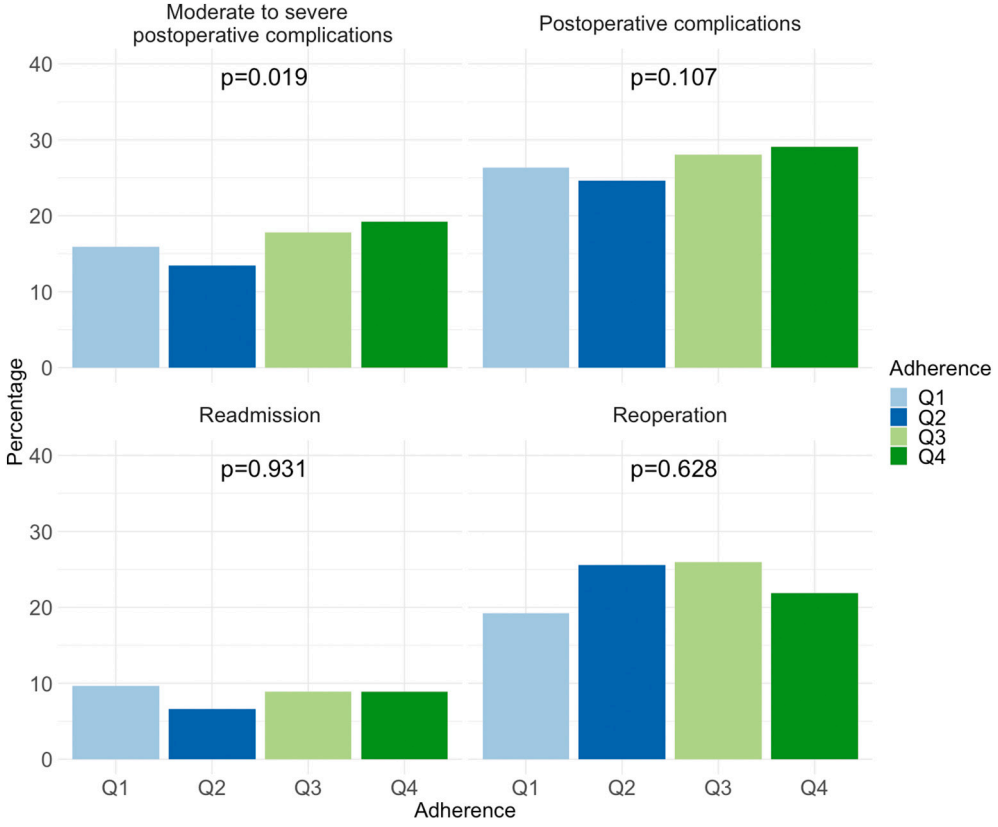

Fig. 4. Postoperative outcomes according to adherence to ERAS quartiles (Q1 vs. Q4).

turn, is converted into a series of recommendations that incorporate evidence and expert opinion (ideally likely to constitute best practice). Implementation of clinical-practice guidelines into daily clinical practice is a complex process that is influenced by factors related to patients, physicians and the health system. One might anticipate that the most recent ERAS Society guidelines might require more time to achieve maximum penetration into clinical practice.

Interestingly, one of the items that was introduced recently—the management of preoperative anemia—was associated with higher odds of postoperative complications, which might be explained by the lack of adjustment for residual confounders. Recently, Hardy and colleagues found that, within an ERAS pathway in colorectal surgery, preoperative anemia was not associated with increased postoperative complications (38.2% vs. 31.2%, $P = 0.12$) or increased LOS, compared with that in patients not suffering from anemia [27]. Furthermore, adherence to the ERAS pathway was not modified by the presence of preoperative anemia. In our study, the only ERAS element that was associated independently with fewer moderate-to-severe postoperative complications was avoidance of abdominal drainage upon surgery. This item has shown consistently its efficacy in reducing postoperative complications [28,29]. Interestingly, even though open surgery was more predominant in the non-ERAS group, patients in this group were more likely to adhere to the recommendation of avoiding abdominal drainage. Unlike previous studies [6], we did not find that laparoscopy per se was associated independently with fewer postoperative complications. In fact, minimally invasive surgery was the most important component of the ERAS pathway in several studies [11,29].

Recently, Ljungqvist and colleagues highlighted the role of malnutrition and frailty as factors contributing to complications [26]. Interestingly, we found that frail patients (Rockwood Clinical Frailty Scale score > 3) and patients suffering from malnutrition had more complications. The Rockwood Clinical Frailty Scale score, MUST score and anemia can be measured readily in the preoperative period, but require weeks for the application of measures aimed at improving them to be successful [30]. Multimodal pre-habilitation addresses three main areas: exercise, nutrition and psychological support [31]. This measure has been shown to reduce postoperative complications and LOS in patients undergoing colorectal surgery [32]. Fewer than 20% of patients in our study received prehabilitation, and it was not associated with improved postoperative outcomes. Whether frail patients would benefit from longer periods of prehabilitation combining "tailored" exercise programs and nutritional support merits additional research [33].

Our study had several strengths. First, this was the first large prospective, European study on the ERAS pathway in colorectal surgery including a representative number of consecutive patients enrolled in a short period. The prospective recruitment period of only 1 month with a specifically designed form for data collection ensured that the changes produced by the progress of perioperative care itself were negligible. Second, we studied each ERAS element individually and measured its relative impact on postoperative complications. One limitation of this study was the lack of control of ERAS implementation at individual sites. Hence, we only considered them as an ERAS center in cases in which there was a dedicated multidisciplinary team with a specific ERAS pathway for patients undergoing colorectal surgery. Although we included a cross-sectional sample, we evaluated the elements recommended by the most recent ERAS Society guidelines [12]. This strategy allowed us to suggest that adherence to these new guidelines may be lower than expected due to the complexity of some of the items. However, we did not control for perioperative variables but tried to conduct a pragmatic observational study. Hence, our results could have been affected by differences in medical and nursing practice, institutional and country-specific resources and policies, as well as adherence to ERAS guidelines.

The low adherence limited our findings because it is the main driver for outcome improvements within the ERAS pathway (rather than merely being self-declared as a center with an established ERAS pathway). We decided not to evaluate one of the ERAS elements (preoperative fluid therapy) because evaluation is very difficult. Therefore, we could not measure the impact of this item on postoperative complications. Furthermore, we did not include postoperative delirium in the complications because we consider its evaluation to be complex and requiring specifically trained staff. Interventions such as prehabilitation may have influenced the incidence of this complication. Several studies have shown that greater involvement by patients in their healthcare is an important factor affecting adherence to medical treatment [34], and that patient satisfaction with their "healthcare experience" also contributes to reducing medical errors and improving the safety of medical care. Before generalized integration of ERAS programs, patient-related and lifestyle-related factors were shown to influence postoperative outcomes significantly [35]. Importantly, lifestyle-related factors are modifiable and include tobacco smoking, abuse of alcohol, overweight/obesity and physical inactivity. The ERAS program in colorectal surgery includes smoking cessation as an evaluable element [12], so it was included as an ERAS element in our study. However, these modifiable lifestyle factors may be dependent upon the patient's involvement in their healthcare to a greater extent than the healthcare provided by each individual center. This factor could act as a confounding factor and explain the variation in reported perioperative outcomes despite patients undergoing optimal perioperative care within the ERAS pathway. Finally, the inclusion of 21 countries and 185 centers led to high heterogeneity, but we adjusted the results by multilevel analysis adjusted for country. However, we did not undertake country-specific analyses because we could not ensure that the centers included were representative of the practice in each country included in our study. We advertised the study on Internet websites aimed specifically at ERAS settings (e.g., UK ERAS Society) and on generalist Internet websites (e.g., European Society of Anaesthesiology and Intensive Care). However, the centers that enrolled may not have been those closest to ERAS protocols, or been more closely involved in perioperative research. Hence, these results may be better than those in other non-enrolled centers, which would limit the external validity of our study. The recruitment period of the study included the onset of the Coronavirus Disease-2019 pandemic, which may have decreased the number of patients included, as well as changed the usual clinical practice and postoperative outcomes.

The EuroPOWER study showed that even though self-designation as an ERAS center did not lead to better postoperative outcomes, increased adherence to perioperative elements was associated with lower rates of moderate-to-severe postoperative complications, mortality and hospital stay. Adherence to the ERAS pathway was low for most of the patients included, independent of the center in which they received care.

Authors contributions

JRM and AAM contributed to the conception and design of the work, the acquisition, analysis, and interpretation of data for the work, and drafting of the manuscript. MC, RP, KS, SJ, NF, AS, JJ, OI, EZ, NMS, SK, NG, OS, TV, PK, AEH, MP, JG, TL, MDS, HM, RZ, AC, MM, MG, YDR, IJ, MVM, ASR JAGE, MLE, CFO, MFV, BUS, JA, AAG, GP, MAGR, GP, ALW, BCP, PGM, CA and JMRR contributed to the conception and design of the work, acquisition and interpretation of data for the work, and revising the manuscript critically for important intellectual content. GEM and AZV contributed to the conception and design of the work, the interpretation of data for the work, and revising the manuscript critically for important intellectual content. All authors approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were investigated appropriately and resolved.

JRM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

JRM and AAM contributed equally as co-first authors. CA and JMRR contributed equally as co-last authors. The data that support the findings

of this study are available from the corresponding author (JRM) upon reasonable request.

Disclosures

JRM reports personal fees from Edwards Lifesciences, Vifor Pharma, MSD and Fresenius Kabi outside the submitted work. RP reports research grants and/or honoraria from Edwards Lifesciences, Intersurgical and GlaxoSmithkline. AS reports personal fees from Johnson and Johnson, Takeda, Pfizer, Janssen, Oasis and Sofar outside the submitted work. NG reports personal fees from PIPRA AG outside the submitted work. ASR reports personal fees from Baxter, MSD, Pfizer, Fresenius Kabi and Nestlé outside the submitted work. JAGE reports grants and conference fees from Vifor, CSL-Behring, Fresenius and Sandoz outside the submitted work. AAG reports personal fees from Edwards Lifesciences, MSD, 3 M, Braun, Ferrer, Rovi and ALTAN outside the submitted work. CA reports personal fees from Fresenius Kabi and Octapharma outside the submitted work. Edwards Lifesciences sells one of the monitoring devices used for goal-directed fluid therapy, which is part of one of the ERAS elements assessed. JRM, RP and AAG report personal fees from Edwards Lifesciences outside the current work. However, we consider the interpretation or discussion of the EuroPOWER results not to be biased in any one direction by this fact. AAM, MC, SJ, KS, NF, JJ, OI, EZ, NMS, SK, OS, TV, PK, AEH, MP, JD, TL, MS, HM, RZ, AC, MM, MG, YDR, IJ, GEM, AZV, MM, MLE, CFO, MLFV, BUS, JA, GP, MGR, GP, AMW, BCP, PGM, CA and JMRR have nothing to declare.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Appendix A. Supplementary data

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