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ORIGINAL SCIENTIFIC REPORT

Implementation of Enhanced Recovery (ERAS) in Colorectal Surgery Has a Positive Impact on Non-ERAS Liver Surgery Patients

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Abstract

Background Enhanced recovery after surgery (ERAS) reduces complications and hospital stay in colorectal surgery. Thereafter, ERAS principles were extended to liver surgery. Previous implementation of an ERAS program in colorectal surgery may influence patients undergoing liver surgery in a non-ERAS setting, on the same ward. This study aimed to test this hypothesis.

Methods Retrospective analysis based on prospective data of the adherence to the institutional ERAS-liver protocol (compliance) in three cohorts of consecutive patients undergoing elective liver surgery, between June 2010 and July 2014: before any ERAS implementation (pre-ERAS $n = 50$), after implementation of ERAS in colorectal (intermediate $n = 50$), and after implementation of ERAS in liver surgery (ERAS-liver $n = 74$). Outcomes were functional recovery, postoperative complications, hospital stay, and readmissions.

Results The three groups were comparable for demographics; laparoscopy was more frequent in ERAS-liver ($p = 0.009$). Compliance with the enhanced recovery protocol increased along the three periods (pre-ERAS, intermediate, and ERAS-liver), regardless of the perioperative phase (pre-, intra-, or postoperative). ERAS-liver group displayed the highest overall compliance rate with 73.8 %, compared to 39.9 and 57.4 % for pre-ERAS and intermediate groups ($p = 0.072/0.056$). Overall complications were unchanged ($p = 0.185$), whereas intermediate and ERAS-liver groups showed decreased major complications ($p = 0.034$). Consistently, hospital stay was reduced by 2 days ($p = 0.005$) without increased readmissions ($p = 0.158$).

Conclusions The previous implementation of an ERAS protocol in colorectal surgery may induce a positive impact on patients undergoing non-ERAS-liver surgery on the same ward. These results suggest that ERAS is safely applicable in liver surgery and associated with benefits.

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Introduction

Enhanced recovery (ERAS) pathways have become standard of care in colorectal surgery due to significant reduction of complications, length of stay (LoS), and costs [1–5]. As a result, ERAS protocols were subsequently extended to other types of surgery, including gastric [6], pancreatic [7], and liver [8] surgery. The use of ERAS protocols in liver surgery appeared to be safe and feasible [9–11]. However, applied protocols widely varied and the assessment of their application (compliance) was rarely reported. Moreover, some ERAS protocols in liver surgery were implemented in centers having an institutional experience of ERAS in colorectal surgery. The previous implementation of ERAS in colorectal surgery presumably influence other types of surgery performed in a non-ERAS setting, provided the patients are on the same ward and treated by the same anesthetists. The usual comparative group "pre-ERAS" may thus be biased by this influence. It may be hypothesized that this impact could be observed in different protagonists: patients and medical staff. Regarding the patients, non-ERAS ones may be influenced by observing early feeding and mobilization in ERAS patients, then requesting similar care. Likewise, surgeons, anesthetists, and nurses potentially modify their management of non-ERAS patients, according to ERAS principles.

The present study aimed to test this hypothesis by analyzing the compliance and the clinical outcomes of patients undergoing elective liver surgery in three different groups: before institutional ERAS implementation for colorectal surgery (pre-ERAS), after ERAS implementation for colorectal but before its application for liver surgery (intermediate), and after the implementation of ERAS in liver surgery (ERAS-liver).

Methods

Enhanced recovery after surgery program (ERAS) for colorectal surgery was implemented in our institution in May 2011 in a systematic manner as recommended by ERAS Society guidelines [12]. Then, ERAS was implemented in liver surgery in July 2013, by the same multidisciplinary team, in the same ward, with the same method [13] applying an institutional formal ERAS-liver protocol. Documentation of adherence to the ERAS pathway (compliance) is key component of ERAS program and was therefore systematically measured for all patients. Systematic comparison with patients before, during, and after implementation was performed and is detailed below. The Institutional Review Board approved the study and all patients provided written consent before surgery. The study was conducted in accordance with the STROBE criteria (http://strobe-statement.org/) and registered under www.researchregistry.com (UIN: 392).

Patients

The implementation of ERAS program for colorectal surgery may presumably influence perioperative care for liver resections. To test this hypothesis, three groups of patients were analyzed: "Pre-ERAS," "Intermediate," and "ERAS-liver," as illustrated in Fig. 1. Each group was a cohort of consecutive patients undergoing elective liver surgery. "Pre-ERAS" patients were included before implementation of any ERAS in colorectal surgery. "Intermediate" included patients after implementation for colorectal but before implementation of ERAS for liver resection. "ERAS-liver" included patients after implementation of the specific ERAS-liver protocol. Of note, no exclusion criteria were applied. Therefore, all consecutive patients were included, regardless of the age or any other parameter.

ERAS protocol and compliance (Table 1)

To date, no validated guidelines for enhanced recovery in liver surgery have been published by the ERAS Society. The present specific ERAS protocol for liver surgery was created by our team and adapted from the enhanced recovery pathway for colorectal surgery, published [14–16] by the ERAS Society, and from the published pancreas ERAS guidelines [17]. ERAS was implemented in our institution for colorectal and pancreatic surgeries in May 2011 and September 2013, respectively. Additional-specific items related to liver surgery were adapted, based on available evidence. Table 1 provides a comprehensive overview of our enhanced recovery protocol for liver surgery with the respective references. Compliance with the ERAS protocol was prospectively assessed for the different phases of perioperative care (pre-, intra-, and postoperative). Briefly, enhanced recovery items were handled as

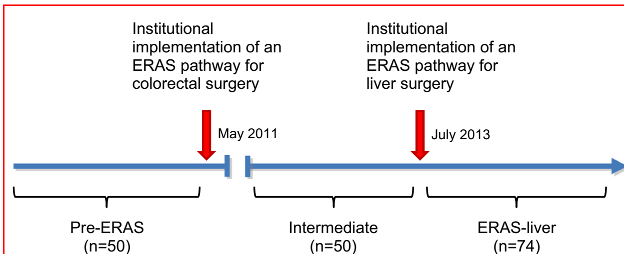


Fig. 1 Comparative groups and time frame

Table 1 The institutional enhanced recovery pathway for colorectal and liver surgery

Item	Colorectal	Liver	Refs.
Preoperative items			
Preoperative counseling	Preadmission counseling and written information	Same	[15]
Bowel preparation	Avoidance of bowel preparation	Not relevant	
Fasting	Clear fluids until 2 h before surgery, solids 6 h before surgery	Same	[29]
Carbohydrate drinks	800 ml the evening before surgery and 400 ml 2 h before surgery	Same	[16]
Immunonutrition (IN)	IN could be considered in open colonic resections	Same	[30]
Premedication	No preoperative long-acting sedative premedication	Same	[16]
Thromboprophylaxis	LMW heparin 12 h before surgery, IPC	Same	[31]
Intraoperative items			
Antibiotic prophylaxis	Cefuroxime 1.5 g + metronidazole 500, 30 min before incision	Cefuroxime 1.5 g, 30 min before incision	[32]
Hypothermia prevention	Active warming with air blanket	Same	
PONV prophylaxis	Droperidol 1 mg at induction, ondansetron 4 mg ± betamethasone 4 mg at the end of surgery[a]	Same	[33]
Postoperative items			
Balanced IV fluids	Intraoperative crystalloid quantity depending on the operation avoiding salt and water overload. Postoperative crystalloids 1000 ml for the first 24 h then 500 ml/24 h for the first postoperative days	Goal directed fluid therapy with low CVP during liver resection, restoration of euvolemia after the resection	[34]
Postoperative analgesia	Epidural or PCA removed after 48 h. Paracetamol, ibuprofen, and oxycodone–naloxone only for breakthrough pain	Epidural removed on POD 4 and switch to oral opioids	[15]
Abdominal drains	No routine abdominal drainage	Same	[35]
Nasogastric tube	No routine postoperative use	Same	[36]
Urinary catheter	Removal on POD 1	Removal on POD 3	[16]
Nutrition	Free fluids 4 h after surgery. Normal diet from day of surgery. Two nutritional supplements (300 kcal/unit) per day	Free fluids 4 h after surgery. Normal diet on POD 1. Two Nutritional supplements per day	[16]
Laxatives	Oral magnesium hydroxide ± chewing gum	Same	
Mobilization	Out of bed more than 15 min on day of surgery, at least 6 h per day thereafter	Same	[37]
Systematic audit	Systematic audit, meeting every 2 weeks	Ongoing implementation	[21]

LMW low molecular weight, *IPC* intermittent pneumatic compression, *PONV* postoperative nausea and vomiting, *PCA* patient-controlled analgesia, *POD* postoperative day

[a] Betamethasone only for women or nonsmokers or those with previous history of PONV

dichotomous variables. Individual adherence to the protocol was calculated as percentage of compliant patients/total patients. The number of fulfilled items divided by the total number of enhanced recovery measures (%) is presented as overall compliance with the pathway.

Data collection

A dedicated-trained ERAS nurse was in charge of completing the prospective database. Demographic and surgical details of all patients in the enhanced recovery pathway were captured along with detailed information on compliance with the protocol and audit of clinical outcome with a minimal follow-up of 30 postoperative days. Control of pain with oral analgesia only, stop of intravenous fluid, full mobilization, and eating solid food were recorded, while postoperative complications were graded according to *Clavien classification* [18] and to the Comprehensive Complication Index (CCI) [19]. CCI is a score that integrates and sum all postoperative complications

Table 2 Patients' characteristics

	Pre-ERAS ($n = 50$)	Intermediate ($n = 50$)	ERAS-liver ($n = 74$)	p value
Age (years)[a]	64 (59–69)	64 (57–73)	60 (49.75–68)	0.073
Sex ratio (M:F)	35:15	25:25	43:31	0.122
Body mass index (kg/m^2)[a]	24.8 (23.3–27.8)	24.5 (21.4–27.5)	25.3 (21.6–29)	0.749
ASA grade[b]				0.77
I–II, n (%)	36 (72 %)	35 (70 %)	56 (75.7 %)	
III–IV, n (%)	14 (28 %)	15 (30 %)	18 (24.3 %)	
Cirrhosis, n (%)[b]	6 (12 %)	6 (12 %)	4 (5.4 %)	0.33
Smoker, n (%)[b]	9 (18 %)	10 (20 %)	16 (21.6 %)	0.885
Diabetes, n (%)[b]	13 (26 %)	6 (12 %)	13 (17.6 %)	0.19
Diagnosis[b]				0.425
Neoplasia, n (%)	43 (86 %)	44 (88 %)	55 (74.3 %)	0.099
HCC, n (%)	6 (12 %)	10 (20 %)	10 (13.5 %)	
Cholangiocarcinoma, n (%)	2 (4 %)	7 (14 %)	9 (12.2 %)	
Metastasis, n (%)	25 (50 %)	21 (42 %)	31 (41.9 %)	
Echinococcosis, n (%)	5 (10 %)	2 (4 %)	11 (14.9 %)	
Benign lesions	2 (4 %)	3 (6 %)	5 (6.8 %)	
Others	10 (20 %)	7 (14 %)	8 (10.8 %)	

Values are median (IQR). Additional procedure: cholecystectomy was not included. Major resection: ≥3 resected segments. Minor resection: <3 resected segments

ASA American Society of Anesthesiologists, *HCC* hepatocellular carcinoma

[a] Kruskal–Wallis

[b] Chi-square test

with their respective severity, on a scale ranging from 0 (no complication) to 100 (death); underreporting of minor complications can thus be avoided and reporting of complication is supposed to be more accurate [19]. Length of stay was counted from day of surgery until discharge. Discharge was decided on pre-established criteria: control of pain with oral analgesia, eating solid food, return of bowel function, and full mobilization. Readmissions were considered within 30 days after surgery.

Statistics

Descriptive statistics for categorical variables were reported as frequency (%), while continuous variables were reported as median (interquartile range). Continuous variables were compared between "pre-ERAS," "Intermediate," and "ERAS-liver" groups with the Kruskal–Wallis test. Chi-square test was used for comparison of categorical variables. All statistical tests were two-sided and a level of 0.05 was used to indicate statistical significance. Data analyses were performed using SPSS v20 statistical software, Chicago, IL.

Results

Patients

Seventy-four patients who underwent liver surgery in the "ERAS-liver" group were compared to 50 patients in the "pre-ERAS" group, and 50 patients in the "intermediate" group. Baseline demographics were similar between the three groups (Table 2). Patients in the ERAS-liver group had more laparoscopic procedures than the comparative groups (4.1 vs. 14 vs. 24.7 %) ($p = 0.009$) and less pedicular clamping (68, 28, 39.2 %, $p < 0.001$). The characteristics of surgery are detailed in Table 3.

ERAS implementation and compliance with the protocol

Compliance with the enhanced recovery pathway steadily increased along the three periods (pre-ERAS, intermediate, and ERAS-liver), regardless of the perioperative phase (pre-, intra-, or postoperative). While intraoperative phase globally displayed the highest compliance rate, preoperative and postoperative items were the most influenced by the implementation of an ERAS pathway (Fig. 2).

Table 3 Types of surgery

	Pre-ERAS ($n = 50$)	Intermediate ($n = 50$)	ERAS-liver ($n = 74$)	p value
Surgical approach[a]				0.009
Laparoscopic, n (%)	2 (4.1 %)	7 (14 %)	18 (24.7 %)	
Open, n (%)	47 (95.9 %)	43 (86 %)	55 (75.3 %)	
Procedure[a]				0.914
Major resection, n (%)	22 (44 %)	21 (42 %)	30 (41.1 %)	
Minor resection, n (%)	27 (54 %)	29 (58 %)	43 (58.9 %)	
Anastomosis, n (%)	4 (8.2 %)	5 (10 %)	11 (14.9 %)	0.481
Clamping, n (%)	34 (68 %)	14 (28 %)	29 (39.2 %)	<0.001

Values are median (IQR). Additional procedure: cholecystectomy was not included. Major resection: ≥3 resected segments. Minor resection: <3 resected segments

ASA American Society of Anesthesiologists, *HCC* hepatocellular carcinoma

[a] Chi-square test

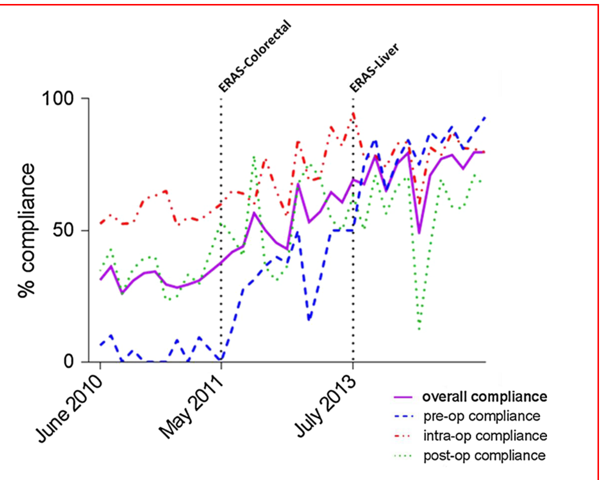


Fig. 2 Compliance with the ERAS pathway over time

Figure 3 illustrates each ERAS items displaying a significant difference across the groups, in term of compliance rate (all ERAS items are detailed in Fig. 5 in Appendix). Regarding preoperative phase, ERAS-liver group displayed greater compliance rate for each item, with a mean rate of 81.1 %, comparing to 32.2 and 4.5 % in intermediate and pre-ERAS groups, respectively ($p < 0.001$). A significant difference was highlighted in three intraoperative items: avoidance of nasogastric tube ($p < 0.001$), PONV prophylaxis ($p < 0.001$), and the use of pneumatic boots ($p < 0.001$). ERAS implementation showed a significant impact on postoperative phase, with most items showing statistical differences between the studied groups: balanced IV fluid at POD 0 ($p < 0.001$), start of intake water and free fluids at POD 0 ($p < 0.001$), mobilization at POD 0 ($p = 0.04$), oral analgesia at POD 1 ($p < 0.001$), normal diet at POD 1 ($p < 0.001$), full mobilization at POD 1 ($p = 0.015$), UC removal at POD 3 ($p = 0.019$), and stop epidural/intravenous analgesia at POD 4 ($p = 0.001$).

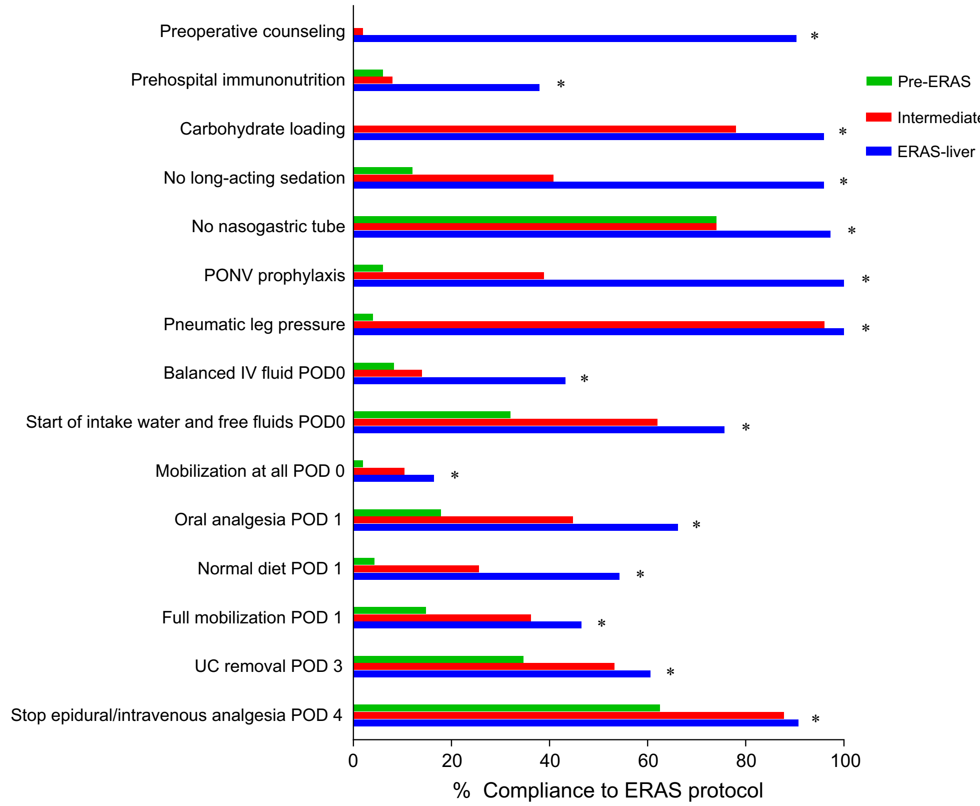
Functional recovery (Fig. 4)

The duration of intravenous or subcutaneous analgesia in liver patients was reduced after both implementations of ERAS in colorectal ($p = 0.001$) and liver surgery ($p < 0.001$). Discontinuation of intravenous fluid ($p = 0.016$) and full mobilization ($p = 0.023$) was mostly influenced by the institutional implementation of ERAS for colorectal surgery. Regarding intake of solid food, the three compared groups did not display any difference ($p = 0.093$). Likewise, the postoperative normalization of serum bilirubin remained comparable across the groups ($p = 0.137$) (data not shown).

Complications, length of stay (Table 4)

Overall postoperative morbidity did not differ between the comparative groups and is summarized in detail in Table 4. However, intermediate and ERAS-liver groups showed a significant reduction of major complications in comparison to pre-ERAS group (10 and 13.5 vs. 28 %, respectively; $p = 0.034$). Consistently, hospital stay was significantly reduced by about 2 days in intermediate and ERAS-liver

Fig. 3 ERAS items with significantly different compliance rate across the groups



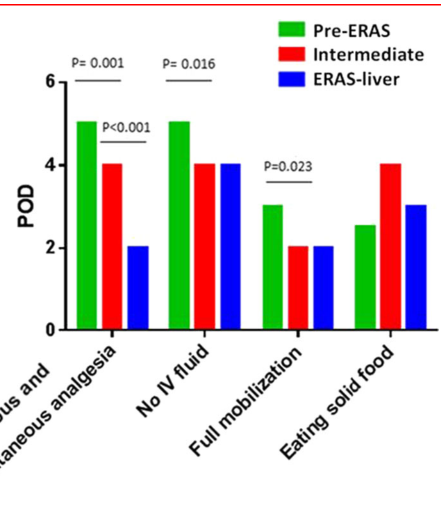


Fig. 4 Functional recovery

groups (10.5, 8.5, 8 days, $p = 0.005$), without increasing readmission rate (2, 12, 8.1 %, $p = 0.158$). Furthermore, introduction of ERAS permitted shorter stays within Intensive Care (3 vs. 2 vs. 2 nights, $p = 0.001$) and intermediate care units (1 vs. 0 vs. 0 night) ($p < 0.001$) with similar admission and discharge criteria.

Discussion

To the best of our knowledge, the collateral impact of an ERAS program implementation on a non-ERAS specialty within the same department—supported by a thorough assessment of the compliance—may has been suspected, but was measured for the first time herein. The present findings suggest that the previous implementation of an ERAS pathway in colorectal surgery had a positive collateral impact on patients undergoing liver surgery in a non-ERAS program. In addition, the present results also confirm that ERAS pathway is applicable and associated with benefits, in liver surgery.

After the successful implementation of ERAS in colorectal surgery, some enhanced recovery items were "unconsciously" introduced and applied in patients undergoing liver surgery in a non-ERAS setting. After the systematic application of a specific liver protocol, compliance was further increased along with improvements of both functional and clinical outcomes. Liver metastases from colorectal cancer represent an important indication for liver resection in the present series. However, the majority of patients with synchronous colorectal liver metastasis underwent "liver first" approach [20], whereas most patients referred from other centers experienced surgery for the primary colorectal tumor, in a non-ERAS setting. As a

Table 4 Complications and hospital stay

	Pre-ERAS ($n = 50$)	Intermediate ($n = 50$)	ERAS-liver ($n = 74$)	p value
30 days complications (No. of patients, %)[a]				
Overall	30 (60 %)	33 (66 %)	37 (50.7 %)	0.224
I–II, n (%)	25 (50 %)	31 (62 %)	36 (48.6 %)	0.306
III–IV, n (%)	14 (28 %)	5 (10 %)	10 (13.5 %)	0.034
V, n (%)	0 (–)	2 (4 %)	1 (1.4 %)	0.291
CCI[b]	20.9 (0–31.5)	20.9 (0–25.6)	8.7 (0–21.3)	0.185
Hospital stay (days)[b]	10.5 (8–17)	8.5 (6.75–14.25)	8 (6–11)	0.005
Nights in ICU[b]	3 (2–5)	2 (1–4)	2 (1–3.25)	0.001
Nights in IC[b]	1 (0–2)	0 (0–1)	0	<0.001
30 days readmissions, n (%)[a]	1 (2 %)	6 (12 %)	6 (8.1 %)	0.158

Values are median (IQR)

POD postoperative day, *CCI* Comprehensive Complications Index, *ICU* intensive care unit, *IC* intermediate care

[a] Chi-square test

[b] Kruskal–Wallis

result, only nine patients (12 %) of the group ERAS-liver were previously operated in a formal ERAS-colorectal setting. This limited subset of patients is unlikely to be the only cause of the increased compliance observed after ERAS implementation.

Strikingly, the results of this study give rise to two major concepts: (I) the landscape of the benefits associated with the implementation of ERAS in colorectal surgery is redrawn and (II) the role of randomized trials addressing the effect of ERAS may be questioned. Regarding the former, it was already established that the implementation of ERAS in colorectal surgery had a positive impact on patients with reduced complications and LoS [1–5]. In addition, ERAS in colorectal surgery was also proven to be cost-effective [13]. Importantly, this present study demonstrates a broader interest of implementing ERAS in colorectal surgery, since it seems to also positively influence patients undergoing other types of surgery, provided they are located on the same ward. Therefore, the present findings are challenging the role of prospective clinical studies to address to effect of ERAS, since the control group (non-ERAS) is at risk to be biased by the previous institutional implementation of ERAS, like the intermediate group in the present study. Blind trials comparing enhanced recovery and traditional care are not a realistic option (drain vs. no drain, bed rest vs. early mobilization, or early feeding vs. traditional postoperative fasting until bowel recovery, etc.). So either prospective randomized study should be conducted in different hospitals and different teams, or enhance recovery programs should be compared with historical cohorts; both designs display intrinsic limitations.

Monitoring compliance is particularly crucial in enhanced recovery program since it determines whether the protocol is actually applied [21, 22]. Comparison with other published studies is somehow awkward for two reasons: high heterogeneity of protocols, and rarely reported compliance with the applied protocol. As a consequence, some negative reported results on recovery programs may presumably be due to a low compliance with the protocol rather than to a failure of the recovery protocol itself.

Furthermore, as no validated ERAS protocol has been published yet for liver surgery, a variety of heterogeneous ERAS-liver protocols has been applied and published [23]. In comparison with other published protocols, the present one was stricter for food intake (normal diet at POD 1) and mobilization (full mobilization at POD 1). Conversely, it was more conservative for urinary catheter removal (POD 3, instead of POD 1–2) [11, 23, 24]. Most reported studies were designed to analyze outcomes, rather than compliance [9, 10, 25]. Of note, the compliance rate measured in this present study was higher than in other studies [23, 26]. As an example, the avoidance of nasogastric tube and abdominal drain was achieved in 97.3 and 54.1 %, respectively, while a recently published multicentric study reported 53 and 41 %, respectively [23].

Comparable to compliance, functional recovery substantially differed between studies. Although several studies supported the positive impact of enhanced recovery pathway on recovery, they did not thoroughly analyze functional recovery following liver surgery [8, 9, 24]. In this regard, the present results showed an improvement of pain control, duration of intravenous fluid, and full mobilization, after liver ERAS implementation. Consistently with previous reports, a reduced length of stay without any increasing in readmission rate was observed [8–10]. It may be hypothesized that this effect is due to the enhanced recovery protocol itself, or to the systematization of perioperative management based on clinical pathway; this is, however, beyond the scope of the present study and deserves further investigations.

Regarding shorter length of stay [8, 10, 27, 28], this reduction could result from reduced complications. However, comparing LoS between different countries with different healthcare systems is often biased, the most important factor being the reduction in LoS after the introduction of a recovery program, rather than its absolute value.

The analysis of the overall morbidity—using the Comprehensive Complication Index (CCI)—showed a median value of 8.7 in ERAS-liver, while CCI reached 20.9 for both pre-ERAS and intermediate groups, which was however not significant ($p = 0.185$).

With a design including three comparative groups along ERAS implementation, this present study was able to measure the unique aspect of an intermediate group after ERAS colorectal but before ERAS-liver.

Several limitations of the present study have to be addressed. Although the three compared groups were similar for most studied variables, ERAS group displayed higher rate of laparoscopic procedures ($p = 0.009$) and less inflow clamping ($p < 0.001$). This probably reflects the current evolution of liver surgery, with the extension of noninvasive techniques. This difference may partially explain the better outcome observed in ERAS-liver, notably the reduced LoS. Although, laparoscopic surgery was increasingly performed over time, its indication was limited to left lateral sectionectomy or anterior wedge resection, thus minimizing its effect on the overall LoS. A potential bias effect can, however, not be completely excluded [25]. Of note, Stoot et al. have showed that enhanced recovery pathway may also be beneficial in laparoscopic liver surgery; laparoscopy may thus be regarded as a constitutive item of enhance recovery. In addition—although the data were collected in a prospective database—its retrospective analysis is associated with intrinsic limitations.

In conclusion, the present study suggests that the implementation of an ERAS protocol for colorectal surgery induces a positive collateral impact on non-ERAS-liver surgery patients, provided they are located on the same ward and treated by the same team. Moreover, these results confirm that ERAS-liver pathway is applicable and beneficial in liver surgery with significantly enhanced functional recovery and reduced LoS, without impairing morbidity or readmission.

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Author contribution Ismail Labgaa: conception and design, analysis, interpretation and writing. Ghada Jarrar: collection of data and interpretation. Gaetan-Romain Joliat: conception and design, interpretation and critical revision. Pierre Allemann: conception and design, interpretation and critical revision. Sylvain Gander: conception and design, interpretation and critical revision. Catherine Blanc: collection of data, interpretation and critical revision. Martin Hübner: conception and design, interpretation, drafting and critical revision. Nicolas Demartines: conception and design, interpretation and major editing.

Compliance with ethical standards

Conflict of interests The authors declare no conflicts of interests and no sources of support and funding for this work.

Appendix

See Fig. 5.

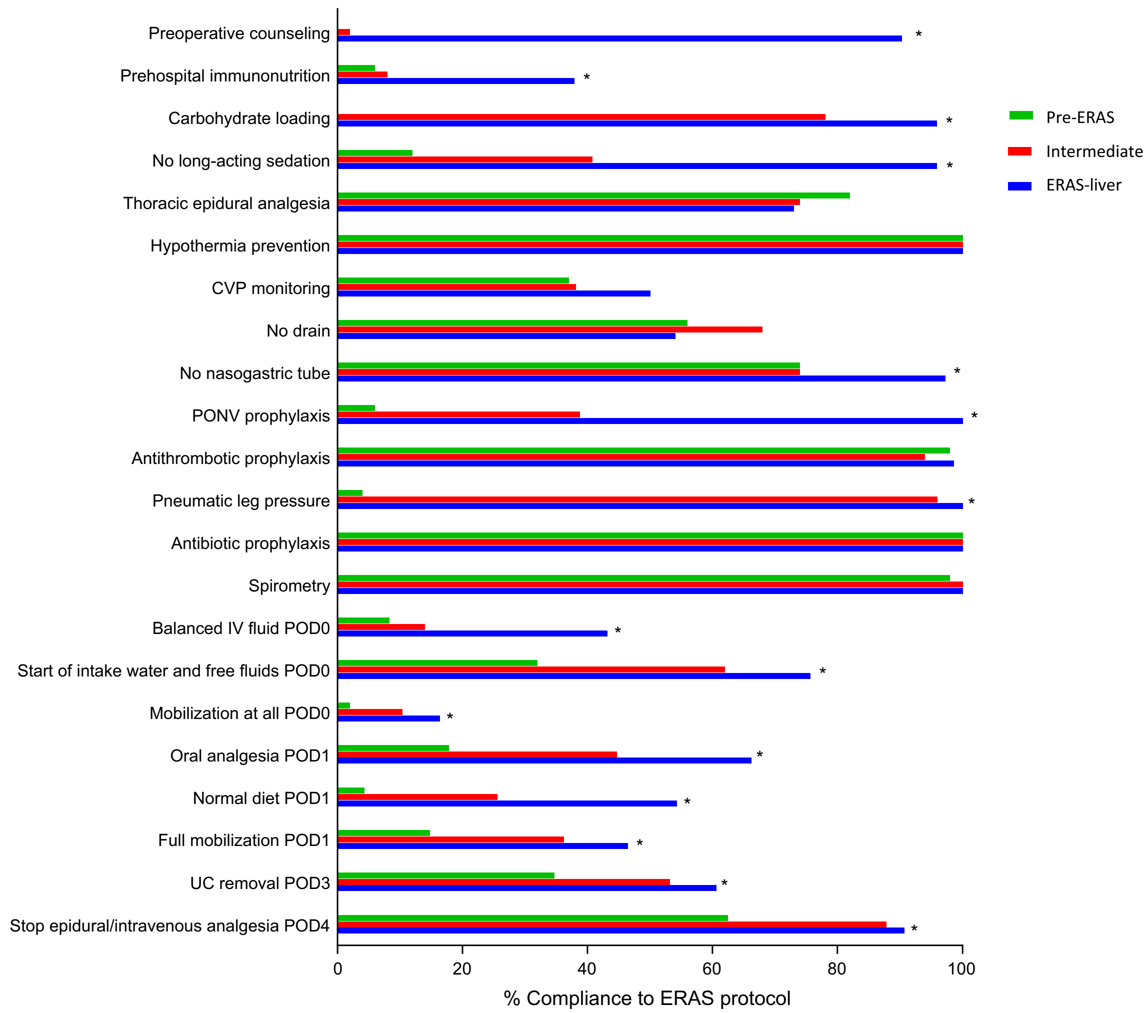

Fig. 5 Compliance rate of each ERAS items fro the three comparative groups. The bars indicate the percentage of patients who adhered to the individual measures of the ERAS protocol. Results are presented for the three comparative groups "pre-ERAS (*green*)", "intermediate (*red*)" and ERAS-liver (*blue*). *Asterisk* indicates statistical significance: $p < 0.05$

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