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ORIGINAL SCIENTIFIC REPORT

Association Between Compliance to an Enhanced Recovery Protocol and Outcome After Elective Surgery for Gastric Cancer. Results from a Western Population-Based Prospective Multicenter Study

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Abstract

Background The association between compliance to an enhanced recovery protocol (ERAS) and outcome after surgery for gastric cancer has been poorly investigated, particularly in Western patients. The aim of the study was to evaluate whether the rate of adherence to the ERAS program was correlated with outcome and time of discharge.

Methods A prospective, observational, multicenter study was designed to be performed at Italian referral centers for gastric surgery. The protocol was discussed and approved by the Italian Research Group on Gastric Cancer. Twenty-three ERAS domains were applied. A multivariate logistic regression was used to assess the association between ERAS compliance and overall and major complication rates. The Poisson regression model (measured as mean ratios) was used to assess the association of ERAS compliance rate and length of stay (LOS).

Results Eight centers participated and 290 subjects with a median age of 73 years were enrolled. The overall rates of adherence to pre-, intra-, and postoperative ERAS items were 69.8%, 60.3%, and 82.5%, respectively. At the multivariate model, there was an association between overall rate of morbidity and an overall ERAS compliance rate greater than 70% (OR 0.413; 95% CI 0.235–0.7240; P 0.002). A similar association was found for major complications (OR 0.328; 95% CI 0.151–0.709; P 0.005). The Poisson regression showed that in patients with ERAS compliance rate >70%, LOS was reduced of approximately 20% (mean ratio 0.812; 95% CI 0.694–0.950; P 0.009).

Conclusions These results suggest a moderate compliance to an ERAS program and a significant association between adherence and outcomes.

Introduction

The available consensus guidelines for enhanced recovery pathways after gastrectomy—by the Enhanced Recovery After Surgery (ERAS) Society—have been defined as an evidence-based framework that provides comprehensive

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advice on optimal perioperative care for patients undergoing gastrectomy [1]. However, due to the lack of procedure-specific data, several recommendations on single ERAS elements were adopted from the evidence produced in other types of surgery [1, 2].

Several randomized controlled trials (RCTs) on the effect of ERAS programs on the outcomes of patients undergoing gastric resection have been published [3–8] and the results polled in meta-analyses and systematic reviews [9–13]. The overall findings indicated that the application of the ERAS principles significantly accelerated patient recovery and function capacity without increasing postoperative morbidity. These advantages translated into a significant reduction in the duration of hospitalization, while in some reports, readmission rate was increased [9]. However, all these RCTs have been conducted in cohorts of Eastern patients. The entering criteria in some of the Eastern trials were quite selective with inclusion of low-risk patients, receiving laparoscopic approach for early disease stages and generally excluding patients with preoperative oncologic therapies [3–8]. The characteristics of the Western populations baring gastric cancer are quite different. Direct series comparison revealed that patients with gastric cancer in the Western world are older, with more and multiple comorbidities and with higher nutritional risk, with more advanced tumor stage, and frequently receive perioperative oncologic treatments [14–17]. These characteristics are well-known determinants of frailty that may negatively affect surgical outcomes [18, 19]. Patient frailty may also partially compromise the compliance and adherence to ERAS pathways [20, 21].

To the best of our knowledge, only two small series [22, 23] on the implementation of ERAS pathways for gastrectomy have been published in this well-defined population.

We aimed to evaluate the compliance of an enhanced recovery program in an unselected large cohort of Italian patients subject to gastrectomy for gastric cancer and to examine the potential associations between the overall compliance rate and the occurrence of overall and major postoperative morbidity, and delayed hospital discharge.

Methods

Study overview and participants

We designed a prospective, observational, multicenter study to be performed at Italian referral centers for gastric surgery. The protocol was discussed and approved by the Italian Research Group on Gastric Cancer (GIRCG Gruppo Italiano Ricerca Cancro Gastrico), a group that collects the vast majority of referral institutes for gastric surgery in Italy. All participating centers were part of the GIRCG, with partial ongoing ERAS protocol implementation. After adherence to the project, all center surgeons were committed to comply as much as possible with the ERAS protocol. Eligible for participation were adults (age >18 years) and candidates for elective gastrectomy with curative intent (total or subtotal) for cancer, either as upfront surgery or as after neoadjuvant chemotherapy. The exclusion criteria were as follows: I. American Society of Anesthesiologists (ASA) score >3, II. decompensated diabetes (HbA1c >7%), and III. gastric outlet obstruction. After the patients were screened according to the inclusion and exclusion criteria, the selected patients or their legal representatives were asked to provide written informed consent. Denied consent was an additional reason for exclusion. Afterward, the patients were enrolled into the study.

Interventions

After recruitment, all patients underwent counseling and were instructed by a surgeon, an anesthetist, a nutritionist, and a nurse on all specific pre-, intra-, and postoperative ERAS interventions. In particular, patients were encouraged, while waiting for the operation, to stop smoking and consuming alcohol, and improvement in all potentially corrigible risk factors (i.e., high blood pressure, hyperglycemia, anemia, etc.) was planned. The preoperative nutritional status and risk were calculated by the Nutritional Risk Score (NRS) [24]. An NRS $\geq$3 identified patients with the need of a specialized nutritional evaluation.

Patients were allowed regular meals until midnight of the day before the operation. Laparoscopic gastric resection was implemented according to defined criteria reported in the national guidelines [25]. Active intraoperative patients warming were carried out with a heated blanket and a 38 °C intravenous infusion. All patients were evaluated for placement of an epidural catheter at T7–T8 level. After the

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operation, patients were encouraged to drink water and oral nutritional supplements from POD 1, while oral feeding with regular diet was allowed from day 3 after the operation. Incentive mobilization was started on POD1.

Detailed description of the single ERAS items is provided in Supplementary Table 1.

Measurements

The overall compliance was calculated as the average of all ERAS elements. The compliance to the single ERAS domains was calculated as the average implementation of each domain.

The occurrence of a complication was a deviation from the regular postoperative course, and it was based on a priori definition [26–28]. The severity of complications was scored according to the Clavien–Dindo classification [29].

Each participating center had two independent outcome assessors. The occurrence of postoperative morbidity was assessed twice a day during hospitalization and for 30 days after the operation. Post-discharge surveillance and follow-up involved weekly outpatient visits.

Statistical analysis

Descriptive statistics were calculated using number with percentages for categorical variables and median with IQR for continuous variables.

Multivariate logistic regression was adopted to select and assess the impact of ERAS items associated with the rate of complications (overall, major, medical, and surgical). The selection procedure was based on a stepwise algorithm according to the Akaike's information criterion (AIC) statistic. Beside ERAS items, some covariates were retained in the final model for adjustment: age, ASA = 3 (vs. <3), and the number of comorbidities ≥3 (vs. <3).

Univariate and multivariate logistic regression models were also employed to assess the association of ERAS compliance with complications and readmission. Two multivariate models were fitted, one including ERAS compliance as a continuous variable and another considering the dichotomized variable (ERAS compliance >70% vs. ≤70%). We decided to use the 70% threshold to dichotomize the compliance rate based on previous results [30, 31].

All multivariate models were adjusted by age, sex, BMI, ASA score = 3 (vs. <3), comorbidities ≥3 (vs. <3), NRS (<3 vs. ≥3), neoadjuvant therapy (yes vs. no), duration of surgery, and type of operation (total vs. subtotal gastrectomy).

Univariate and multivariate Poisson's regression was used to assess the association of ERAS compliance with LOS (in day unit) among patients without major complications. Kaplan–Meier curves were drawn to show the cumulative incidence of discharge according to ERAS compliance (>70% vs. ≤70%).

Results

Eight centers adhered to the study, and during the study period, 323 patients were screened for eligibility. After applying the exclusion criteria, 290 subjects were enrolled in the study.

Demographic, clinical, operative data and cancer stage of the enrolled patients are summarized in Table 1. Some ERAS domains such as pre-admission counseling, evaluation and optimization of patient risk factors, antibiotic, and deep venous thrombosis prophylaxis were implemented in all patients before the beginning of the study. Thus, these items were not considered as relevant variables in evaluating the ERAS compliance. The ERAS pathway and the rate of compliance to the single domains are given in Supplementary Table 2. The overall rates of adherence to pre-, intra-, and postoperative ERAS items were 69.8%, 60.3%, and 82.5%, respectively.

The distribution of the individual compliance to the ERAS domains according to each center is depicted in Fig. 1. The median number was 11 items.

Overall, postoperative morbidity rate was 34.1% (99/290), and the rate of major complication was 15.5% (45/290). The rate of medical complication was 31.0% (90/290), and surgical morbidity occurred in the 20.7% (60/290) of the patients. The readmission rate was 6.4% (18/290), and 90-day mortality was 1.7% (5/290).

The multivariate analysis (Table 2) showed that several ERAS domains were associated with the risk of developing or not developing overall and major complications. Carbohydrate load, goal-directed fluid therapy, resumption of oral diet, and no use of opioids were associated with a protective effect on overall and major morbidity, while no-drain policy was associated with an increased risk for complications.

By analyzing medical and surgical morbidity, we observed that carbohydrate load, PONV, stop IV fluid, resumption of regular oral diet, and no use of opioids were associated with a protective effect on both medical and surgical complications (Supplementary Table 3).

In a multiple logistic regression model for postoperative complications, considering age, sex, BMI, and ASA score, more than three comorbidities, duration of surgery, and compliance to ERAS protocol as continuous variables or as variables dichotomized at 70%, these last 2 parameters were both associated with a significant reduction in overall morbidity and major complications (Table 3).

Table 1 Description of the cohort (n = 290)

Variable	
Age, years	73.0 (64.2–78.7)
Sex (male)	166 (57.2)
Body weight (kg)	68 (59–80)
Body mass index (kg/m^2)	24.3 (21.9–27.5)
ASA score	
1	26 (9.0)
2	149 (51.4)
3	115 (39.6)
Smokers	
Active	44 (16.9)
Former	78 (29.9)
No	139 (53.3)
Missing	29 (10)
Comorbidities	
0–1	79 (32.4)
2–3	127 (43.8)
>3	84 (28.9)
Missing	6 (2.1)
Nutritional risk score ≥3	64 (22.2)
Preoperative nutritional therapy	22 (7.6)
Preoperative fasting time (h)	13.2 (12.5–15.3)
Neoadjuvant therapy	84 (29.0)
Total gastrectomy	160 (55.2)
Roux-en-Y reconstruction	276 (95.2)
Minimally invasive approach	77 (26.6)
D2 or more lymph node dissection	260 (89.6)
Duration of surgery (min)	255 (215–300)
Blood loss (mL)	150 (100–250)
Cancer stage	
I	75 (25.9)
II	78 (26.9)
III	137 (47.2)
Body weight at discharge (kg)	65 (57–76)

Values are numbers (%) or median (IQR)

The logistic regression models for medical and surgical complication suggested an association between an ERAS compliance >70% and a reduced risk of events (Supplementary Table 4).

Discharge criteria were achieved after a median of 7 days (IQR 6–9), while the actual hospital discharge occurred after 8 (IQR 6–11) days.

The Poisson's regression model for LOS showed that for every 10% increase in ERAS compliance, it could be possible to gain a 10% reduction in LOS (e.g., for an expected LOS of 10 days, nearly 1 day is gained) (Table 4). The Kaplan–Meier curve showed a reduction in LOS when ERAS compliance was greater than 70% (Fig. 2; log-rank test = 0.048).

ERAS compliance >70% was associated with a 70% reduced risk of readmission (OR: 0.283; 95% CI: 0.082–0.983; P: 0.047) (Supplementary Table 5).

Discussion

The large amount of available data—in colorectal patients—indisputably demonstrate that the implementation of the ERAS pathway results in a significant shorter time required for full recovery and in a reduction in postoperative morbidity [32, 33]. Furthermore, there are a progressively increasing number of reports suggesting that the implementation of the ERAS protocols offers benefit in more challenging surgical scenarios [34]. However, the ERAS program has some weaknesses and barriers that may limit the spread such as the complexity of the process, the resistance to change from clinicians, and the need of a consolidated multidisciplinary teamwork [35, 36]. The lack of implementation of the ERAS pathway in major gastric resections in Western population may be a good example of latter concern. The experience in Western patients is nearly anecdotic. Grantcharov et al. [23] reported in 32 patients that minimally invasive gastrectomy, within an ERAS program, resulted in a short hospital stay and low morbidity rate. More recently, Underwood and colleagues [22] published a multicenter experience with an enhanced recovery pathway for major laparoscopic esophagogastric resections, which included 24 gastrectomies. However, the authors did not report separate rates of compliance to ERAS domains for this small subset.

The concern of applying or directly transferring Eastern protocols [3–7] to Western populations may be due to the considerable differences in the subject characteristics between the two realities. Most of the patients included in the Eastern studies were young, at low surgical risk, with early cancer stage, and candidate to upfront gastric resection if compared with the epidemiology of subjects undergoing gastrectomy in Europe and USA. For these reasons, we designed a study aimed to evaluate the compliance of an enhanced recovery program in an unselected large cohort of Italian patients candidate to gastrectomy. We excluded patients with ASA score >3 because the underlined severe systemic diseases—with constant threat to life—are major determinants of outcomes, and patients with decompensate diabetes since the safety of some ERAS items in this subgroup are still under safety investigation [37, 38]. Considering advanced age, high proportion of comorbid conditions, high ASA score, poor nutritional status, and advanced cancer staging, the overall compliance rate to the ERAS program was about 70%, nor far from the

Table 2 Estimates of the multivariate logistic regression model to assess the association between baseline characteristics, ERAS domains, and overall or major complications

Variable	Overall complications		Major complications	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, per year	0.993 (0.961;1.026)	0.680	1.001 (0.958;1.046)	0.955
ASA ≥3 (vs. 1 and 2)	1.940 (0.922;4.082)	0.081	0.818 (0.299;2.239)	0.696
Comorbidities <3 (vs. ≥3)	0.716 (0.333;1.537)	0.354	0.839 (0.296;2.378)	0.741
Cancer stage III (vs. I and II)	1.167 (0.624;2.183)	0.628	1.375 (0.6;3.149)	0.452
Carbohydrate load (yes vs. no)	0.386 (0.176;0.849)	0.018	0.172 (0.056;0.533)	0.002
GDFT (no vs. yes)	3.711 (0.826;16.665)	0.087	6.898 (1.249;38.096)	0.027
Minimally invasive approach (yes vs. no)	2.353 (1.011;5.479)	0.047	2.6 (0.915;7.384)	0.073
Drains (no vs. yes)	3.224 (1.099;9.459)	0.033	5.27 (1.405;19.762)	0.014
Stop IV fluid (yes vs. no)	0.250 (0.108;0.577)	0.001	0.128 (0.047;0.347)	<0.001
Regular diet (yes vs. no)	0.198 (0.1;0.391)	<0.001	0.281 (0.116;0.681)	0.005
Opioids (no vs. yes)	0.358 (0.15;0.856)	0.021	0.239 (0.084;0.681)	0.007
PONV (yes vs. no)	0.232 (0.096;0.559)	0.001	–	–
Premedication (yes vs. no)	3.007 (1.313;6.887)	0.009	–	–
Urinary catheter (yes vs. no)	–	–	0.398 (0.15;1.055)	0.064

OR Odd ratio, *CI* Confidential interval, *ASA* American Society of Anesthesiologists, *GDFT* Goal-directed fluid therapy, *IV* Intravenous, *PONV* prevention of nausea and vomiting

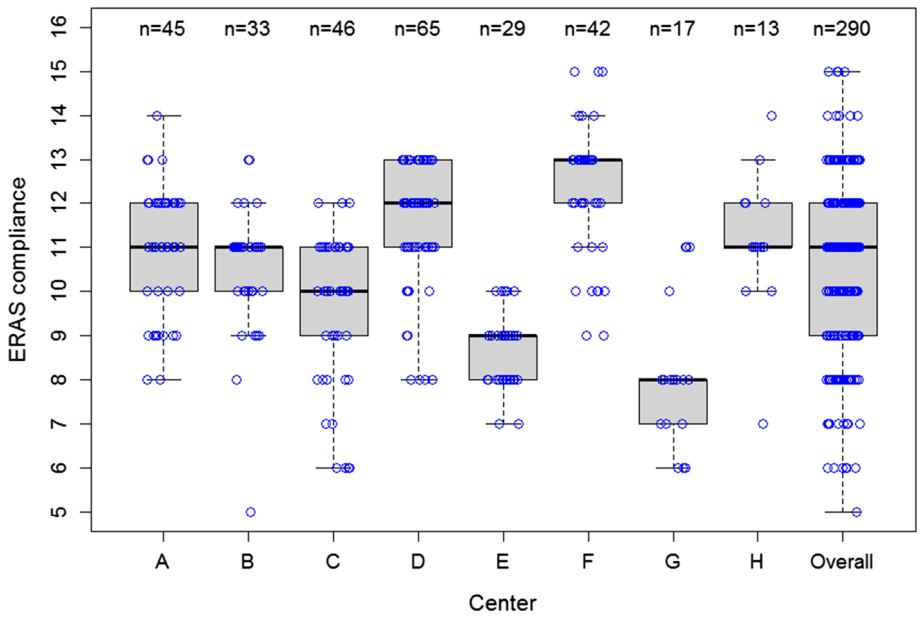

Fig. 1 Distribution of the individual compliance to the ERAS domains according to each center

proportion reported in lower-risk patients [6, 7], and at the multivariate analysis, none of the above variables were associated with adverse outcomes.

Some ERAS domains were not routinely adopted. The low rate of laparoscopic resection was of no surprise because as per guidelines [25] a minimally invasive approach is recommended only in early cancer stages. The no-drain policy was almost never implemented, suggesting that there is not sufficient evidence in gastric surgery to abandon the use of abdominal drains. No-drain policy, in our experience, was associated with an increased risk of complications. This result is somehow in contrast with what is generally reported in the literature [39].

Table 3 Estimates of the univariate and multivariate logistic regression models to assess the association between compliance to ERAS protocol (as 10% increase or dichotomized according to 70% threshold) and overall or major complications

Outcome	Factors	Univariate models		Multivariate models	
		OR (95% CI)	*p*	OR (95% CI)	*p*
Overall complications	ERAS compliance (%), per 10%	0.645 (0.525;0.792)	<0.001	0.674 (0.532;0.854)	0.001
	ERAS compliance >70%	0.411 (0.250;0.676)	<0.001	0.418 (0.238;0.736)	0.003
Major complications	ERAS compliance (%), per 10%	0.577 (0.437;0.761)	<0.001	0.581 (0.419;0.805)	0.001
	ERAS compliance >70%	0.328 (0.166;0.647)	0.001	0.335 (0.154;0.728)	0.006

All multivariate models were adjusted by age, sex, BMI, ASA score = 3 (vs. <3), comorbidities ≥3 (vs. <3), cancer stage III (vs. I and II), NRS (<3 vs. ≥3), type of operation (total vs. subtotal gastrectomy), and duration of surgery

OR Odd ratio

CI Confidential interval

Table 4 Estimates of the univariate and multivariate Poisson regression models to assess the association between compliance to ERAS protocol (as 10% increase or dichotomized according to 70% threshold) and length of stay among patients without major complications

Factors	Univariate models		Multivariate models	
	Mean ratio (95% CI)	*p*	Mean ratio (95% CI)	*p*
ERAS compliance (%), per 10%	0.927 (0.863;0.994)	0.034	0.899 (0.834;0.970)	0.006
ERAS compliance >70%	0.857 (0.741;0.991)	0.038	0.811 (0.696;0.945)	0.007

All multivariate models were adjusted by age, sex, BMI, ASA score = 3 (vs. <3), comorbidities ≥3 (vs. <3), cancer stage III (vs. I and II), NRS (<3 vs. ≥3), type of operation (total vs. subtotal gastrectomy), and duration of surgery

CI Confidential interval

Notwithstanding, we observed a 20% of our population be at nutritional risk, and only one-third of the patients was referred to a nutritionist for a tailored nutritional support. This observation confirms that surgeons still underestimate the role of an adequate nutritional support although malnutrition is one of the few corrigible preoperative risk factors affecting the outcomes [40].

Our logistic regression model suggested that among the preoperative and intraoperative ERAS elements, carbohydrate load, no use of premedication, PONV, and GDFT were associated with a decreased risk of developing overall morbidity, while carbohydrate load and GDFT with major complications. These findings are quite consistent with the recent literature [41, 42].

The early resumption of regular oral diet, no use of opioids, and discontinuation of intravenous fluids were the ERAS postoperative domains mainly associated with a protective effect on both overall and major morbidity. Since the confounding effect of postoperative recovery on ERAS component compliance is well recognized [43–45], it is possible that the occurrence of a complication impaired the adherence to several postoperative domains and not vice versa. Nevertheless, the rate of compliance to ERAS protocol was associated with a significant reduction in the postoperative overall morbidity, major complication, and readmission rates, consistent with what is reported by others for low-risk patients [4, 5].

Hospital discharge criteria were achieved after a median of 7 days, similar to data reported by others [46] and 4 days earlier than what is reported by Italian healthcare quality agencies for the same type of surgery [47]. Besides, a significant 2-day reduction in the duration of hospitalization was observed for patients with compliance greater than 70%.

Our study has several drawbacks. The first is the lack of randomization and accordingly the impossibility to compare our data with a non-ERAS control group. However, analyzing the downstream effect using a regression analysis may be useful to study the impact of single interventions and compliance rates rather than relying on unrealistic randomized clinical trials to test the effect of each specific item [33]. The second limitation is the center selection. The study was run in institutions with high experience in gastric surgeries, having already in place some personalized enhanced recovery pathways and a manifest interest in complying with a standardized and full ERAS protocol.

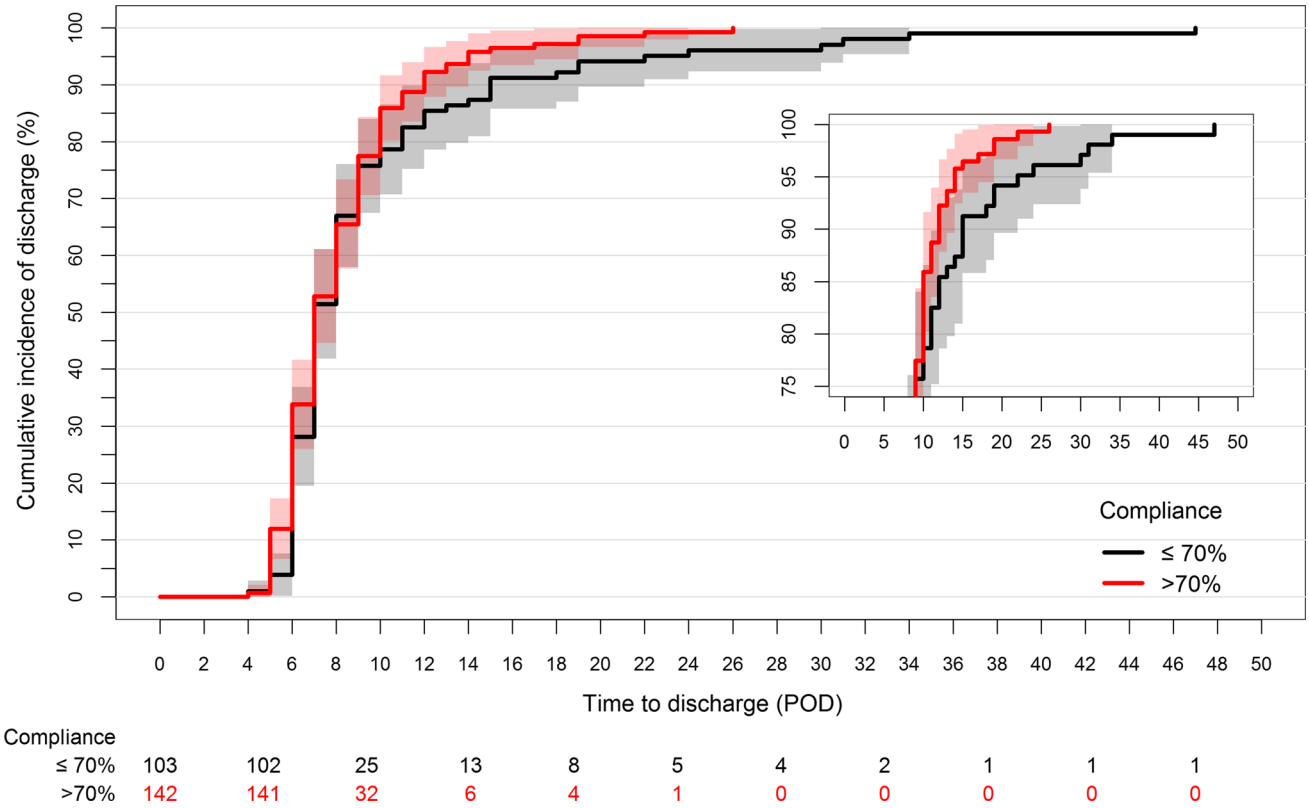

Fig. 2 Association between cumulative incidence of discharge and time to discharge in patients without major complications (n = 245). Log-rank test 0.048

In conclusion, the present report suggests that an ERAS protocol is feasible also in aging Western patients, with a high prevalence of comorbid conditions, advanced disease stage, and mostly undergoing open gastric resection with promising effects on morbidity and duration of hospitalization.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The study was approved by the institution ethics committee (authorization number 1383). All authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. All authors participated in drafting the article or revising it critically for important intellectual content. All authors gave final approval of the version to be submitted and any revised version to be published.

Informed consent Informed consent was obtained from all individual participants included in the study.

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