

Original article

Association between use of enhanced recovery after surgery protocols and postoperative complications after gastric surgery for cancer (POWER 4): a nationwide, prospective multicentre study



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ABSTRACT

Introduction: The effectiveness of the Enhanced Recovery After Surgery (ERAS) protocols in gastric cancer surgery remains controversial.

Methods: Multicentre prospective cohort study of adult patients undergoing surgery for gastric cancer. Adherence with 22 individual components of ERAS pathways were assessed in all patients, regardless of whether they were treated in a self-designed ERAS centre. Each centre had a three-month recruitment period between October 2019 and September 2020. The primary outcome was moderate-to-severe postoperative complications within 30 days after surgery. Secondary outcomes were overall postoperative complications, adherence to the ERAS pathway, 30 day-mortality and hospital length of stay (LOS).

Results: A total of 743 patients in 72 Spanish hospitals were included, 211 of them (28.4 %) from self-declared ERAS centres. A total of 245 patients (33 %) experienced postoperative complications, graded as moderate-to-severe complications in 172 patients (23.1 %). There were no differences in the incidence of moderate-to-severe complications (22.3% vs. 23.5%; OR, 0.92 (95% CI, 0.59 to 1.41); $P = 0.068$), or overall postoperative complications between the self-declared ERAS and non-ERAS groups (33.6% vs. 32.7%; OR, 1.05 (95 % CI, 0.70 to 1.56); $P = 0.825$). The overall rate of adherence to the ERAS pathway was 52% [IQR 45 to 60]. There were no differences in postoperative outcomes between higher (Q1, > 60 %) and lower (Q4, ≤ 45 %) ERAS adherence quartiles.

Conclusions: Neither the partial application of perioperative ERAS measures nor treatment in self-designated ERAS centres improved postoperative outcomes in patients undergoing gastric surgery for cancer.

Trial Registration: ClinicalTrials.gov Identifier NCT03865810

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Asociación entre el uso de protocolos de recuperación intensificada y complicaciones postoperatorias tras cirugía gástrica por cáncer (POWER 4): estudio nacional, prospectivo multicéntrico

RESUMEN

Palabras clave:

ERAS
cirugía gástrica
complicaciones postoperatorias
manejo perioperatorio
recuperación intensificada

Introducción: La efectividad de los protocolos de recuperación intensificada o ERAS en la cirugía del cáncer gástrico sigue siendo controvertida.

Métodos: Estudio de cohortes prospectivo multicéntrico de pacientes intervenidos de cáncer gástrico. Se evaluó la adherencia a 22 elementos ERAS en todos los pacientes, independientemente de la existencia de un protocolo ERAS. Cada centro tuvo un período de reclutamiento de tres meses, con un seguimiento de 30 días. La medida de resultado primario fue el número de complicaciones posoperatorias moderadas a graves. Las medidas de resultado secundarias fueron el número total de complicaciones, la adherencia a los elementos ERAS, la mortalidad y la estancia.

Resultados: Se incluyeron 743 pacientes en 72 hospitales, 211 (28,4 %) en centros ERAS. 245 pacientes (33 %) experimentaron complicaciones posoperatorias, moderadas o graves en 172 (23,1 %). No hubo diferencias en la incidencia de complicaciones moderadas a graves (22,3 % vs. 23,5 %; OR, 0,92 (IC 95 %, 0,59 a 1,41); $P = 0,068$), o complicaciones posoperatorias totales entre los centros ERAS y no ERAS (33,6 % vs. 32,7 %; OR, 1,05 (IC 95 %, 0,70 a 1,56); $P = 0,825$). La adherencia a los elementos ERAS fue del 52% [IQR 45 a 60]. No hubo diferencias entre los cuartiles de cumplimiento ERAS más alto (Q1, > 60 %) y más bajo (Q4, ≤ 45 %).

Conclusiones: Ni la aplicación parcial de medidas ERAS ni el tratamiento en centros ERAS mejoraron los resultados en pacientes sometidos a cirugía gástrica por cáncer.

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Introduction

Gastric cancer is the fifth most frequent malignant tumour worldwide, and accounts for 732,000 deaths per year, ranking it as the fourth leading cause of cancer-related death.¹ Gastrectomy for cancer is a technically challenging procedure, with postoperative complications occurring in 20 to 46 % of patients^{2,3}

Enhanced Recovery After Surgery (ERAS) is a multidisciplinary perioperative approach that provides standardized evidence-based recommendations for the care of patients undergoing specific types of surgery.⁴ ERAS began in patients undergoing colorectal surgery,⁵ and resulted in a decrease in postoperative complications and length of hospital stay (LOS) when adequate adherence to the protocols was achieved.^{6,7} The ERAS model is well established for colorectal surgery as the optimal perioperative care. ERAS implementation in gastric surgery⁸ has shown discrete decreases in LOS.⁹ Moreover, despite the clinical reported benefits of ERAS, its implementation in clinical practice has been quite slow for a variety of reasons, such as lack of convincing data, low level of knowledge about ERAS, or expertise and institutional limitations,^{10,11} and lack of large studies assessing the association between ERAS adherence and postoperative outcomes.

The aim of this study was to assess perioperative care in patients undergoing elective gastric surgery for cancer in Spain, and to analyse the association between the individual ERAS elements and postoperative complications.

Methods

Study design and participants

The POWER 4 study was a multicentre, prospective, three-month cohort study. The study was approved by the Ethics Committee of the Instituto Aragonés de Ciencias de la Salud, Zaragoza, Spain (C.P.-C.I. PI19/106, March 27, 2019) and was prospectively registered (NCT03865810). The study protocol was published,¹² and approved by the ethics committees or institutional review boards of each centre. All patients signed a written informed consent before inclusion. This study followed the STROBE reporting guideline for cohort studies,¹³ and the Reporting on ERAS Compliance, Outcomes, and Elements Research Checklist.¹⁴ The hospital and investigator involvement were provided through the Spanish Perioperative Audit and Research Network (RedGERM). All Spanish centres were invited to participate regardless of having or not an established ERAS pathway.

Procedures

All consecutive adult patients scheduled for elective gastric surgery for cancer were assessed for inclusion during a single period of three months of recruitment at each participating hospital between October 2019 and October 2020. Subtotal and total gastrectomies were included, both laparoscopic and open. Exclusion criteria were emergency surgery, endoscopic

procedures, non-oncological gastric surgery and patient refusal. Each patient was followed up for 30 days after surgery. Patient information was acquired from hospital and primary care medical records.

Data was collected using the Castor EDC platform¹⁵ in a case record form designed specifically for POWER 4. Centres declared themselves as centres with or without an established multidisciplinary ERAS pathway for gastric surgery, regardless of the items that conformed the pathway and their current adherence.

The definition of the individual ERAS components was based on the ERAS Society® Guidelines for gastric surgery.⁸ For a simpler and more accurate data collection, some of the 25 items of these guidelines⁸ were grouped and POWER4 included 22 elements of perioperative care¹² (Table S1 supplementary data).

Data included patient characteristics, surgical procedure, surgical approach, duration of surgery, preoperative laboratory results, ERAS elements, and 30-day outcomes (postoperative complications, LOS, readmission, reoperation, and 30-day mortality). Thirty-day postoperative complications were predefined and graded as mild, moderate, or severe as described by the European Perioperative Clinical Outcome definitions (EPCO)¹⁶ (Table S2, supplementary data).

Data was censored at 30 days following surgery for patients who remained at the hospital. To ensure the validity of the data, they were validated and audited by another site investigator who was not involved in the initial data collection. Our aim was to recruit as many hospitals and patients in Spain as possible.

Outcomes

The primary outcome measure was 30-day moderate-to-severe postoperative complications. Secondary outcomes were occurrence of overall postoperative complications, adherence to the ERAS pathway, 30 day-mortality and LOS.

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.

Statistical analysis

The results were analysed according to whether the patient underwent surgery in a self-designed ERAS centre or in a non-ERAS centre. Discrete variables were described as absolute frequencies and percentages and their differences were analysed using Fisher's or Pearson's exact tests. Continuous variables were presented with medians with their corresponding interquartile ranges (IQR) and statistical differences were calculated using the Wilcoxon rank sum test. Adherence to the ERAS pathway was calculated for each individual patient according to the number of the ERAS items achieved over the 22 analysed items (ERAS adherence). Subsequently, the analysis was repeated, subdividing the entire sample into four quartiles according to the rate of adherence to the ERAS items (Q1: highest adherence, Q4: lowest adherence), regardless of whether or not the patients was treated at a self-designed ERAS centre. Highest and lowest adherence quartiles

were compared, and linear adjustments of adherence were performed for each ERAS element. We then analysed the rate of moderate-to-severe complications for each ERAS element using Fisher's exact test, and we performed a multivariate analysis to study the association between the rate of each of the ERAS elements and the clinical and demographic variables. We also used the same model in a multilevel multivariable logistic regression model to explore independent factors associated with moderate-to-severe postoperative complications assessing the variability of each centre.

In order to avoid errors in the multiple comparisons, the respective q value was calculated for each P value in order to maintain a false discovery rate of less than 5 %. Comparisons in which the P value and q value were less than 0.05 were considered statistically significant.

Results

Participants

A total of 743 patients from 72 centres were included in the analysis (Fig. 1), of which 211 (28.4%) were included in self-declared ERAS centres; 444 (60 %) were men, and median age was 70 years [IQR 61 to 77]. Other characteristics are shown in Table 1. More patients in the ERAS group received preoperative neoadjuvant therapy and were treated in a centre with a Patient Blood Management (PBM) program. Duration of surgery was longer in the ERAS group. (Table 1).

Outcomes in self-declared ERAS vs. non-ERAS groups

A total of 172 patients (23.1%) suffered moderate-to-severe complications, and 245 patients (33 %) experienced overall postoperative complications. There were no differences in the

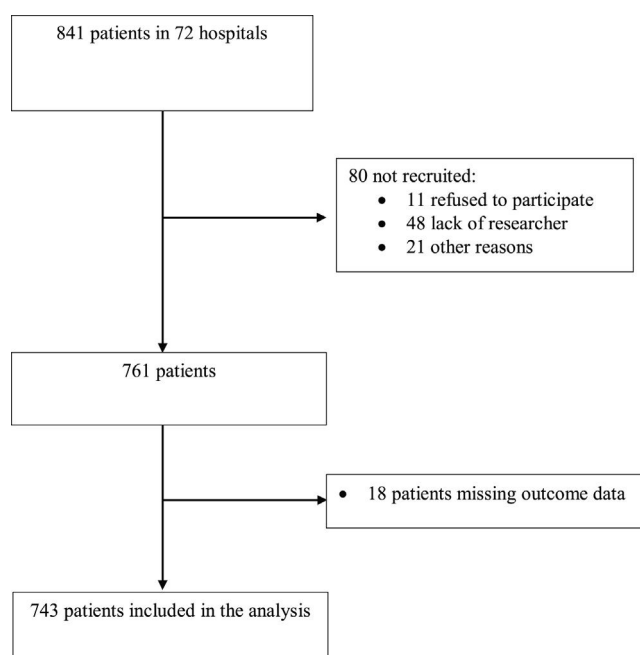


Fig. 1 – STROBE flow diagram for included patients.

Table 1 – Patient characteristics.

	All patients (N = 743)	Self-declared ERAS (N = 211)	Non-ERAS (N = 532)	P overall
Age, years	70 [61-77]	69 [59-77]	70 [61-77]	0.379
Sex: male	444 (60%)	136 (65%)	308 (58%)	0.118
BMI, kg/m ²	25.6 [23 - 28.7]	26 [23.1 - 29.2]	25.6 [22.9 - 28.6]	0.366
ASA physical status				
I	27 (4%)	8 (4%)	19 (4%)	0.111
II	353 (48%)	110 (52%)	243 (46%)	.
III	336 (45%)	82 (39%)	254 (48%)	.
IV	27 (4%)	11 (5%)	16 (3%)	.
Smoking status				
Smoker	107 (14%)	33 (16%)	74 (14%)	0.188
Ex-smoker > 1 year	207 (28%)	61 (29%)	146 (27%)	.
Ex-smoker < 1 year	30 (4%)	13 (6%)	17 (3%)	.
Rockwood Clinical Frailty Scale				
Score ≤ 4	656 (88%)	190 (90%)	466 (88%)	0.417
Score > 4	87 (12%)	21 (10%)	66 (12%)	.
Hypertension	369 (50%)	102 (48%)	267 (50%)	0.709
Diabetes Mellitus	178 (24%)	46 (22%)	132 (25%)	0.440
Ischaemic heart disease	88 (12%)	22 (10%)	66 (12%)	0.531
Heart Failure	46 (6%)	13 (6%)	33 (6%)	1.000
Stroke	2 (0.3%)	0 (0%)	2 (0.4%)	1.000
Chronic obstructive pulmonary disease	103 (14%)	31 (15%)	72 (14%)	0.769
Chronic kidney disease	64 (9%)	14 (7%)	50 (9%)	0.287
Liver cirrhosis	11 (2%)	2 (1%)	9 (2%)	0.737
Preoperative laboratory tests				
Haemoglobin (g/dl)	12.4 [11.1- 13.6]	12.6 [11.2 -13.7]	12.4 [11- 13.5]	0.264
Creatinine (mg/dl)	0.8 [0.7 - 0.9]	0.8 [0.7- 0.9]	0.8 [0.7- 1]	0.872
Albumin (g/dl)	3.9 [3.5 - 4.3]	3.9 [3.4 - 4.3]	3.9 [3.5 - 4.3]	0.672
TNM staging				
I A	120 (16.5%)	32 (15.5%)	88 (16.9%)	0.130
I B	102 (14.1%)	21 (10.2%)	81 (15.6%)	.
II A	128 (17.6%)	38 (18.5%)	90 (17.3%)	.
II B	112 (15.4%)	30 (14.6%)	82 (15.8%)	.
III A	114 (15.7%)	30 (14.6%)	84 (16.2%)	.
III B	73 (10.1%)	28 (13.6%)	45 (8.7%)	.
III C	21 (2.9%)	10 (4.9%)	11 (2.1%)	.
IV	56 (7.7%)	17 (8.3%)	39 (7.5%)	.
Preoperative neoadjuvancy	292 (39%)	106 (50%)	186 (36%)	<0.001
Surgical Procedure				
Subtotal Gastrectomy	472 (64%)	123 (58%)	349 (66%)	0.065
Total Gastrectomy	269 (36%)	88 (42%)	181 (34%)	.
Duration of surgery, minutes	235 [180 - 300]	245 [188 - 300]	215 [170 - 270]	<0.001
Intraoperative fluid balance, ml	850 [493 -1394]	851 [490 - 1369]	850 [495 -1437]	0.777
Centre with an established PBM protocol	444 (60%)	171 (81%)	273 (51%)	<0.001

ASA: American Society of Anesthesiology; ERAS: Enhanced recovery after surgery; PBM: Patient Blood Management.
 Percentage reflects over non-missing sample size. Discrete variables n (%). Continuous variables Median[Q1-Q3].

incidence of moderate-to-severe complications (47 (22.3%) vs. 125 (23.5%); OR, 0.92 (95% CI, 0.59 to 1.41); P = 0.068) or overall postoperative complications (71 (33.6%) vs. 174 (32.7%); OR, 1.05, 95 % CI, 0.70 to 1.56; P = 0.825) between the self-declared ERAS and non-ERAS groups. Patients in the ERAS group had less bloodstream infection compared to the non-ERAS group. There were no differences in the rest of the predefined complications and there were no differences in readmissions, reoperations, mortality and LOS. (Fig. 2).

Adherence data

The overall adherence rate to the ERAS individual items was 52% [IQR 45 to 60]. Adherence was significantly higher in self-declared ERAS centres compared to non-ERAS centres 60%

[IQR 52 to 70] vs. 50% [IQR 43 to 57] (P < 0.001). Adherence to most of the individual ERAS elements was higher in the self-declared ERAS cohort. Table 2 shows the adherence for each of the individual ERAS elements.

Outcomes in higher versus lower ERAS adherence groups

Adherence to the ERAS elements in the highest adherence quartile (Q1) was > 60 %, while in the lowest adherence quartile (Q4) ≤ 45 %. There were no differences in the number of patients with moderate to severe complications, overall complications, readmissions, mortality or LOS. Patients in the Q1 had more anastomotic leak compared with those in the low adherence group (Q4). There were no other differences in any of the predefined complications between the highest and

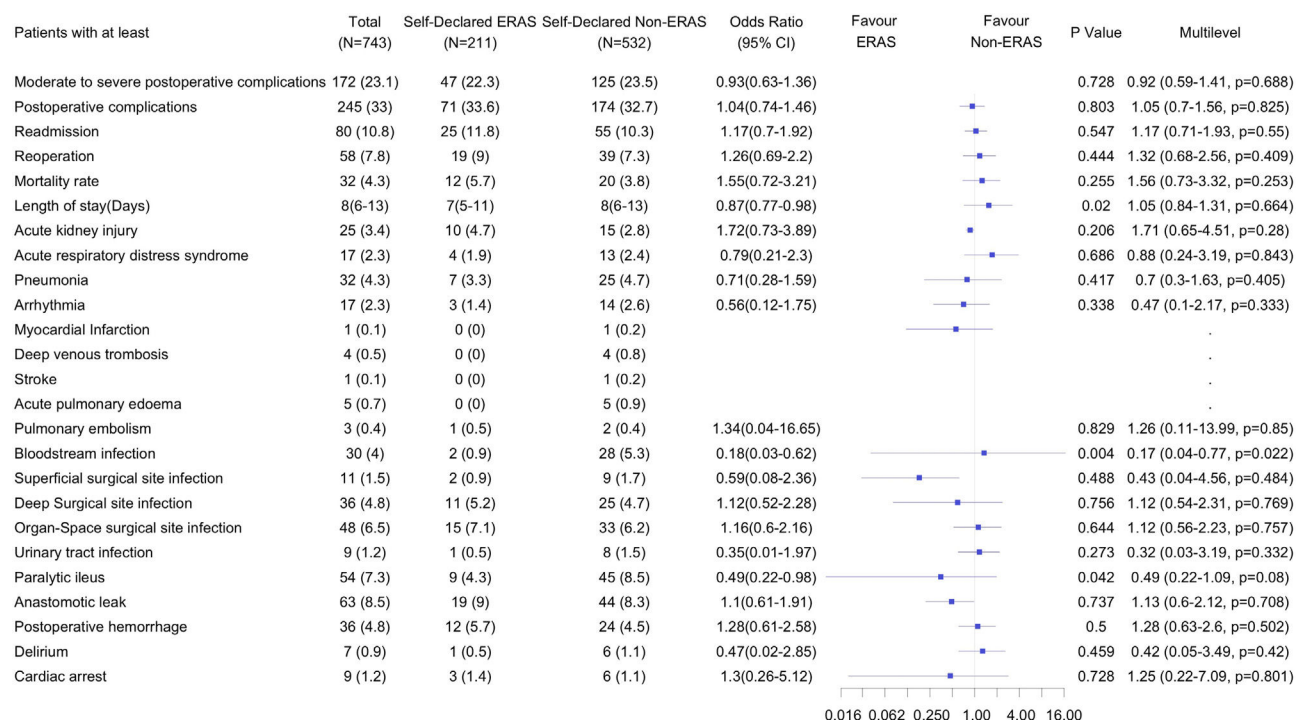


Fig. 2 – Title: Postoperative outcomes. Complications in all included patients and in patients who did or did not receive the Enhanced Recovery After Surgery (ERAS) protocol.

Note. Data are expressed as number (%) or median (Q1-Q3).

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

	All patients (N = 743)	Self-declared ERAS (N = 211)	Non-ERAS (N = 532)	P value
ERAS overall adherence	52 [45 - 60]	60 [52 - 70]	50 [43 - 57]	<0.001
Preadmission information, education and counselling	145 (19.5%)	114 (54%)	31 (5.8%)	<0.001
Preoperative exercise and prehabilitation	115 (16%)	90 (43.9%)	25 (4.9%)	<0.001
Preoperative optimisation	15 (14%)	5 (15.2%)	10 (13.5%)	0.773
Preoperative nutrition	217 (65.4%)	79 (79%)	138 (59.5%)	0.001
Avoid bowel preparation	632 (85.3%)	188 (89.5%)	444 (83.6%)	0.053
Preoperative fasting	281 (37.9%)	135 (64%)	146 (27.5%)	<0.001
Preoperative carbohydrate loading	129 (17.4%)	86 (40.8%)	43 (8.1%)	<0.001
Avoid preoperative administration of immediate or long-acting sedatives	604 (81.4%)	162 (76.8%)	442 (83.3%)	0.053
Perioperative fluid management	202 (27.3%)	64 (30.3%)	138 (26%)	0.274
Deep neuromuscular block	361 (48.9%)	88 (41.7%)	273 (51.7%)	0.018
Anesthetic depth monitoring	699 (94.5%)	197 (93.4%)	502 (94.9%)	0.520
Laparoscopic approach	415 (55.85%)	116 (54.98%)	299 (56.20%)	0.731
Avoid nasogastric tube	446 (60%)	160 (75.8%)	286 (53.8%)	<0.001
Avoid surgical drains	132 (17.8%)	38 (18%)	94 (17.7%)	0.998
Analgesia	458 (61.6%)	179 (84.8%)	279 (52.4%)	<0.001
Antithrombotic prophylaxis	713 (96.1%)	210 (99.5%)	503 (94.7%)	0.005
Prevention of nausea and vomiting	717 (96.6%)	206 (97.6%)	511 (96.2%)	0.468
Prevention of intraoperative hypothermia	720 (97.3%)	208 (98.6%)	512 (96.8%)	0.269
Postoperative nutrition	419 (56.4%)	113 (53.6%)	306 (57.5%)	0.368
Postoperative glycaemic control	642 (86.4%)	185 (87.7%)	457 (85.9%)	0.604
Early mobilization n (%)	439 (60.2%)	143 (69.8%)	296 (56.5%)	0.001
Early feeding n (%)	51 (7%)	22 (10.7%)	29 (5.6%)	0.022
Time to oral intake (hours)	48 [24 - 96]	30 [24 - 72]	72 [25 - 120]	<0.001
Time to mobilization (hours)	24 [22 - 48]	24 ²¹⁻³⁰	24 [23 - 48]	0.001

Percentage reflects over non-missing sample size. Discrete variables n (%). Continuous variables Median [Q1-Q3].

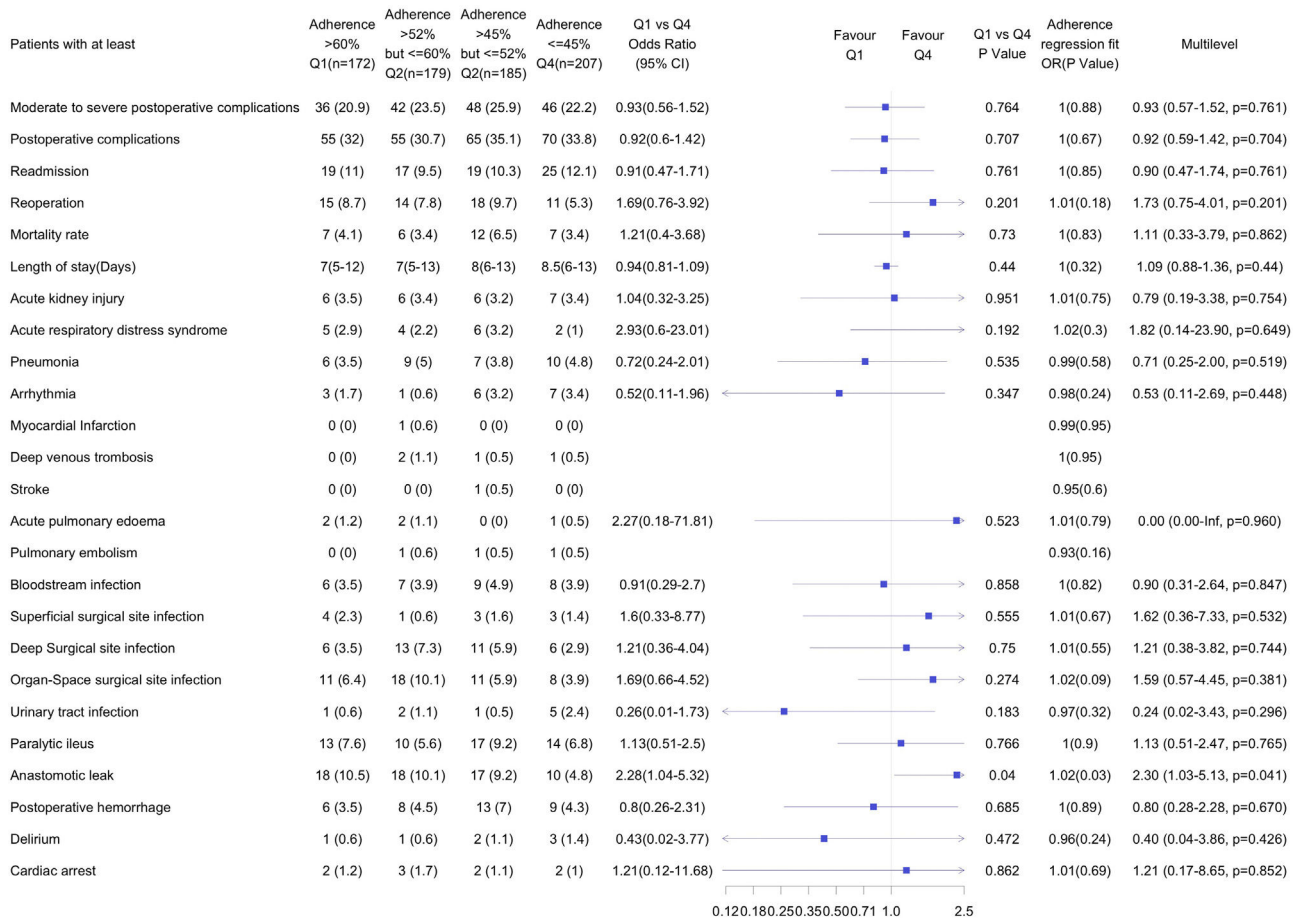


Fig. 3 – Title: Postoperative outcomes and Enhanced Recovery After Surgery (ERAS) adherence.

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).

lowest adherence groups (Fig. 3). Linear adherence adjustment also showed that additional adherence to the ERAS pathway in the Q1 did not improve any of the outcomes compared to Q4.

Individual ERAS elements, patients characteristics and moderate-to-severe postoperative complications

Multivariable and multilevel analyses of individual ERAS elements showed a statistically significant reduction of moderate-to-severe complications in those patients in which early mobilization was achieved while patients not receiving preoperative mechanical bowel preparation and postoperative nutritional care had more moderate-severe postoperative complications. No other associations were found for the other ERAS elements (Table S3, supplementary data).

Patients who received neoadjuvant therapy had a lower risk of moderate-severe postoperative complications. Frail patients, patients with cirrhosis, patients undergoing total gastrectomy, and patients with a longer lasting surgery had a higher risk of moderate-to-severe complications (Table S3, supplementary data).

Individual ERAS elements and patients characteristics and LOS

LOS was significantly lower in patients in whom nasogastric tube was not used, and in those who received early feeding. However, patients who underwent total gastrectomy and those who received postoperative nutritional support had a longer LOS. None of the other ERAS elements, neither being treated at a self-declared ERAS centre, were associated with shorter LOS (Table S4, supplementary data).

Discussion

The main finding of this study was that neither treatment at a self-declared ERAS centre nor high compliance (Q1) with ERAS measures were associated with improved outcomes after elective gastric cancer surgery.

Given the success of ERAS in colorectal surgery, this multimodal perioperative care approach has emerged as an optimal perioperative strategy to improve clinical outcomes in

gastric cancer surgery and in many other procedures. However, numerous controversies exist regarding the practice of ERAS in patients undergoing gastrectomy. A recent meta-analysis of randomized controlled trials which assessed the role of ERAS in radical gastrectomy showed that ERAS results in accelerated convalescence, improved nutritional status, and improved quality of life for gastric cancer patients.¹⁷ Similarly to our findings, Blumenthaler et al did not find that the application of an ERAS pathway in gastric surgery resulted in fewer postoperative complications.¹⁸ It has been reported that the efficacy of protocols that are incompletely or incipiently applied is markedly reduced.^{18,19} Although this has been mainly reported for colorectal surgery^{6,20} it was also recently shown that greater adherence to ERAS recommendations for gastric surgery resulted in improved postoperative outcomes.²¹ However, we did not find that greater adherence to protocols was associated with better outcomes, although the adherence in our highest adherence quartile was lower than previously reported as required to improve postoperative outcomes⁶, so it is possible that our low overall adherence in Spain was one of the determinants of the ineffectiveness of the ERAS protocol in this cohort.

Early mobilization was the only ERAS element that was associated with fewer moderate-severe complications. Several studies have shown that the application of this part of the ERAS program can significantly accelerate the recovery of postoperative intestinal function^{22,23} and improve postoperative outcomes.^{7,24,25} On the other hand, those who received postoperative nutritional support had more postoperative complications and higher LOS probably due to a previous poorer nutritional status or the presence of postoperative complications. The length of stay was also shorter in patients who did not have a nasogastric tube and who received an early feeding. The number and relative combination of ERAS elements implemented, and the relative importance of individual items, especially those considered as "core elements" of ERAS is currently a debated topic.^{26,27} It is accepted that early mobilization is a core element in most ERAS guidelines⁴, its fulfilment may be due to both a dedicated effort by the postoperative multidisciplinary team and a sign of favourable clinical outcome,²⁸ and conversely, the inability to mobilize early in the immediate postoperative period may be considered as a warning sign of poor clinical outcome.²⁹ Early deviation of postoperative ERAS elements appears to be the most significant in terms of association with ERAS failure and delayed discharge.²⁹ Early restoration of the oral feeding promotes early recovery of normal bowel function, so it seems logical that patients who achieve early tolerance will have a shorter LOS,³⁰ while those with impediments to achieving this, such as the presence of a nasogastric tube or the need for nutritional support, will have a longer LOS. Once again, this postoperative element could be considered as a success of the pathway, or as an early warning sign in those cases in which compliance is not achieved.³¹

A recent study provided unique insight into changes in gastric cancer presentation, management and outcomes over a 30-year period and highlighted the importance of perioperative chemotherapy in long-term survival, as well as the reduction in the number of total gastrectomy as a milestone in the management of patients undergoing gastric cancer surgery to improve postoperative outcomes.³² We found similar results, patients with neoadjuvant therapy presented fewer complica-

tions, but longer surgeries and total gastrectomy were associated with more postoperative complications. On the other hand, although the partial application of ERAS did not lead to better outcomes, it was not associated with more readmissions or more reoperations, so its practice seems safe, and efforts should be undertaken to achieve greater adherence to the protocol, since it is ultimately the standard of care in many cases.

Most of the studies on gastric surgery were performed in the Asian population, and this study is the largest study to date on gastric surgery in the ERAS setting in a Western population; however, we must acknowledge some limitations of the study. First, in an optimally designed study, the groups would be blindly assigned to ERAS or non-ERAS for the same period of time to avoid allocation bias. However, we consider that a randomized clinical trial comparing an ERAS protocol versus a clinical practice in which none of the ERAS elements were used would be unethical. On the other hand, information bias may be inherent in the design of this study, and could have influenced an increase in adherence to the ERAS elements, so that the actual ERAS adherence could even be lower. The elements of ERAS themselves are interrelated. For example, conservative intraoperative fluid administration is arguably more applicable in patients who did not receive preoperative bowel preparation, and administration of carbohydrate drinks mandates adequate adherence to preoperative fasting time. In addition, the use of some of the ERAS elements are related to the severity of the patient, e.g., goal-directed fluid therapy, usually recommended for the high-risk patient.^{33,34} We tried to avoid selection bias by including a majority of Spanish centres that were performing gastrectomy, regardless of whether they self-designated as ERAS or not. The effect of these problems was partly offset by the large sample size and the number of institutions reporting data, but we also have to recognize that gastrectomy is not as frequent a procedure as, for example, colorectal surgery, and many centres recruited a low number of patients.

The application of ERAS protocols for gastric surgery in our cohort was very low. Neither partial compliance with ERAS protocols nor treatment with self-designated ERAS centres improved postoperative outcomes in patients undergoing gastric surgery for cancer.

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Appendix A. Supplementary data

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