Surgical Endoscopy

Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study

--Manuscript Draft--

Manuscript Number:	SEND-D-24-00007R1
Full Title:	Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study
Article Type:	Original Article
Corresponding Author:	Gabriel THIERRY Liege University Hospital - Sart Tilman Hospital Cardiology: CHU de Liege - Hopital du Sart Tilman Cardiologie BELGIUM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Liege University Hospital - Sart Tilman Hospital Cardiology: CHU de Liege - Hopital du Sart Tilman Cardiologie
Corresponding Author's Secondary Institution:	
First Author:	Gabriel THIERRY
First Author Secondary Information:	
Order of Authors:	Gabriel THIERRY
	Florian BECK
	Pierre-Yves HARDY
	Abdourahmane KABA
	Arielle BLANJEAN
	Morgan VANDERMEULEN
	Pierre HONORE
	Jean JORIS
	Vincent BONHOMME
	Olivier DETRY
Order of Authors Secondary Information:	
Author Comments:	
Response to Reviewers:	Professor Jaap Bonjer Editor-in-Chief, Surgical Endoscopy Amsterdam University Medical Centre, the Netherlands SEND-D-24-00007R1 – Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study – submission of a revision Dear Professor Bonjer, We have now submitted electronically a new version of our manuscript entitled ‘Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study' for possible publication in Surgical Endoscopy. You will see that this new version has been carefully revised, according to the constructive comments made by you and the Reviewers on the precedent version of our manuscript. Each raised point has been given full consideration. The way in

which Reviewers concerns were addressed is detailed in the point-by-point reply below. In addition, each change made to the manuscript, tables or supplementary materials has been highlighted in yellow.
First and foremost, the authors would like to thank the reviewers for their comments and their pertinent suggestions. We feel that they clearly improved the quality of our manuscript.
We attest that this paper is not currently submitted for publication to another journal, nor has it been published in whole or in part elsewhere. We also attest that all the authors have read the manuscript and agree to its submission to Surgical Endoscopy.
We hope that this paper will now be suitable for publication in Surgical Endoscopy and we thank you again for considering our work.

Yours sincerely,

Gabriel THIERRY, on behalf of all co-authors
Department of Anaesthesia and Intensive Care Medicine
Liege University Hospital
Avenue de l'Hôpital, 1-B35
4000 Liege, Belgium
Email: Gabriel.thierry@chuliege.be Tel: +32 4 323 4133

Response to the Editor and Reviewers

Reviewer #1
This is a well conducted study which is well written and outlined. The authors have compared two well matched groups of patients who underwent liver resections before and after formal designation of their center as an enhanced recovery center for liver surgery and have demonstrated correlation between this designation, and its associated increased adherence to ERAS protocol components AND the decreased length of stay and postoperative complications, including postoperative ileus. I have no major changes or questions to suggest but I do have a couple of minor questions for clarification purposes:

1. To understand table 5, what does "overall adherence to ERP items" and "adherence to postoperative ERP items" refer to? Do these numbers refer to how many of each of the ERP items were adhered to out of the total number of ERP items? For example, did the ERP group achieve acceptable adherence in 17 out of the 21 ERP items and the NERP group 13/21 as shown in the table? The 17 and 13 do not correspond to how many items are adhered to on the table by count.
Response:
First, we would like to thank this reviewer for his positive feedback regarding the quality of our study and for his constructive comments.
Adherence to ERP was defined in the methods section (page 7): adherence to ERP means the number of protocol items that were adhered to; and adherence to postoperative items of ERP means the number of postoperative items from the ERP that were adhered to. To clarify the results in table 5, the definition of adherence to ERP items is now given in the legend of Table 5.
In table 5, the value for each item is the proportion of all patients and of patients from each group that adheres to this particular item. The values for overall adherence to ERP items and adherence to postoperative items are the median number of ERP items and postoperative items respectively that were adhered to in each group.

Thanks to this reviewer's comment, we verified our statistics and found a mistake. Cessation of perfusion was mistakenly included in the postoperative items of ERP although this item is not considered as an ERP item neither in ERAS nor in GRACE recommendations. Early cessation of perfusion was used in our statistical analysis as factors potentially affecting ileus (as you can see in supplementary material 2). This led us to wrongly include this parameter in the postoperative items of ERP. This mistake explains the aberrant results (8) for the P75 of postoperative items in the groups.

Adherence to postoperative items data are now corrected for each group in table 5.

2. Following from question #1 above, if the 17 (ERP) and 13 (NERP) are not direct count of the ERP items, how was they arrived at? Is it by a certain % cut off of adherence to the 21 items, likely how many items were adhered to by 50% or more patients for example? Please clarify and include this in the methods for definition of "adherence to ERP"
Response:
As mentioned above, in table 5, the value for each item is the proportion of all patients and of patients from each group that adheres to this particular item. The values for overall adherence to ERP items and adherence to postoperative items are the median number of ERP items and postoperative items respectively that were adhered to in each group.
This is now clearly stated in the legend of Table 5.

Reviewer #2:

Congratulations on a nicely written manuscript

I only have few questions/comments

1. Would you please comment on your standard intraoperative volume management during liver surgery and if any adjustments needed/observed in ERAS pts?

Response:
Thank you for your positive comment regarding the quality of our study.
As for any major surgery, especially with a risk of bleeding, we use goal-directed fluid therapy. All our liver surgery patients are monitored using an invasive arterial catheter. This allows us to estimate changes in preloading using variations of systolic and pulsatile pressure. These parameters are provided by our standard monitoring (Carescape MonitorTM B850 2013, General Electric HealthCare, the monitors used are now stated in the method section). We sometimes use a hemodynamic monitoring equipment such as pulse wave contour analysis (Clearsight®2021 Edwards Lifesciences Corporation) to optimize our fluid management.

We always use balanced crystalloids for volume management. If necessary, in the event of aggressive fluid therapy, we use albumin as the colloid of choice.

Our management of intraoperative fluid therapy has not changed with the implementation of enhanced rehabilitation. We already used goal-directed fluid therapy for all major surgery before implementation of ERP for liver surgery. All patients in the 2 groups were therefore managed in the same way. This is now stated in the method section.

2. Would you elaborate on why more tranexamic acid was given/needed in ERAP patients?

Response:
Editing our protocol for liver surgery in 2021 led us to consider several patient cares that are not necessarily included in enhanced recovery program, such as the systematic use (in the absence of contraindications) of tranexamic acid. The benefit of tranexamic acid has been debated for several years. Nevertheless, a recent article reported less blood loss during major oncologic hepatectomies with tranexamic acid (https://doi.org/10.1016/j.hpb.2020.06.004). Therefore, our team decided to systematically use this drug (in the absence of contraindications) for major hepatectomies since 2021. More patients in the ERP group were therefore given tranexamic acid, in most of the cases preventively.

3. I am curious about the incident of urine retention and need for foley reinsertion when removed at the end of procedure especially those receiving intrathecal morphine.

Response:
In supplementary material 1, "urinary retention" shows the number of patients who

needed postoperative foley reinsertion. Only four patients had urinary retention requiring reinsertion of urinary catheter and only one of these patients had an intrathecal injection of morphine (70 years old woman, surgery by laparotomy, also suffered from bilioma, ileus and pleural effusion).
Only 10 patients out of our total cohort of 150 patients had an intrathecal injection of morphine. Among these patients, eight were women, less prone to urinary retention. So, our data are certainly not conclusive to determine the risk of urinary retention after intrathecal morphine. However, one of the reasons why we rarely use intrathecal injections of morphine is to avoid its negative impacts on gastrointestinal and urinary functions. As a result, we only use this analgesia in cases of planned laparotomy, which are infrequent (at least as rare as possible) in our center.

Reviewer #3
Dear authors,
This is an interesting retrospective study investigating the effects of a labeled and structured Enhanced Recovery Program (ERP) after hepatic surgery on patient related postoperative outcomes. The data is drawn from a prospectively filled database, the methodology is well defined and the number of included patients in each group is enough for the investigation of the primary outcome as shown by the performed power analysis. The authors conclude that the formal application of the labeled ERP achieved a 53% reduction in perioperative morbidity mainly by reduction of postoperative ileus. The labeled ERP also achieved significantly better compliance with the required interventions even though the authors had adopted them in their dairy practice before the implementation of the ERP. In addition, they report that before the implementation of the ERP (between 2015 and 2020) they had increased the use of laparoscopy from 50% to 70% but did not have a benefit on postoperative
outcomes. As such they strongly support that in order to have a benefit for the patients, it is important to adopt a comprehensive and structured ERP program and not a sporadic use of ERP items. Overall, the paper is well written with good use of English and is easy to follow.
There are some questions that need to be addressed concerning this paper.

1. Why did the authors choose to create a new ERP and not adopt officially the ERAS society guidelines?

Response:
First, we would like to thank this reviewer for his positive feedback regarding our study. For our ERP in liver surgery, we use a personalized institutional protocol that we update frequently. This allows us to maintain up-to-date knowledge of the literature, to have this protocol available in our native language to facilitate its application, and to adjust the items and elements of the protocol to our institution practice and habits (e.g. telephone number to contact the nutritionist or physiotherapist, location of our documentation for patients, prescription preference, etc.). Several studies concerning the application of ERAS protocols mention methods of improving the application of recommendations. Writing an institutional protocol is one way of improving compliance (Developing an implementation strategy for a digital health intervention: an example in routine healthcare. BMC Health Serv Res 2018;18:794. doi:10.1186/s12913-018-3615-7 ; Enhanced recovery after surgery: a review. JAMA Surg 2017;152:292. doi:10.1001/jamasurg.2016.4952).
However, for this protocol to be of high quality, it must be based on the recommendations of the most important scientific societies in enhanced recovery, and of course primarily on those of the ERAS Society. The 2016 ERAS Society recommendations included 23 items. Some of them were changed before implementation into our protocol or were not included at all. The reasons for this are detailed hereafter:
-We have combined nutrition and immunonutrition into a unified item (because immunonutrition has a low level of evidence and is not eligible for medical insurance coverage in our country - immunonutrition costs twice as much as standard oral nutritional supplement).
-We have not included oral bowel preparation or systematic stimulation of bowel movements since it is not indicated in liver surgery.
-The item concerning the shape of the incision seemed irrelevant to us. Moreover, it is not included in the 2022 recommendations.
-We wanted to separate intra- and postoperative analgesia to assess them individually,

	as well as loco-regional analgesia. Intra- and postoperative analgesia are also considered separately in the recommendations of GRACE, of which we are members. The 2022 ERAS recommendations do now likewise. -Glycemic monitoring is part of our daily practice, and we are very concerned by the importance of glycemic control. Therefore, all patients in the two groups of this study benefited from intraoperative and postoperative glycemic monitoring and a glycemic correction using intravenous or subcutaneous insulin, even if it was not an item of the ERP. Glycemic monitoring and control are particularly required in case of Pringle maneuvers, that, when repeated, cause severe perioperative hyperglycemia. Our two groups were taken care of in the same way. 2. The rate of postoperative atelectasis is given as significantly less frequent in the ERP group. However, in the supplemental material Atelectasis is shown to have an incidence of 10.7% in the ERP group vs 2,7% in the NERP group (p=0,05). Is this an error? How do the authors explain this finding? Response: Thank you for this comment. We made in fact an inadvertent mistake. The atelectasis rate was indeed significantly lower in the ERP group. Actually, the mistake was even larger because the two columns of the table were inverted. All the complications in the ERP column were those of the NERP group and vice versa. This has now been corrected. 3. Even though the overall morbidity was lower in the ERP group, this was mainly because of the reduced postoperative ileus in these patients. Serious surgical complications linked to liver resection did not differ between the ERP and NERP groups. This should be clarified in the abstract to avoid confusion and misconceptions about the benefits of ERP. It would also be beneficial to have an indicator for the severity of complications (e.g. major [Clavien >III], vs minor complications) between the compared groups. Response: In response to this reviewer's comment, we have now compared the incidence of complications following the Clavien-Dindo classification. Minor complications (Clavien Dindo grade < III) were significantly less frequent in the ERP group. Complications grade II were particularly less frequent. There was no difference with regards major complications. This has now been added in the result section (supplementary material 1). The distribution of surgical complications now appears in supplementary material 1. The abstract result section has also been modified in response to your comment and now reads: Patient demographics, comorbidities, and intraoperative data were similar in the two groups. Our ERP resulted in shorter length of stay (3 days [1–6] vs. 4 days [2–7.5], p = 0.03) and fewer postoperative complications (24% vs. 45.3%, p = 0.0067). This reduction in postoperative morbidity can be attributed exclusively to a lower rate of minor complications (Clavien-dindo grade < IIIa), and in particular to a lower rate of postoperative ileus, after labeling. (5.3% vs. 25.3%, p = 0.0019). Other medical and surgical complications were not significantly reduced. Adherence to protocol improved after labeling (17 [16–18] vs. 14 [13–16] items, p < 0.001).
Funding Information:	
Abstract:	Introduction It is still unclear whether enhanced recovery programs (ERPs) reduce postoperative morbidity after liver surgery. This study investigated the effect on liver surgery outcomes of labeling as a reference center for ERP. Materials and methods Perioperative data from 75 consecutive patients who underwent hepatectomy in our institution after implementation and labeling of our ERP were retrospectively compared to 75 patients managed before ERP. Length of hospital stay, postoperative complications, and adherence to protocol were examined. Results Patient demographics, comorbidities, and intraoperative data were similar in the two

	groups. Our ERP resulted in shorter length of stay (3 days [1–6] vs. 4 days [2–7.5], p = 0.03) and fewer postoperative complications (24% vs. 45.3%, p = 0.0067). This reduction in postoperative morbidity can be attributed exclusively to a lower rate of minor complications (Clavien-Dindo grade < IIIa), and in particular to a lower rate of postoperative ileus, after labeling. (5.3% vs. 25.3%, p = 0.0019). Other medical and surgical complications were not significantly reduced. Adherence to protocol improved after labeling (17 [16–18] vs. 14 [13–16] items, p < 0.001). Conclusions The application of a labeled enhanced recovery program for liver surgery was associated with a significant shortening of hospital stay and a halving of postoperative morbidity, mainly ileus.

Observational study (cohort study)

Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study

Gabriel Thierry,[1,2,4] Florian Beck,[1,3] Pierre-Yves Hardy,[1,2,4] Abdourahmane Kaba,[1,4] Arielle Blanjean,[1,2] Morgan Vandermeulen,[5] Pierre Honoré,[5] Jean Joris,[1,2] Vincent Bonhomme,[1,3] Olivier Detry[5].

[1] Department of Anesthesia and Intensive Care Medicine, Liege University Hospital, Liege, Belgium

[2] Groupe francophone de Réhabilitation Améliorée après Chirurgie (GRACE ; Francophone Group for Enhanced Recovery after Surgery) Beaumont, France (www.grace-asso.fr)

[3] Anesthesia and Perioperative Neuroscience Laboratory, GIG-Consciousness Thematic Unit, GIGA-Research, Liege University, Liege, Belgium (www.gigaanesthesiaicm.uliege.be)

[4] Inflammation and Enhanced Rehabilitation Laboratory (Regional Anesthesia and Analgesia), GIGA-I3 Thematic Unit, GIGA-Research, Liege University, Liege, Belgium

[4] Department of Abdominal Surgery and Transplantation Liege University Hospital, Liege, Belgium

Correspondence to: Dr. Gabriel Thierry, Department of Anesthesiology, CHU Liege, Domaine du Sart Tilman, Liege, Belgium; Tel: +32/43237180, E-mail: gabriel.thierry@chuliege.be

Short title: Enhanced recovery program for liver surgery.

Keywords: Enhanced recovery program; enhanced rehabilitation; length of hospital stay; postoperative outcome; postoperative ileus; surgery: hepatectomy, liver surgery.

Ethical compliance: All procedures were performed in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its subsequent amendments or comparable ethical standards.

Data access statement: Research data supporting this publication are available on demand to the authors.

Abbreviations:

ASA: American Society of Anesthesiologists.

BMI: Body mass index

COPD: Chronic obstructive pulmonary disease

CRC: Colorectal cancer

DVT: Deep vein thrombosis

ERP: Enhanced recovery programs

GRACE: Groupe francophone de Réhabilitation Améliorée après Chirurgie (French Group for Enhanced Recovery after Surgery)

ICU: Intensive care unit

LOS: Length of hospital stay

MELD: Model for End-stage Liver Disease

NSAIDs: Non-steroidal anti-inflammatory drugs

PACU: Postoperative anesthetic care unit

PONV: Postoperative nausea and vomiting

TAP: Transversus abdominis plane

TRD: Time of readiness for discharge

Abstract

Introduction

It is still unclear whether enhanced recovery programs (ERPs) reduce postoperative morbidity after liver surgery. This study investigated the effect on liver surgery outcomes of labeling as a reference center for ERP.

Materials and methods

Perioperative data from 75 consecutive patients who underwent hepatectomy in our institution after implementation and labeling of our ERP were retrospectively compared to 75 patients managed before ERP. Length of hospital stay, postoperative complications, and adherence to protocol were examined.

Results

Patient demographics, comorbidities, and intraoperative data were similar in the two groups. Our ERP resulted in shorter length of stay (3 days [1–6] vs. 4 days [2–7.5], p = 0.03) and fewer postoperative complications (24% vs. 45.3%, p = 0.0067). This reduction in postoperative morbidity can be attributed exclusively to a lower rate of minor complications (Clavien-dindo grade < IIIa), and in particular to a lower rate of postoperative ileus, after labeling. (5.3% vs. 25.3%, p = 0.0019). Other medical and surgical complications were not significantly reduced. Adherence to protocol improved after labeling (17 [16–18] vs. 14 [13–16] items, p < 0.001).

Conclusions

The application of a labeled enhanced recovery program for liver surgery was associated with a significant shortening of hospital stay and a halving of postoperative morbidity, mainly ileus.

Introduction

Enhanced recovery after surgery programs (ERPs) forms a multidisciplinary, multimodal approach designed to control the surgical stress response and hasten postoperative recovery [1]. ERPs reduce the incidence of postoperative morbidity and length of hospital stay (LOS) in colorectal surgery [2]. First developed for this type of surgery, ERPs have been applied to several other surgical specialties and procedures with similar benefits [3]. Drawing on the guidelines for ERPs in colorectal surgery, specific recommendations for perioperative care in liver surgery have been developed considering the differences between liver and colorectal surgeries [4]. Recent meta-analyses demonstrate that ERPs for liver surgery are associated with shorter LOS [5], [6], [7]. However, the existing literature on the impact of ERPs on postoperative morbidity in liver surgery is inconclusive [8]. Meta-analyses suggest that ERPs may be specifically associated with lower complication rates in laparoscopic liver resection [9], but less clearly when liver surgery is performed through laparotomy [10], [11]. Furthermore, in the existing literature, ERP protocols also vary widely among studies, patients are often selected to be eligible for ERPs, and actual adherence to each ERP items is seldom documented (4-11).

An ERP for colorectal surgery was progressively introduced in the early 2000s in the Department of Abdominal Surgery at the Liege University Hospital in Belgium [12] and has been formally applied as a standard labeled program for all colorectal surgery patients since 2015, regardless of comorbidities, surgical approach, indication, or site [13]. Although no specific protocol had been developed for liver surgery at that time, since then, the perioperative management of patients scheduled for liver surgery was indirectly influenced by colorectal patient care.

In a preliminary unpublished study, the authors compared the data of 49 consecutive patients who underwent elective liver surgery in 2015 (when our formal ERP for colorectal surgery began) with the data of 50 consecutive patients scheduled for elective liver surgery in 2020, just prior to the implementation of a formal ERP in hepatic surgery. There were more laparoscopic hepatectomies in 2020 than in 2015 (69.1% vs. 44.9%, respectively, $p = 0.018$). The median length of stay (LOS) was significantly shorter in 2020 (4 [2-8] days) than in 2015 (9 [3-12] days) ($p = 0.004$). There were no significant differences in overall postoperative complications (43.6% vs. 53.1% in 2020 and 2015 respectively, $p = 0.50$), medical

complications (25.5% vs. 30.6%, respectively, p = 0.56), surgical complications (40% vs. 42.9%, respectively, p = 0.77), or ileus (21.8% vs. 28.6%, respectively, p = 0.43).

Formal specific pathways and the complete enhanced recovery protocol designed for liver surgery were finally implemented in December 2020, and the Liege University Hospital was labeled as a reference medical center for ERP in liver surgery by the "Groupe Francophone pour la Réhabilitation Améliorée après Chirurgie" (GRACE, Beaumont, France; www.grace-asso.fr) in 2021. Here we assessed to what degree an institutionalized ERP for liver surgery and of the labeling of our center shortened length of hospital stay and reduced postoperative morbidity.

Material and methods

Patients

After approval by the Institutional Ethics Committee of the Liege University Hospital (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège, Belgium; President: Prof. V. Seutin; IRB number: 707; internal reference: 2022/121), the authors retrospectively analyzed and compared the data of the first 75 consecutive patients scheduled for liver surgery after implementing ERP for liver surgery (ERP group) at the Liege University Hospital and of the last 75 consecutive patients who underwent elective liver surgery before ERP for liver surgery was implemented (no enhanced recovery program group; NERP group). All 75 patients from the ERP group were managed with the same ERP protocol, regardless of their age, comorbidities, surgical approach, and type and indication of liver surgery. Data were prospectively uploaded in the GRACE audit database. Data and database entries were monitored by G.T. and J.J. This study was conducted and reported in accordance with the STROBE Checklist.

Perioperative management

The formalized, consensual protocol was edited for anesthesia management, surgical procedures, and perioperative care. This protocol drew on our colorectal surgery protocol [13] and was adapted for liver surgery. The ERP comprised 21 items consisting of pre-, intra-, and post-operative measures. Information and training sessions for paramedical staff were organized. An anesthesiologist gave the patients oral information at the time of the preoperative visit. An information brochure was provided to the patients, explaining

perioperative optimization and management, enhanced recovery pathways, and the importance of patient involvement. The ERP protocol included the following items:

- Fasting was as short as possible, aiming for 6 h for food and 2 h for clear fluids.
- A preoperative carbohydrate load was given 2 h before induction of anesthesia (except in case of insulin-requiring diabetes mellitus or known gastroparesis).
- Preoperative oral immunonutrition or nutrition therapy was prescribed to patients with preoperative malnutrition.
- No sedative premedication was administered.
- Antibioprophylaxis was started before surgery and followed guidelines.
- Active prevention of perioperative hypothermia was applied.
- A laparoscopic approach was always preferred, when possible.
- Multimodal analgesia was performed intra-and post-operatively, combining the use of locoregional techniques with systemic analgesia. Epidural analgesia was not used even in laparotomy cases. Patients sometimes received intrathecal morphine (0.3 mg) in cases of laparotomy and absence of coagulation disorders.
- A bilateral subcostal transversus abdominis plane (TAP) block (40 ml of 0.375% levobupivacaine, containing epinephrine at a 1:200000 ratio) was used in all patients.
- A continuous intravenous infusion of lidocaine and ketamine was administered intraoperatively (2 $mg.kg.h^{-1}$ of lidocaine and 0.1 $mg.kg.h^{-1}$ of ketamine, 45 minutes after the TAP block) and prolonged postoperatively (1 $mg.kg.h^{-1}$ of lidocaine and 0.05 $mg.kg.h^{-1}$ of ketamine) unless contra-indicated (renal failure, epilepsy, second- and third-degree atrio-ventricular blocks, major liver resection potentially resulting in reduced clearance of lidocaine).
- Use of dexamethasone was systematic in the absence of uncontrolled insulino-requiring diabetes.
- Use of non-steroidal anti-inflammatory drugs (NSAIDs) was systematic in the absence of contraindications (renal failure, ischemic cardiopathy, peptic ulcer).
- Intravenous fluids and norepinephrine were titrated using a goal-directed therapy (Variations of systolic and pulsatile pressure estimated using Carescape Monitor™ B850 2013, GE HealthCare or Clearsight® 2021 Edwards Lifesciences Corporation).

- Prevention of postoperative nausea and vomiting combined the effect of dexamethasone and 4 mg of ondansetron or 0.625 mg of dehydrobenzperidol if necessary.
- No prophylactic abdominal drains were placed.
- Systematically, a nasogastric tubes and urinary catheters were either not used or withdrawn at the end of surgery.
- Thromboprophylaxis was performed using intra-operative pneumatic compression stockings and low-molecular-weight heparin was prescribed as soon as possible after surgery.
- Early mobilization with the help of a physiotherapist and early feeding were started within the first 24 h postoperative.

Besides ERP items, glycemia was monitored and maintained below 200 $mg.dL^{-1}$ using intravenous insulin, if necessary, from the intraoperative period particularly in case of repeated vascular clamping [14]. Finally, an intraoperative protective ventilation strategy (tidal volume = 6-7 $ml.kg^{-1}$ of ideal body weight) was used with no or minimal end-expiratory pressure during the dissection phase to reduce bleeding. The respiratory rate was adjusted to maintain an arterial CO_2 partial pressure < 45 mmHg.

Endpoints

The primary endpoints were the overall postoperative complication rate 30 days after surgery. Postoperative complications were described according to the European Perioperative Clinical Outcome Definitions [15]. Complications were also rated following Clavien-Dindo classification.

Secondary endpoints were LOS and adherence to ERP (number of protocol items that were adhered to), adherence to postoperative items of ERP (number of postoperative items from the ERP that were adhered to, since a major effect of these items on optimal recovery is attested [16]), and postoperative medical and surgical complications (parietal complications, intra-abdominal complications, redo surgery) including ileus (defined as the absence of flatus or feces during the first 72 h postoperatively). Time of readiness for discharge (TRD) was also recorded. The criteria for discharge were tolerance of feeding, flatus, pain amenable to oral

analgesics, mobilization, and ambulation without assistance. Incidence of postoperative nausea and vomiting, unplanned hospital readmission, and 30-day and 90-day mortality were also recorded.

The variables retrospectively retrieved from the prospective database (ERP group) and the medical records of all patients were age, weight, height, preoperative comorbidities, surgical approach (laparotomy vs. laparoscopy), type of surgery (minor or major hepatectomy), and indication for surgery (primary cancer, metastasis, cyst, or echinococcus).

Statistical analysis.

Descriptive analyses were performed by group for all the variables collected. The normality of distribution for quantitative variables was numerically assessed by comparing the value of the mean and the value of the median, and graphically using the histogram and quantile-quantile plot as well as using the Shapiro-Wilk normality test. Data are presented as mean (SD) or median [interquartile range] and were analyzed using Student's t-test or the Mann–Whitney U test for parametric and non-parametric variables, respectively. Proportions were analyzed using chi-squared tests or Fisher's exact tests and are presented as percentages (%). Sequential univariate and multivariate binary logistic regression modelling of the risk of developing an ileus as a function of each item of the improved recovery protocol was performed. The items that showed a statistically significant relationship in the univariate analyses were included in the final model.

As the complication rate before ERP labeling was approximately 45%, we ran a sample size calculation (using G*Power, version 3.1.9.2, Franz Faul, Universität Kiel, Germany) and estimated that 75 patients per group would allow the detection of a 50% reduction in postoperative complications after ERP implementation at an alpha level of 0.05, with 80% power. This 50% reduction in postoperative morbidity was expected from a meta-analysis published in Journal of Visceral Surgery in 2019 (7). All statistical analyses were performed on all available data, and missing data were not replaced (between-subject design). All analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, USA).

Results.

Patients and surgery characteristics

There were no differences in demographic characteristics, indications for liver surgery (Table 1), or preoperative risk factors (Table 2) between groups. Table 3 shows the operative data. More tranexamic acid was administered in the ERP group (p = 0.0019). However, large (> 500mL) intraoperative blood loss or the need for transfusion during hospitalization were similar in the two groups (p > 0.05). Fewer patients in the ERP group had to stay overnight in the post-anesthesia care unit (p = 0.0002).

Primary outcome

The implementation of a labeled ERP resulted in a 53% reduction in postoperative morbidity (24% vs. 45.3%, respectively after and before labeling (p = 0.0067) (Table 4).

There were significantly fewer minor complications, i.e. Clavien-Dindo grade < IIIa (9.3% in the ERP group vs. 29.3% in the NERP group, p = 0.002) in the ERP group. More particularly, the Clavien-Dindo grade II complications were less in the ERP group (6.7% in the ERP group vs. 13.3% in the NERP group, p = 0.001) . On the other hand, there were no significant differences between the two groups for major complications, i.e. Clavien-Dindo grade ≥ IIIa.

Secondary outcomes

ERP labeling significantly shortened LOS (ERP: 3 days [1-6] vs. NERP: 4 days [2-7.5], p = 0.03) and TRD (ERP: 2 days [1-4] vs. NERP: 3 days [1-7], p < 0.001).

Overall adherence to ERP items, meaning adherence to the 21 ERP items from our institutional protocol, and adherence to the 7 postoperative items, assessed as medians, were better in the ERP group than in the NERP group (p < 0.001, Table 5). More patients in the ERP group received preoperative information on ERP (p < 0.0001) and nutritional support (p = 0.014) and were given a preoperative carbohydrate load (p = 0.0037). Intravenous crystalloid infusions were stopped earlier in the ERP group (2 days [1-2]) than in the NERP group (2 days [2-5]) (p < 0.0001). More patients in the ERP group had early mobilization within the first 24 postoperative hours (p < 0.0001) as well as early feeding (p < 0.0001). Intraoperative NSAIDs were given to more patients in the ERP group (p = 0.0001). Postoperative surgical drains were avoided significantly more often in the ERP group (p = 0.024). Similarly, more patients in the ERP group had their bladder catheter removed at the end of the procedure (p < 0.0001).

Details on the incidence of each possible complication are given in the supplementary materials (Supplementary Material 1). Rate of ileus was significantly lower after labeling (5.3

and 25.3% in the ERP and NERP group, respectively; p=0.0019). The rates of other medical and surgical complications were not significantly different between the groups, although atelectasis was less frequent in the ERP group (p = 0.05).

The risks of readmission to the hospital on the 30 or 90 postoperative day, unscheduled consultation within 3 months postoperatively or redo surgery were not significantly affected by ERP (Supplementary Material 1). Death rates within 30- and 90-days after surgery were comparable in the two groups (Supplementary Material 1).

Discussion

This study found that labeling as a reference center by GRACE, which involves meeting a set of requirements for ERP assessment, improved the implementation of the ERP protocol for liver surgery and halved overall postoperative complications. The incidence of postoperative ileus was most markedly decreased. It also hastened TRD and shortened LOS. These benefits were observed despite the absence of patient selection.

To the best of our knowledge, this is the first study demonstrating the impact of labeling as a reference center for ERP after liver surgery since the publication of the ERAS® Society (Enhanced Recovery After Surgery Society; erassociety.org) guidelines in 2016 [4].

We report a halving of postoperative complications associated with implementing our enhanced recovery program, although the rate of complications in the NERP group was in the range reported in studies using ERP [17]. The benefit of ERP for liver surgery on postoperative outcomes remains controversial [18]. A recent meta-analysis described positive effects of ERP on postoperative outcomes in liver surgery [19]. Conflicting findings may result from patient selection, surgical approach (laparoscopy vs. laparotomy), ERP protocol and adherence to protocol.

In this study, all patients scheduled for elective liver surgery were managed with the same ERP regardless of age, comorbidities, surgical approach (laparoscopic or open surgery), surgical indication (cancer or not), and size of hepatic resection (major or minor hepatectomy).

Recently, the EuroPOWER international observational study reported that treating complications in a self-declared ERAS center did not improve outcome after colorectal surgery [20]. However, increased adherence to the ERAS® pathway is associated with a significant reduction in overall postoperative complications. Interestingly, management of our liver surgery patients in the spirit of ERP but without an actual institutional protocol shortened LOS, but with no impact on the rate of postoperative complications. The implementation of our ERP and our labeling resulted in improved adherence to the items of the protocol. Adherence to the postoperative items of the protocol, considered critically important for optimal recovery [16], was also better. Moreover, adherence of our patients to ERP was greater than in other reports from large series of patients [5], [19]. Our findings suggest that the reduction in postoperative complications observed in our study was due to the high adherence rates in our ERP patients. We should not rely on key factors such as the use of laparoscopy, but rather on the whole protocol, as described in previous ERP studies [20], [21]. Between 2015 and 2020, we increased the use of laparoscopy from 50% to 70%, but with no benefit on postoperative outcomes. Taken overall, our data confirm that the protocol alone is not enough to ensure efficient patient management [22].

The beneficial impact of ERP on postoperative complication after colorectal surgery mainly concerns medical rather than surgical complications [2]. We observed a near-significant ($p = 0.055$) reduction in postoperative pulmonary complications and a significant reduction in postoperative atelectasis ($p = 0.05$) in the ERP group. Our study was probably not powerful enough to specifically detect a significant reduction in medical complications. Among postoperative complications, we observed a marked reduction in the incidence of postoperative ileus. The beneficial impact on postoperative ileus is probably multifactorial: greater use of laparoscopy [23], early mobilization and feeding [24], opioid-sparing multimodal analgesia [25], and the use of NSAIDs [26]. We compared patients who experienced postoperative ileus with those who did not, with the aim of identifying ERP items that may have influenced the risk of postoperative ileus. Statistical results are consistent with the literature and are available in the supplementary materials (Supplementary Material 2), but the infrequent occurrence of ileus and our sample size prevented us from trying to determine factors responsible for its reduced incidence.

This study also confirms that an ERP for hepatic surgery can produce a significant reduction in LOS [27]. The duration of hospitalization after liver surgery had already been reduced by 4 days to 5-days in our institution between 2015 and 2020, despite the lack of any formal institutional ERP for liver surgery. The perioperative management of patients scheduled for liver resection had been indirectly influenced by colorectal patient care managed with an ERP since 2016 [12], [13]. The proportion of laparoscopic liver surgeries significantly increased between 2015 and 2020, with a significant effect on LOS, as described in the literature [28]. However, there was no decrease in postoperative morbidity. Nevertheless, formal implementation of our ERP for liver surgery associated with our labeling as reference center, which implies internal and external audits, optimized the adherence of our patients to the ERP, thereby accelerating patient TRD and further shortening LOS.

Our study has some limitations. First, although the analyzed data of the ERP group were prospectively collected and entered in our GRACE database, the study remains a retrospective one. No selection was carried out and all the patients undergoing elective liver surgery were included. Second, the data from the control group (before labeling) were retrospectively retrieved from the medical records fully digitized since the end of the 2010s. Although length of hospital stay is systematically recorded, some complications may be missing. Third, there were more cases of liver fibrosis in the ERP post-labeling group, known to increase the risk of postoperative complications. Differences in postoperative complications might be even greater without these limitations.

For conclusion, this study shows that implementation of an institutional ERP in liver surgery associated with the requirements imposed for labeling as a reference center shortened LOS and decreased postoperative morbidity, mainly postoperative ileus. Our observations point to a marked impact of adherence to the protocol on improving postoperative outcomes.

Disclosures

Gabriel THIERRY and Jean JORIS received financial support from GRACE (Francophone Group for Enhanced Recovery after Surgery, Beaumont, France, www.grace-asso.fr) for correction and translation of this manuscript. The funding source was not involved in study design, in collection, analysis, or interpretation of data, in the writing of the report, or in the decision to

submit this article for publication. Jean JORIS is an honor member of GRACE. However, Gabriel THIERRY (first author) and Jean JORIS have no conflicts of interest relative to this study. Vincent BONHOMME has no conflicts of interest relative to this study but has received an unrestricted grant from Orion Pharma for research support, support for a specific training from Medtronic, support for attending meetings from Edwards Medical, support for publication of a book chapter from Elsevier and reports speaker's consultancy fees on behalf of Grünenthal. Florian BECK has no conflicts of interest relative to this study but has received honoraria from Fresenius-Kabi and Viatris for logistic implementations at Liege University Hospital in Belgium. Morgan VANDERMEULEN has no conflicts of interest relative to this study but has received a research grant from the Belgian national scientific research foundation (FNRS). Olivier DETRY has no conflicts of interest relative to this study but has received contracts from Medtronic, Corza, Applied, Boston medical, a research grant from the Belgian national scientific research foundation (FNRS) and received equipment and materials from Medtronic and Johnson & Johnson. Abdourahmane KABA, Arielle BLANJEAN, Pierre-Yves HARDY and Pierre HONORE declare they have no conflicts of interest.

References

1. Scott MJ, Baldini G, Fearon KCH, et al (2015) Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery, part 1: Pathophysiological considerations. Acta Anaesthesiol Scand 59:1212–1231
2. Greco M, Capretti G, Beretta L, Gemma M, Pecorelli N, Braga M (2014) Enhanced recovery program in colorectal surgery: A meta-analysis of randomized controlled trials. World J Surg 38:1531–1541
3. Visioni A, Shah R, Gabriel E, Attwood K, Kukar M, Nurkin S (2018) Enhanced Recovery after Surgery for Noncolorectal Surgery? Ann Surg 267:57–65
4. Melloul E, Hübner M, Scott M, et al (2016) Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg 40:2425–2440
5. Hughes MJ, McNally S, Wigmore SJ (2014) Enhanced recovery following liver surgery: A systematic review and meta-analysis. HPB 16:699–706
6. Page AJ, Ejaz A, Spolverato G, et al (2015) Enhanced Recovery After Surgery Protocols for Open Hepatectomy—Physiology, Immunomodulation, and Implementation. Journal of Gastrointestinal Surgery 19:387–399
7. Brustia R, Slim K, Scatton O (2019) Enhanced recovery after liver surgery. J Visc Surg 156:127–137
8. Damania R, Cocieru A (2017) Impact of enhanced recovery after surgery protocols on postoperative morbidity and mortality in patients undergoing routine hepatectomy: Review of the current evidence. Ann Transl Med. https://doi.org/10.21037/atm.2017.07.04

9. Yang R, Tao W, Chen Y yang, Zhang B hong, Tang J ming, Zhong S, Chen X xiang (2016) Enhanced recovery after surgery programs versus traditional perioperative care in laparoscopic hepatectomy: A meta-analysis. International Journal of Surgery 36:274–282
10. Li M, Zhang W, Jiang L, Yang J, Yan L (2016) Fast track for open hepatectomy: A systemic review and meta-analysis. International Journal of Surgery 36:81–89
11. Jones C, Kelliher L, Dickinson M, Riga A, Worthington T, Scott MJ, Vandrevala T, Fry CH, Karanjia N, Quiney N (2013) Randomized clinical trial on enhanced recovery versus standard care following open liver resection. British Journal of Surgery 100:1015–1024
12. Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, Joris JL (2007) Intravenous Lidocaine Infusion Facilitates Acute Rehabilitation after Laparoscopic Colectomy.
13. Daenen C, Coimbra C, Hans G, Joris J (2018) Labelling as reference Centre of GRACE (Groupe francophone de Réhabilitation Améliorée après ChirurgiE) for colorectal surgery: its impact on the implementation of enhanced recovery programme at the University Hospital of Liège. Acta Chir Belg 118:294–298
14. Maeda H, Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, Hanazaki K (2010) Hyperglycemia during hepatic resection: continuous monitoring of blood glucose concentration. Am J Surg 199:8–13
15. Jammer I, Wickboldt N, Sander M, et al (2015) Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 32:88–105
16. Aarts MA, Rotstein OD, Pearsall EA, Victor JC, Okrainec A, McKenzie M, McCluskey SA, Conn LG, McLeod RS (2018) Postoperative ERAS Interventions Have the Greatest Impact on Optimal Recovery. Ann Surg 267:992–997
17. Chua DW, Sim D, Syn N, Abdul Latiff JB, Lim KI, Sim YE, Abdullah HR, Lee SY, Chan CY, Goh BKP (2022) Impact of introduction of an enhanced recovery protocol on the outcomes of laparoscopic liver resections: A propensity-score matched study. Surgery (United States) 171:413–418
18. Ovaere S, Boscart I, Parmentier I, Steelant PJ, Gabriel T, Allewaert J, Pottel H, Vansteenkiste F, D'Hondt M (2018) The Effectiveness of a Clinical Pathway in Liver Surgery: a Case-Control Study. Journal of Gastrointestinal Surgery 22:684–694
19. Brustia R, Mariani P, Sommacale D, et al (2021) The impact of enhanced recovery program compliance after elective liver surgery: Results from a multicenter prospective national registry. Surgery (United States) 170:1457–1466
20. Ripollés-Melchor J, Abad-Motos A, Cecconi M, et al (2022) Association between use of enhanced recovery after surgery protocols and postoperative complications in colorectal surgery in Europe: The EuroPOWER international observational study. J Clin Anesth. https://doi.org/10.1016/j.jclinane.2022.110752
21. Jurt J, Slieker J, Frauche P, Addor V, Solà J, Demartines N, Hübner M (2017) Enhanced Recovery After Surgery: Can We Rely on the Key Factors or Do We Need the Bel Ensemble? World J Surg 41:2464–2470

22. Byrne BE, Faiz OD, Bottle A, Aylin P, Vincent CA (2021) A Protocol is not Enough: Enhanced Recovery Program-Based Care and Clinician Adherence Associated with Shorter Stay After Colorectal Surgery. World J Surg 45:347–355
23. Magne Augestad K, Delaney Knut Magne Augestad CP, Delaney CP (2010) Postoperative ileus: Impact of pharmacological treatment, laparoscopic surgery and enhanced recovery pathways. World J Gastroenterol 16:2067–2074
24. Kehlet H, Holte K (2001) Review of Postoperative Ileus.
25. Wick EC, Grant MC, Wu CL (2017) Postoperativemultimodal analgesia pain management with nonopioid analgesics and techniques a review. JAMA Surg 152:691–697
26. Brolet EA, Joris JL, Monseur JJ, Donneau AFH, Slim K (2021) Impact of non-steroidal anti-inflammatory drugs on the efficiency of enhanced recovery programmes after colorectal surgery: a retrospective study of the GRACE database. Anaesth Crit Care Pain Med. https://doi.org/10.1016/j.accpm.2021.100880
27. Zhao Y, Qin H, Wu Y, Xiang B (2017) Enhanced recovery after surgery program reduces length of hospital stay and complications in liver resection. Medicine (United States). https://doi.org/10.1097/MD.0000000000007628
28. Wong-Lun-Hing EM, van Dam RM, van Breukelen GJP, et al (2017) Randomized clinical trial of open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery after surgery programme (ORANGE II study). British Journal of Surgery 104:525–535

Table 1: Demographic parameters and indication for hepatectomy

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Age	61 [52 - 70]	61 [51 - 71]	61 [54 - 69]	*0.906*
Sex: Male / Female	69 (46) / 81 (54)	34 (45.3) / 41 (54.7)	35 (46.7) / 40 (52.3)	*0.870*
BMI ($kg.m^{-2}$)	25.6 [22.3-28.3]	24.6 [21.3 - 28.9]	25.3 [22.9 - 27.9]	*0.861*
Obesity (BMI > 30 $kg.m^{-2}$)	23 (15.3)	14 (18.7)	7 (9.3)	*0.157*
ASA physical status (I/II/III/IV)	23/78/47/2 (15.3/24/31.3/1.3)	12/36/25/2 (7.7/55.8/32.7/3.8)	11/42/22/0 (14.7/56/29.3/0)	*0.520*
Child-Pugh score	5 [5 - 5]	5 [5 - 5]	5 [5 - 5]	*0.439*
MELD score	6.5 [6 - 8]	7 [6 - 8]	6 [6 - 8]	*0.604*
Preoperative chemotherapy	50 (44.2)	28 (38.5)	22 (29.3)	*0.058*
Cancer	113 (75.3)	52 (69.3)	61 (81.3)	*0.088*
Cancer type:				*0.280*
Hepatocellular carcinoma	31 (27.4)	10 (13.3)	21 (28)	
Cholangiocarcinoma	14 (12.4)	7 (9.3)	7 (9.3)	
CRC metastasis	54 (47.8)	29 (38.7)	25 (33.3)	
Metastasis (other cancer)	14 (12.4)	6 (8)	8 (10.7)	

Data are median [P25 – P75] or count (%).

ERP: enhanced recovery program. NERP: no enhanced recovery program

BMI = body mass index. ASA = American Society of Anesthesiologists.

MELD = model for end-stage liver disease. CRC = colorectal cancer.

Table 2: Preoperative risk factors

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Malnutrition	15 (10)	9 (12)	6 (8)	*0.410*
Albuminemia: g/L	43 [40 - 46]	43 [40 - 45]	43 [40 - 46]	*0.955*
Diabetes mellitus	33 (22)	19 (25.3)	14 (18.7)	*0.320*
Insulin-dependent diabetes	8 (5.3)	5 (6.7)	3 (4)	*0.719*
Immunodepression	33 (22)	12 (16)	21 (28)	*0.076*
Smoking	29 (19.3)	16 (21.3)	13 (17.3)	*0.540*
Coronaropathy	5 (3.3)	4 (5.3)	1 (1.3)	*0.367*
Arterial hypertension	57 (38)	30 (40)	27 (36)	*0.610*
Cardiac arrhythmia	13 (8.7)	5 (6.7)	8 (10.7)	*0.380*
Dyslipidemia	29 (19.3)	17 (22.7)	12 (16)	*0.409*
Cardiac insufficiency	4 (2.7)	1 (1.3)	3 (4)	*0.620*
Peripheral arteriopathy	5 (3.3)	5 (6.7)	0 (0)	*0.058*
COPD	23 (15.3)	11 (14.7)	12 (16)	*0.820*
Stroke	11 (7.3)	6 (8)	5 (6.7)	*0.750*
Anemia	51 (34)	25 (33.3)	26 (34.7)	*0.860*
Chronic renal failure	13 (8.7)	9 (12)	4 (5.3)	*0.245*
Preoperative creatininemia	0.82 [0.69 – 0.96]	0.8 [0.69 – 1]	0.85 [0.69 – 0.94]	*0.904*
Antiaggregant therapy	28 (18.7)	18 (24)	10 (13.3)	*0.094*
Anticoagulant therapy	14 (9.3)	6 (8)	8 (10.7)	*0.570*

Data are count (%) or median [P25 – P75].
ERP: enhanced recovery program. NERP: no enhanced recovery program.
COPD: chronic obstructive pulmonary disease.

Table 3: Intraoperative data of hepatectomy

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Type of Hepatectomy:				*0.40*
Major hepatectomy	55 (36.7)	25 (33.3)	30 (40)	
Minor hepatectomy	95 (63.3)	50 (66.7)	45 (60)	
Duration of surgery				*0.18*
< 90 min	37 (24.7)	19 (51.4)	18 (48.6)	
90-180 min	64 (42.7)	27 (42.2)	37 (57.8)	
> 180 min	49 (32.7)	29 (59.2)	20 (40.8)	
Laparoscopic approach	112 (74.7)	60 (80)	52 (69.3)	*0.19*
Blood loss > 500 mL	30 (20)	15 (20)	15 (20)	*0.99*
Tranexamic acid	71 (47.3)	45 (60)	26 (34.7)	***0.0019***
Need for transfusion	11 (7.3)	4 (5.3)	7 (9.3)	*0.35*
Pringle maneuver	99 (66.0)	53 (70.7)	46 (61.3)	*0.23*
Clamping time (min)	39.5 (20-55)	40 (20-53)	39 (20-60)	*0.81*
Hepatic cytology:				***0.0052***
Normal liver	101 (67.3)	48 (64)	53 (70.7)	*0.38*
Steatosis	21 (43.8)	10 (13.3)	11 (14.7)	*1*
Fibrosis	17 (35.4)	14 (18.7)	3 (4)	***0.008***
Cirrhosis	10 (20.8)	2 (2.7)	8 (10.7)	*0.098*
Size of tumor (cm)	3.3 [2 – 6.5]	2.8 [2 - 5.5]	4 [2.1 – 8]	*0.063*
Stay overnight in PACU	25 (16.7)	4 (5.3)	21 (28)	***0.0002***
Need for ICU	3 (2)	1 (1.3)	2 (2.7)	*0.99*

Data are count (%).

ERP: enhanced recovery program. NERP: no enhanced recovery program.

PACU: postanesthetic care unit. ICU: intensive care unit.

Table 4: Postoperative complications

	All patients N = 150	ERP N = 75	NERP N = 75	*Coefficient*	*P*
Overall	52 (34.7)	18 (24)	34 (45.3)	*0.381 (0.189-0.765)*	***0.0067***
Medical	30 (20.0)	11 (14.7)	16 (21.3)	*0.636 (0.245-1.595)*	*0.288*
Surgical	50 (33.3)	18 (24)	32 (42.7)	*0.396 (0.181-0.844)*	***0.016***
Surgical ileus excepted	27 (18.0)	14 (18.7)	21 (28)	*0.592 (0252-1.358)*	*0.177*
Ileus	23 (15.3)	4 (5.3)	19 (25.3)	*0.166 (0.053-0.516)*	***0.0019***

Data are count (%).

ERP: enhanced recovery program. NERP: no enhanced recovery program.

Table 5: Adherence to the ERP items

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Preoperative items				
1. ERP patients' information	75 (50)	75 (100)	0 (0)	***<.0001***
2. Nutritional therapy	7 (4.7)	7 (9.3)	0 (0)	***0.014***
3. No premedication	140 (93.3)	73 (97.3)	67 (89.3)	*0.05*
4. Modern fasting rules	150 (100)	75 (100)	75 (100)	*1*
5. Carbohydrate load	97 (64.7)	57 (76.0)	40 (53.3)	*0.0037*
Intraoperative items				
6. Antibioprophylaxis	146 (97.3)	71 (94.7)	75 (100.0)	*0.12*
7. Prevention of hypothermia	150 (100)	75 (100)	75 (100)	*1*
8. Goal-directed fluid administration	150 (100)	75 (100)	75 (100)	*1*
9. Laparoscopic approach	112 (74.7)	60 (80)	52 (69.3)	*0.188*
10. PONV prevention	12 (8.0)	8 (10.7)	4 (5.3)	*0.23*
11. Corticoid administration	138 (92.0)	67 (89.3)	71 (94.7)	*0.23*
12. Multimodal analgesia	148 (98.7)	74 (98.7)	74 (98.7)	*0.99*
13. Use of per-operative NSAIDs	63 (42.0)	43 (57.3)	20 (26.7)	***0.0001***
14. TAP block	127 (84.7)	65 (86.7)	62 (82.7)	*0.651*
Postoperative items				
15. Thromboprophylaxis	146 (97.3)	71 (94.7)	75 (100.0)	*0.12*
16. No abdominal drain	100 (66.7)	57 (76.0)	43 (57.3)	***0.015***
17. No nasogastric tube	148 (98.7)	75 (100)	73 (97.3)	*0.497*
18. No urinary catheter	96 (64.0)	62 (82.7)	34 (45.3)	***< 0.001***
19. Early feeding	131 (87.3)	74 (98.7)	57 (76)	***< 0.001***
20. Early mobilization	125 (83.3)	72 (96)	53 (70.7)	***< 0.001***
21. Multimodal analgesia	133 (88.7)	69 (92)	64 (85.3)	*0.303*
Overall adherence to ERP items	15 [14.5 – 17]	17 [16 - 18]	13 [13 - 16]	***< 0.001***
Adherence to postoperative ERP items	6 [5 – 7]	6 [6 – 7]	6 [4 - 6]	***< 0.001***

Data for each item are count (%) and data for adherence to items are median [P25 – P75]. Adherence to ERP means the number of protocol items that were adhered to; and adherence to postoperative items of ERP, the number of postoperative items from the ERP that were adhered to, since a major effect of these items on optimal recovery is attested [16].

ERP: enhanced recovery programs. NERP: no enhanced recovery program.

PONV: postoperative nausea and vomiting.

NSAIDs: nonsteroidal anti-inflammatory drugs. TAP: transversus abdominis plane.

Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery.

A monocentric retrospective study

Implementation of an enhanced rehabilitation protocol in liver surgery in December 2020

Application of 21 items Based on ERAS recommendations

Labeling of our hospital through an annual audit by the GRACE association

2 cohorts of 75 patients
(before and after ERP implementation)

	BEFORE	VS	AFTER
	14 [13-16] Items		17 [16-18] Items
Early mobilization	70,7 %		96 %
Early refeeding	76 %		98,7 %
No urinary catheter	45,3 %		82,7 %
Postoperative morbidity	45,3 %		25 %
Ileus	25,3 %		5,3 %
Length of stay	4 [2 - 7,5]		3 [1 - 6]

CHU de Liège GRACE ERAS®

Gabriel Thierry & al, *Surgical Endoscopy*, March 2024

Professor Jaap Bonjer
Editor-in-Chief, Surgical Endoscopy
Amsterdam University Medical Centre, the Netherlands

SEND-D-24-00007R1 – Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study – submission of a revision

Dear Professor Bonjer,

We have now submitted electronically a new version of our manuscript entitled 'Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study' for possible publication in Surgical Endoscopy. You will see that this new version has been carefully revised, according to the constructive comments made by you and the Reviewers on the precedent version of our manuscript. Each raised point has been given full consideration. The way in which Reviewers concerns were addressed is detailed in the point-by-point reply below. In addition, each change made to the manuscript, tables or supplementary materials has been highlighted in yellow.
First and foremost, the authors would like to thank the reviewers for their comments and their pertinent suggestions. We feel that they clearly improved the quality of our manuscript.
We attest that this paper is not currently submitted for publication to another journal, nor has it been published in whole or in part elsewhere. We also attest that all the authors have read the manuscript and agree to its submission to Surgical Endoscopy.
We hope that this paper will now be suitable for publication in Surgical Endoscopy and we thank you again for considering our work.

Yours sincerely,

Gabriel THIERRY, on behalf of all co-authors
Department of Anaesthesia and Intensive Care Medicine
Liege University Hospital
Avenue de l'Hôpital, 1-B35
4000 Liege, Belgium
Email: Gabriel.thierry@chuliege.be Tel: +32 4 323 4133

Response to the Editor and Reviewers

Reviewer #1

This is a well conducted study which is well written and outlined. The authors have compared two well matched groups of patients who underwent liver resections before and after formal designation of their center as an enhanced recovery center for liver surgery and have demonstrated correlation between this designation, and its associated increased adherence to ERAS protocol components AND the decreased length of stay and postoperative complications, including postoperative ileus. I have no major changes or questions to suggest but I do have a couple of minor questions for clarification purposes:

1. To understand table 5, what does "overall adherence to ERP items" and "adherence to postoperative ERP items" refer to? Do these numbers refer to how many of each of the ERP items were adhered to out of the total number of ERP items? For example, did the ERP group achieve acceptable adherence in 17 out of the 21 ERP items and the NERP group 13/21 as shown in the table? The 17 and 13 do not correspond to how many items are adhered to on the table by count.

Response:

First, we would like to thank this reviewer for his positive feedback regarding the quality of our study and for his constructive comments.

Adherence to ERP was defined in the methods section (page 7): adherence to ERP means the number of protocol items that were adhered to; and adherence to postoperative items of ERP means the number of postoperative items from the ERP that were adhered to. To clarify the results in table 5, the definition of adherence to ERP items is now given in the legend of Table 5.

In table 5, the value for each item is the proportion of all patients and of patients from each group that adheres to this particular item. The values for overall adherence to ERP items and adherence to postoperative items are the median number of ERP items and postoperative items respectively that were adhered to in each group.

Thanks to this reviewer's comment, we verified our statistics and found a mistake. Cessation of perfusion was mistakenly included in the postoperative items of ERP although this item is not considered as an ERP item neither in ERAS nor in GRACE recommendations. Early cessation of perfusion was used in our statistical analysis as factors potentially affecting ileus (as you can see in supplementary material 2). This led us to wrongly include this parameter in the postoperative items of ERP. This mistake explains the aberrant results (8) for the P75 of postoperative items in the groups. Adherence to postoperative items data are now corrected for each group in table 5.

2. Following from question #1 above, if the 17 (ERP) and 13 (NERP) are not direct count of the ERP items, how was they arrived at? Is it by a certain % cut off of adherence to the 21

items, likely how many items were adhered to by 50% or more patients for example? Please clarify and include this in the methods for definition of "adherence to ERP"

Response:

As mentioned above, in table 5, the value for each item is the proportion of all patients and of patients from each group that adheres to this particular item. The values for overall adherence to ERP items and adherence to postoperative items are the median number of ERP items and postoperative items respectively that were adhered to in each group.
This is now clearly stated in the legend of Table 5.

Reviewer #2:

Congratulations on a nicely written manuscript

I only have few questions/comments

1. Would you please comment on your standard intraoperative volume management during liver surgery and if any adjustments needed/observed in ERAS pts?

Response:

Thank you for your positive comment regarding the quality of our study.

As for any major surgery, especially with a risk of bleeding, we use goal-directed fluid therapy. All our liver surgery patients are monitored using an invasive arterial catheter. This allows us to estimate changes in preloading using variations of systolic and pulsatile pressure. These parameters are provided by our standard monitoring (Carescape Monitor™ B850 2013, General Electric HealthCare, the monitors used are now stated in the method section). We sometimes use a hemodynamic monitoring equipment such as pulse wave contour analysis (Clearsight®2021 Edwards Lifesciences Corporation) to optimize our fluid management.

We always use balanced crystalloids for volume management. If necessary, in the event of aggressive fluid therapy, we use albumin as the colloid of choice.

Our management of intraoperative fluid therapy has not changed with the implementation of enhanced rehabilitation. We already used goal-directed fluid therapy for all major surgery before implementation of ERP for liver surgery. All patients in the 2 groups were therefore managed in the same way. This is now stated in the method section.

2. Would you elaborate on why more tranexamic acid was given/needed in ERAP patients?

Response:

Editing our protocol for liver surgery in 2021 led us to consider several patient cares that are not necessarily included in enhanced recovery program, such as the systematic use (in the absence of contraindications) of tranexamic acid. The benefit of tranexamic acid has been

debated for several years. Nevertheless, a recent article reported less blood loss during major oncologic hepatectomies with tranexamic acid (https://doi.org/10.1016/j.hpb.2020.06.004). Therefore, our team decided to systematically use this drug (in the absence of contraindications) for major hepatectomies since 2021. More patients in the ERP group were therefore given tranexamic acid, in most of the cases preventively.

3. I am curious about the incident of urine retention and need for foley reinsertion when removed at the end of procedure especially those receiving intrathecal morphine.

Response:

In supplementary material 1, "urinary retention" shows the number of patients who needed postoperative foley reinsertion. Only four patients had urinary retention requiring reinsertion of urinary catheter and only one of these patients had an intrathecal injection of morphine (70 years old woman, surgery by laparotomy, also suffered from bilioma, ileus and pleural effusion).

Only 10 patients out of our total cohort of 150 patients had an intrathecal injection of morphine. Among these patients, eight were women, less prone to urinary retention. So, our data are certainly not conclusive to determine the risk of urinary retention after intrathecal morphine. However, one of the reasons why we rarely use intrathecal injections of morphine is to avoid its negative impacts on gastrointestinal and urinary functions. As a result, we only use this analgesia in cases of planned laparotomy, which are infrequent (at least as rare as possible) in our center.

Reviewer #3

Dear authors,
This is an interesting retrospective study investigating the effects of a labeled and structured Enhanced Recovery Program (ERP) after hepatic surgery on patient related postoperative outcomes. The data is drawn from a prospectively filled database, the methodology is well defined and the number of included patients in each group is enough for the investigation of the primary outcome as shown by the performed power analysis. The authors conclude that the formal application of the labeled ERP achieved a 53% reduction in perioperative morbidity mainly by reduction of postoperative ileus. The labeled ERP also achieved significantly better compliance with the required interventions even though the authors had adopted them in their dairy practice before the implementation of the ERP. In addition, they report that before the implementation of the ERP (between 2015 and 2020) they had increased the use of laparoscopy from 50% to 70% but did not have a benefit on postoperative
outcomes. As such they strongly support that in order to have a benefit for the patients, it is important to adopt a comprehensive and structured ERP program and not a sporadic use of ERP items. Overall, the paper is well written with good use of English and is easy to follow. There are some questions that need to be addressed concerning this paper.

1. Why did the authors choose to create a new ERP and not adopt officially the ERAS society guidelines?

Response:

First, we would like to thank this reviewer for his positive feedback regarding our study.

For our ERP in liver surgery, we use a personalized institutional protocol that we update frequently. This allows us to maintain up-to-date knowledge of the literature, to have this protocol available in our native language to facilitate its application, and to adjust the items and elements of the protocol to our institution practice and habits (e.g. telephone number to contact the nutritionist or physiotherapist, location of our documentation for patients, prescription preference, etc.). Several studies concerning the application of ERAS protocols mention methods of improving the application of recommendations. Writing an institutional protocol is one way of improving compliance (Developing an implementation strategy for a digital health intervention: an example in routine healthcare. BMC Health Serv Res 2018;18:794. doi:10.1186/s12913-018-3615-7 ; Enhanced recovery after surgery: a review. JAMA Surg 2017;152:292. doi:10.1001/jamasurg.2016.4952).
However, for this protocol to be of high quality, it must be based on the recommendations of the most important scientific societies in enhanced recovery, and of course primarily on those of the ERAS Society. The 2016 ERAS Society recommendations included 23 items. Some of them were changed before implementation into our protocol or were not included at all. The reasons for this are detailed hereafter:

- We have combined nutrition and immunonutrition into a unified item (because immunonutrition has a low level of evidence and is not eligible for medical insurance coverage in our country - immunonutrition costs twice as much as standard oral nutritional supplement).
- We have not included oral bowel preparation or systematic stimulation of bowel movements since it is not indicated in liver surgery.
- The item concerning the shape of the incision seemed irrelevant to us. Moreover, it is not included in the 2022 recommendations.
- We wanted to separate intra- and postoperative analgesia to assess them individually, as well as loco-regional analgesia. Intra- and postoperative analgesia are also considered separately in the recommendations of GRACE, of which we are members. The 2022 ERAS recommendations do now likewise.
- Glycemic monitoring is part of our daily practice, and we are very concerned by the importance of glycemic control. Therefore, all patients in the two groups of this study benefited from intraoperative and postoperative glycemic monitoring and a glycemic correction using intravenous or subcutaneous insulin, even if it was not an item of the ERP. Glycemic monitoring and control are particularly required in case of Pringle maneuvers, that, when repeated, cause severe perioperative hyperglycemia. Our two groups were taken care of in the same way.

2. The rate of postoperative atelectasis is given as significantly less frequent in the ERP group. However, in the supplemental material Atelectasis is shown to have an incidence of 10.7% in the ERP group vs 2,7% in the NERP group (p=0,05). Is this an error? How do the authors explain this finding?

Response:

Thank you for this comment. We made in fact an inadvertent mistake. The atelectasis rate was indeed significantly lower in the ERP group. Actually, the mistake was even larger because the two columns of the table were inverted. All the complications in the ERP column were those of the NERP group and vice versa. This has now been corrected.

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Hepatobiliary	27 (18)	14 (18.7)	13 (17.3)	*0.83*
Angiocholitis	0	0	0	-
Bilioma	18 (12)	10 (13.3)	8 (10.7)	*0.62*
Biliary fistula	11 (7.3)	6 (8)	5 (6.7)	*0.75*
Hepatic insufficiency	9 (6)	4 (5.3)	5 (6.7)	*0.73*
Ascites	6 (4)	2 (2.7)	4 (5.3)	*0.4*
Digestive	26 (17.3)	5 (6.7)	21 (28)	***0.0006***
Peritonitis	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Intestinal fistula	0	0	0	-
Gastroparesis	3 (2)	0	3 (4)	*0.08*
Ileus	23 (15.3)	4 (5.3)	19 (25.3)	***0.0019***
General	23 (15.3)	9 (12)	14 (18.7)	*0.26*
Deep abscess	14 (9.3)	7 (9.3)	7 (9.3)	*0.99*
Deep hematoma	7 (4.7)	4 (5.3)	3 (4)	*0.7*
Thrombopenia	7 (4.7)	1 (1.3)	6 (8)	*0.053*
Sepsis	5 (3.3)	2 (2.7)	3 (4)	*0.65*
DVT	1 (0.7)	0	1 (1.3)	*0.32*
Cardiac	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Acute coronary syndrome	0	0	0	-
Tachy-arrhythmia	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Cardiac insufficiency	0	0	0	-
Neurologic	6 (4)	3 (4)	3 (4)	*0.99*
Stroke	1 (0.7)	1 (1.3)	0	*0.32*
Cognitive dysfunction	5 (3.3)	2 (2.7)	3 (4)	0.65
Peripheric deficit	0	0	0	-
Pulmonary	20 (13.3)	6 (8)	14 (18.7)	*0.055*
Atelectasis	10 (6.7)	2 (2.7)	8 (10.7)	***0.05***
Bronchopneumonia	2 (1.3)	0	2 (2.7)	*0.15*
Pulmonary embolism	0	0	0	-
Pleural effusion	17 (11.3)	6 (8)	11 (14.7)	*0.20*
Pneumothorax	3 (2)	0	3 (4)	*0.08*
Uro-nephrological	11 (7.3)	5 (6.7)	6 (8)	*0.75*

Urinary infection	2 (1.3)	1 (1.3)	1 (1.3)	*0.99*
Acute renal failure	6 (4)	2 (2.7)	4 (5.3)	*0.40*
Urinary retention	4 (2.7)	2 (2.7)	2 (2.7)	*0.99*
Parietal complications	8 (5.3)	2 (2.7)	6 (8)	*0.15*
Hematoma	3 (2)	0 (0)	3 (4)	*0.08*
Infection	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Wound dehiscence	2 (1.3)	2 (2.7)	0 (0)	*0.15*
Eventration	0	0	0	-
Evisceration	1 (0.7)	0 (0)	1 (1.3)	*0.32*
PONV	19 (12.7)	9 (12)	10 (13.3)	*0.81*
30-day readmission	20 (13.3)	8 (10.7)	12 (16)	*0.34*
90-day readmission	26 (17.3)	9 (12)	17 (22.7)	*0.089*
90-day unplanned consultation	15 (10)	5 (6.7)	10 (13.3)	*0.18*
Early redo surgery	6 (4)	4 (5.3)	2 (2.7)	*0.4*
30-day death	1 (0.7)	1 (1.3)	0 (0)	*0.99*
90-day death	3 (2)	1 (1.3)	2 (2.7)	*0.99*

3. Even though the overall morbidity was lower in the ERP group, this was mainly because of the reduced postoperative ileus in these patients. Serious surgical complications linked to liver resection did not differ between the ERP and NERP groups. This should be clarified in the abstract to avoid confusion and misconceptions about the benefits of ERP. It would also be beneficial to have an indicator for the severity of complications (e.g. major [Clavien >III], vs minor complications) between the compared groups.

Response:

In response to this reviewer's comment, we have now compared the incidence of complications following the Clavien-Dindo classification. Minor complications (Clavien Dindo grade < III) were significantly less frequent in the ERP group. Complications grade II were particularly less frequent. There was no difference with regards major complications. This has now been added in the result section (supplementary material 1). The distribution of surgical complications has been added to supplementary material 1, which now appears as follows:

Clavien-dindo classification:				
I	4 (2.7)	2 (2.7)	2 (2.7)	*0.99*
II	25 (16.7)	5 (6.7)	20 (13.3)	***0.001***
IIIa	11 (7.3)	5 (6.7)	6 (8)	*0.75*
IIIb	9 (6)	5 (6.7)	4 (5.3)	*0.73*
IV	2 (1.3)	0 (0)	2 (2.7)	*0.15*
V	1 (0.7)	1 (1.3)	0 (0)	*0.32*

The abstract result section has also been modified in response to your comment and now reads:

Patient demographics, comorbidities, and intraoperative data were similar in the two groups. Our ERP resulted in shorter length of stay (3 days [1–6] vs. 4 days [2–7.5], $p = 0.03$) and fewer postoperative complications (24% vs. 45.3%, $p = 0.0067$). This reduction in postoperative morbidity can be attributed exclusively to a lower rate of minor complications (Clavien-dindo grade < IIIa), and in particular to a lower rate of postoperative ileus, after labeling. (5.3% vs. 25.3%, $p = 0.0019$). Other medical and surgical complications were not significantly reduced. Adherence to protocol improved after labeling (17 [16–18] vs. 14 [13–16] items, $p < 0.001$).

Supplementary material: Postoperative complications (details)

	All patients N = 150	ERP N = 75	NERP N = 75	*p*
Hepatobiliary	27 (18)	14 (18.7)	13 (17.3)	*0.83*
Angiocholitis	0	0	0	-
Bilioma	18 (12)	10 (13.3)	8 (10.7)	*0.62*
Biliary fistula	11 (7.3)	6 (8)	5 (6.7)	*0.75*
Hepatic insufficiency	9 (6)	4 (5.3)	5 (6.7)	*0.73*
Ascites	6 (4)	2 (2.7)	4 (5.3)	*0.4*
Digestive	26 (17.3)	5 (6.7)	21 (28)	***0.0006***
Peritonitis	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Intestinal fistula	0	0	0	-
Gastroparesis	3 (2)	0	3 (4)	*0.08*
Ileus	23 (15.3)	4 (5.3)	19 (25.3)	***0.0019***
General	23 (15.3)	9 (12)	14 (18.7)	*0.26*
Deep abscess	14 (9.3)	7 (9.3)	7 (9.3)	*0.99*
Deep hematoma	7 (4.7)	4 (5.3)	3 (4)	*0.7*
Thrombopenia	7 (4.7)	1 (1.3)	6 (8)	*0.053*
Sepsis	5 (3.3)	2 (2.7)	3 (4)	*0.65*
DVT	1 (0.7)	0	1 (1.3)	*0.32*
Cardiac	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Acute coronary syndrome	0	0	0	-
Tachy-arrhythmia	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Cardiac insufficiency	0	0	0	-
Neurologic	6 (4)	3 (4)	3 (4)	*0.99*
Stroke	1 (0.7)	1 (1.3)	0	*0.32*
Cognitive dysfunction	5 (3.3)	2 (2.7)	3 (4)	0.65
Peripheric deficit	0	0	0	-
Pulmonary	20 (13.3)	6 (8)	14 (18.7)	*0.055*
Atelectasis	10 (6.7)	2 (2.7)	8 (10.7)	***0.05***
Bronchopneumonia	2 (1.3)	0	2 (2.7)	*0.15*
Pulmonary embolism	0	0	0	-
Pleural effusion	17 (11.3)	6 (8)	11 (14.7)	*0.20*
Pneumothorax	3 (2)	0	3 (4)	*0.08*
Uro-nephrological	11 (7.3)	5 (6.7)	6 (8)	*0.75*
Urinary infection	2 (1.3)	1 (1.3)	1 (1.3)	*0.99*
Acute renal failure	6 (4)	2 (2.7)	4 (5.3)	*0.40*
Urinary retention	4 (2.7)	2 (2.7)	2 (2.7)	*0.99*

Parietal complications	8 (5.3)	2 (2.7)	6 (8)	*0.15*
Hematoma	3 (2)	0 (0)	3 (4)	*0.08*
Infection	3 (2)	1 (1.3)	2 (2.7)	*0.56*
Wound dehiscence	2 (1.3)	2 (2.7)	0 (0)	*0.15*
Eventration	0	0	0	-
Evisceration	1 (0.7)	0 (0)	1 (1.3)	*0.32*
PONV	19 (12.7)	9 (12)	10 (13.3)	*0.81*
30-day readmission	20 (13.3)	8 (10.7)	12 (16)	*0.34*
90-day readmission	26 (17.3)	9 (12)	17 (22.7)	*0.089*
90-day unplanned consultation	15 (10)	5 (6.7)	10 (13.3)	*0.18*
Early redo surgery	6 (4)	4 (5.3)	2 (2.7)	*0.4*
30-day death	1 (0.7)	1 (1.3)	0 (0)	*0.99*
90-day death	3 (2)	1 (1.3)	2 (2.7)	*0.99*
Clavien-dindo classification:				
I	4 (2.7)	2 (2.7)	2 (2.7)	*0.99*
II	25 (16.7)	5 (6.7)	20 (13.3)	***0.001***
IIIa	11 (7.3)	5 (6.7)	6 (8)	*0.75*
IIIb	9 (6)	5 (6.7)	4 (5.3)	*0.73*
IV	2 (1.3)	0 (0)	2 (2.7)	*0.15*
V	1 (0.7)	1 (1.3)	0 (0)	*0.32*

Data are count (%).
ERP: enhanced recovery program; NERP: no enhanced recovery program.
DVT = deep vein thrombosis. PONV = postoperative nausea and vomiting.

Supplementary material: ERP items influencing postoperative ileus.

Of all the patients included in both study groups, 23 (15.3%) had postoperative ileus. Some ERP components may have affected the presence of postoperative ileus: laparoscopy ((OR (95% CI): 0.24 (0.09–0.60), p = 0.0022)), early mobilization (OR (95% CI): 0.22 (0.08–0.60), p = 0.003), early feeding in the first 24 h (OR (95% CI): 0.18 (0.06–0.51), p = 0.0014), intraoperative prescription of NSAIDs (OR (95% CI): 0.33 (0.12–0.95), p = 0.039), not having an abdominal drain (OR (95% CI): 0.39 (0.16–0.97), p = 0.042), and not having a bladder catheter (OR (95% CI): 0.19 (0.07–0.49), p = 0.0007) decreased the risk of ileus. Conversely, intrathecal morphine injection may have increased the risk of ileus (OR (95% CI): 4.25 (1.10–16.45), p = 0.036). Finally, the longer the intravenous infusions were stopped after the operation, the higher the risk of ileus (OR (95% CI): 2.07 (1.49-2.88), $p < 0.0001$). Other ERP elements did not significantly affect the risk of ileus ($p > 0.05$). Multivariate analysis showed that only early cessation of intravenous infusions postoperatively significantly impacted the risk of developing ileus (OR (95% CI): 1.77 (1.01-3.13), p = 0.048).

ERP: enhanced recovery programs. NSAIDs: non-steroidal anti-inflammatory drugs. OR: odds ratio.

Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery.

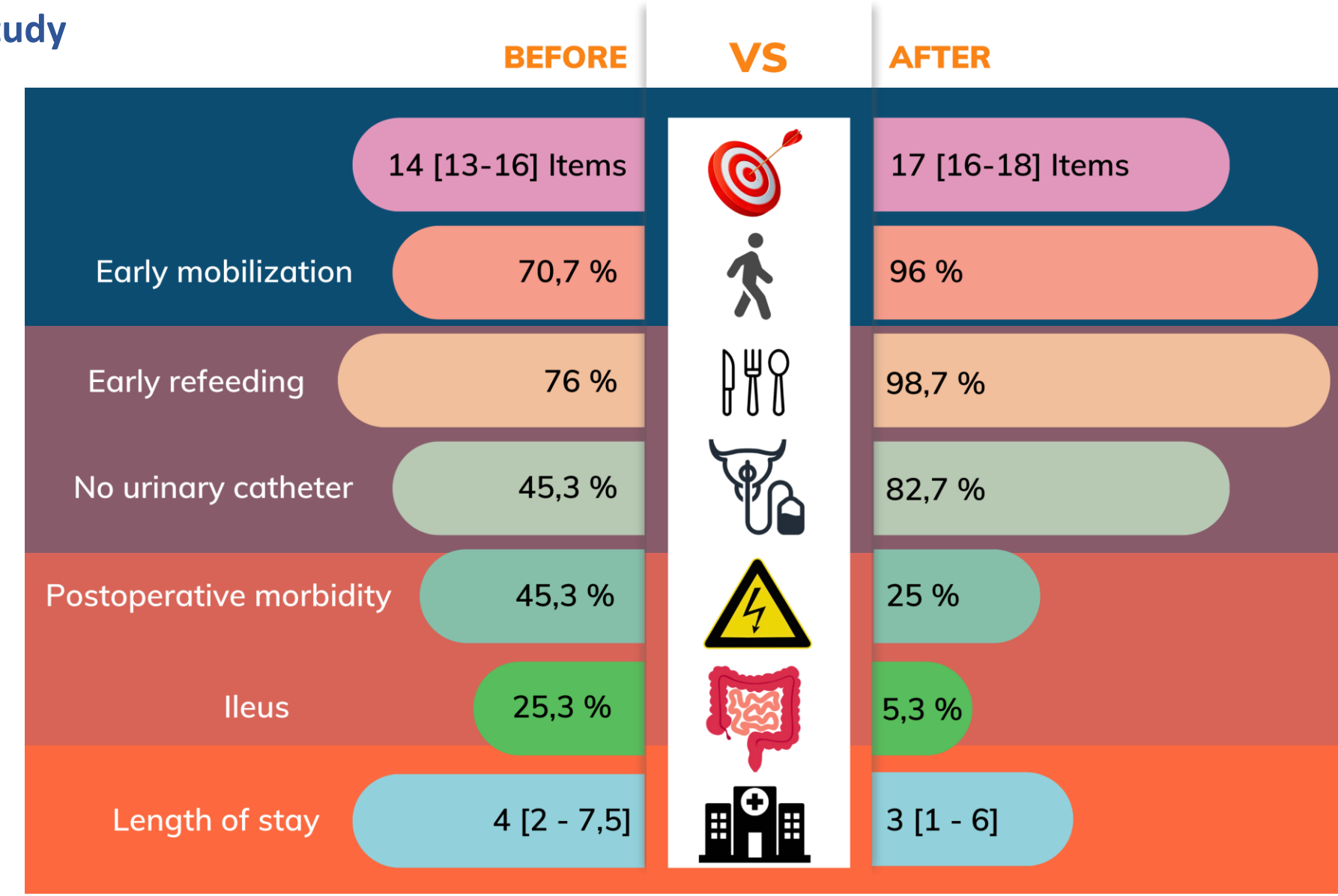
A monocentric retrospective study

Implementation of an enhanced rehabilitation protocol in liver surgery in December 2020

Application of 21 items Based on ERAS recommendations

Labeling of our hospital through an annual audit by the GRACE association

2 cohorts of 75 patients
(before and after ERP implementation)



Gabriel Thierry & al, *Surgical Endoscopy*, March 2024

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Arielle BLANJEAN

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Abdourahmane KABA

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Florian BECK

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☐ **None**	
		Fresenius-Kabi	Honoraria for logistic implementation at the Liege University Hospital, Liege, Belgium
		Viatris	Honoraria for logistic implementation at the Liege University Hospital, Liege, Belgium

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Gabriel THIERRY

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ None	
		GRACE (Francophone Group for Enhanced Recovery after Surgery), Beaumont, France	Financial support for translation. The funding source was not involved in study design, in collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit this article for publication.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Jean JORIS

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☐ None	
		GRACE (Francophone Group for Enhanced Recovery after Surgery), Beaumont, France	Financial support for translation. The funding source was not involved in study design, in collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit this article for publication.
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☐ **None**	
		GRACE (Francophone Group for Enhanced Recovery after Surgery), Beaumont, France	Honor member

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Morgan VANDERMEULEN

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Belgian national scientific research foundation (FNRS)	Research grant
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☐ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Department of Abdominal Surgery and Transplantation, Liege University Hospital, Liege, Belgium	Attending to
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/25/2023

Your Name: Olivier DETRY

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ **None**	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Medtronic, Corza, Applied, Boston	Institution
		FNRS	Institution
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☐ **None**	
		Medtronic	Institution
		J&J	Institution
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Pierre HONORE

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Pierre-Yves HARDY

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☒ **None**	
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☒ **None**	
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☒ **None**	

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.

ICMJE DISCLOSURE FORM

Date: 12/20/2023

Your Name: Vincent BONHOMME

Manuscript Title: **Impact of enhanced recovery program implementation on postoperative outcomes after liver surgery. A monocentric retrospective study**

Manuscript Number (if known): Click or tap here to enter text.

In the interest of transparency, we ask you to disclose all relationships/activities/interests listed below that are related to the content of your manuscript. "Related" means any relation with for-profit or not-for-profit third parties whose interests may be affected by the content of the manuscript. Disclosure represents a commitment to transparency and does not necessarily indicate a bias. If you are in doubt about whether to list a relationship/activity/interest, it is preferable that you do so.

The author's relationships/activities/interests should be defined broadly. For example, if your manuscript pertains to the epidemiology of hypertension, you should declare all relationships with manufacturers of antihypertensive medication, even if that medication is not mentioned in the manuscript.

In item #1 below, report all support for the work reported in this manuscript without time limit. For all other items, the time frame for disclosure is the past 36 months.

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
Time frame: Since the initial planning of the work			
1	All support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.) **No time limit for this item.**	☒ None	
			Click the tab key to add additional rows.
Time frame: past 36 months			
2	Grants or contracts from any entity (if not indicated in item #1 above).	☐ **None**	
		Orion Pharma	Research support
3	Royalties or licenses	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
4	Consulting fees	☒ **None**	
5	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	☒ **None**	
		Grunenthal	Amount paid to me.
6	Payment for expert testimony	☒ **None**	
7	Support for attending meetings and/or travel	☐ **None**	
		Edwards Medical	Amount paid to me.
8	Patents planned, issued or pending	☒ **None**	
9	Participation on a Data Safety Monitoring Board or Advisory Board	☒ **None**	
10	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	☒ **None**	

		Name all entities with whom you have this relationship or indicate none (add rows as needed)	Specifications/Comments (e.g., if payments were made to you or to your institution)
11	Stock or stock options	☒ **None**	
12	Receipt of equipment, materials, drugs, medical writing, gifts or other services	☒ **None**	
13	Other financial or non-financial interests	☐ **None**	
		Medtronic	Support for a specific training
		Elsevier	Support for publication of a book chapter

Please place an "X" next to the following statement to indicate your agreement:

☒ I certify that I have answered every question and have not altered the wording of any of the questions on this form.