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SCIENTIFIC REVIEW

Guidelines for Perioperative Care for Liver Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations

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Abstract

Background Enhanced Recovery After Surgery (ERAS) is a multimodal pathway developed to overcome the deleterious effect of perioperative stress after major surgery. In colorectal surgery, ERAS pathways reduced perioperative morbidity, hospital stay and costs. Similar concept should be applied for liver surgery. This study presents the specific ERAS Society recommendations for liver surgery based on the best available evidence and on expert consensus.

Methods A systematic review was performed on ERAS for liver surgery by searching EMBASE and Medline. Five independent reviewers selected relevant articles. Quality of randomized trials was assessed according to the Jadad score and CONSORT statement. The level of evidence for each item was determined using the GRADE system. The Delphi method was used to validate the final recommendations.

Results A total of 157 full texts were screened. Thirty-seven articles were included in the systematic review, and 16 of the 23 standard ERAS items were studied specifically for liver surgery. Consensus was reached among experts after 3 rounds. Prophylactic nasogastric intubation and prophylactic abdominal drainage should be omitted. The use of postoperative oral laxatives and minimally invasive surgery results in a quicker bowel recovery and shorter hospital stay. Goal-directed fluid therapy with maintenance of a low intraoperative central venous pressure induces faster recovery. Early oral intake and mobilization are recommended. There is no evidence to prefer epidural to other types of analgesia.

Conclusions The current ERAS recommendations were elaborated based on the best available evidence and endorsed by the Delphi method. Nevertheless, prospective studies need to confirm the clinical use of the suggested protocol.

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Introduction

Enhanced Recovery After Surgery (ERAS) is a multimodal pathway developed to improve recovery after major surgery. The ERAS strategy has been validated in colorectal surgery and is applied in other specialties including urology, thoracic, vascular and orthopedic surgery [1–3]. In colorectal surgery, ERAS pathways allow significant reduction in postoperative complications, faster functional recovery, shorter hospital stays and reduced costs, even in elderly patients [4–6]. Patients within ERAS pathways mainly benefit from reduced medical complications, while surgical morbidity remains generally unchanged [5].

Liver surgery is a major and challenging procedure for both anesthesiologists and surgeons, and for the patient. Major morbidity ranges from 17 % in benign to 27 % in malignant disease, with a mortality risk of up to 5 % [7]. In particular, pulmonary complications may reach 30 % with increased risk of thromboembolic events of 5 % [7–10]. In addition, about 50 % of patients experience nausea and adverse digestive events [11]. Perioperative stress is increased during major liver surgery, and all measures implemented to reduce the metabolic stress response could potentially reduce medical complications [5]. A recent meta-analysis demonstrated that enhanced recovery pathways for liver surgery was associated with a significant decrease in postoperative complications and length of hospital stay compared to standard care [12]. However, the majority of studies including ERAS protocols in liver surgery were performed in patients with normal liver parenchyma, while data in cirrhotic and obstructive jaundiced patients remained scarce. Unfortunately, published protocols vary widely, and actual application of the intended protocol (compliance) was provided in one single study only [13]. Furthermore, hepatic and colorectal surgeries differ in terms of underlying disease, comorbidities, metabolic stress response and organ-specific complications. It is currently unclear whether the ERAS elements validated for colorectal surgery can be extrapolated and applied for liver surgery.

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The present systematic review elaborates specific ERAS Society guidelines for enhanced recovery care after liver surgery by systematic review of the literature and expert consensus with the Delphi method.

Methods

Literature search and data selection

According to the PRISMA statements [14], EMBASE and Medline (through PubMed) were searched systematically using the medical subject headings (MeSH) “Hepatectomy AND the 23 pre-, intra- and postoperative validated ERAS items.” Only full-text articles in English were analyzed. Eligible articles included meta-analyses, randomized controlled trials (RCTs) or prospective cohort studies with control group published between January 1997 (1st landmark published study on ERAS [15]) and December 1, 2015. Retrospective series were considered only if data of better quality could not be identified.

Inclusion and exclusion criteria

According to our literature search, there are no data on the use of ERAS protocol in patients with obstructive jaundice or cirrhosis. The expert panel agreed in the first round of the Delphi process to focus the systematic review on non-obstructive jaundiced patients without cirrhosis. All types of hepatectomy according to the Brisbane classification were included [16]. Major hepatectomy was defined as resection of 3 or more *Couinaud’s* segments. Patients with choledocho-jejunostomy or vascular reconstruction were also included. All series including liver transplantation and patients with additional non-liver surgery (e.g., hepato-pancreaticoduodenectomy, colorectal-associated resection) were excluded.

Data extraction and quality assessment

The first literature search was performed independently by 5 authors (EM, MH, MS, CS and JP) in January 2015. The terms of interest were first identified in the title, secondly in the abstract or medical subject headings. All studies of interest were screened with thorough full-text reading. The quality of RCTs included was assessed using the Jadad score (range 0–5) and the Consolidated Standards of Reporting Trials (CONSORT) statement checklist [17, 18]. According to the published ERAS recommendations for pancreaticoduodenectomy [19], the level of evidence for each item was determined using the Grading of

Table 1 Summary of ERAS recommendations for each item and the respective level of evidence

ERAS items	Summary	Evidence level	Grade of recommendation
1. Preoperative counseling	Patients should receive routine dedicated preoperative counseling and education before liver surgery	Moderate	Strong
2. Perioperative nutrition	Patients at risk (weight loss >10–15 % within 6 months, BMI < 18.5 kg/m^2 and serum albumin <30 g/l in the absence of liver or renal dysfunction) should receive oral nutritional supplements for 7 days prior to surgery. For severely malnourished patients (>10 % WL), surgery should be postponed for at least 2 weeks to improve nutritional status and allow patients to gain weight	High	Strong
3. Perioperative oral immunonutrition	There is limited evidence for the use of IN in liver surgery	Low	Weak
4. Preoperative fasting and preoperative carbohydrates load	Preoperative fasting does not need to exceed 6 h for solids and 2 h for liquids. Carbohydrate loading is recommended the evening before liver surgery and 2 h before induction of anesthesia	No preoperative fasting more than 6 h: moderate Carbohydrate loading: low	No preoperative fasting more than 6 h: strong Carbohydrate loading: weak
5. Oral bowel preparation	Oral MBP is not indicated before liver surgery	Low	Weak
6. Pre-anesthetic medication	Long-acting anxiolytic drugs should be avoided. Short-acting anxiolytics may be used to perform regional analgesia prior to the induction of anesthesia	Moderate	Strong
7. Anti-thrombotic prophylaxis	LMWH or unfragmented heparin reduces the risk of thromboembolic complications and should be started 2–12 h before surgery, particularly in major hepatectomy. Intermittent pneumatic compression stockings should be added to further decrease this risk	Use of heparin: moderate Use of intermittent pneumatic compression devices: low	Use of heparin: strong Use of intermittent pneumatic compression devices: weak
8. Perioperative steroids administration	Steroids (methylprednisolone) may be used before hepatectomy in normal liver parenchyma, since it decreases liver injury and intraoperative stress, without increasing the risk of complications. Steroids should not be given in diabetic patients	Moderate	Weak
9. Antimicrobial prophylaxis and skin preparation	Single dose Intravenous antibiotics should be administered before skin incision and less than 1 h before hepatectomy. Postoperative “prophylactic” antibiotics are not recommended Skin preparation with chlorhexidine 2 % is superior to povidone-iodine solution	Antimicrobial prophylaxis: moderate Skin preparation: moderate	Antimicrobial prophylaxis: strong Skin preparation: strong
10. Incision	The choice of incision is at the surgeon’s discretion. It depends on the patient’s abdominal shape and location in the liver of the lesion to be resected. Mercedes-type incision should be avoided due to higher incisional hernia risk	Moderate	Strong
11. Minimally invasive approach	LLR can be performed by hepato-biliary surgeons experienced in laparoscopic surgery, in particular left lateral sectionectomy and resections of lesions located in anterior segments There is currently no proven advantage of robotic liver resection in ERAS. Its use should be reserved for clinical trials	Minimally invasive approach: moderate Robotic surgery: low	Minimally invasive approach: strong Robotic surgery: weak
12. Prophylactic Nasogastric intubation	Prophylactic nasogastric intubation increases the risk of pulmonary complications after hepatectomy. Its routine use is not indicated	High	Strong
13. Prophylactic abdominal drainage	The available evidence is non-conclusive and no recommendation can be given for the use of prophylactic drainage or against it after hepatectomy	Low	Weak

Table 1 continued

ERAS items	Summary	Evidence level	Grade of recommendation
14. Preventing intraoperative hypothermia	Perioperative normothermia should be maintained during liver resection	Moderate	Strong
15. Postoperative nutrition and early oral intake	Most patients can eat normal food at day one after liver surgery. Postoperative enteral or parenteral feeding should be reserved for malnourished patients or those with prolonged fasting due to complications (e.g., ileus >5 days, delayed gastric emptying)	Early oral intake: moderate Oral nutritional supplements: moderate No routine postoperative artificial nutrition: high	Early oral intake: strong Oral nutritional supplements: weak No routine postoperative artificial nutrition: strong
16. Postoperative glycaemic control	Insulin therapy to maintain normoglycemia is recommended	Moderate	Strong
17. Prevention of delayed gastric emptying (DGE)	An omentum flap to cover the cut surface of the liver reduces the risk of DGE after left-sided hepatectomy	High	Strong
18. Stimulation of bowel movement	Stimulation of bowel movement after liver surgery is not indicated	High	Strong
19. Early mobilization	Early mobilization after hepatectomy should be encouraged from the morning after the operation until hospital discharge	Low	Weak
20. Analgesia	Routine TEA cannot be recommended in open liver surgery for ERAS patients. Wound infusion catheter or intrathecal opiates can be good alternatives combined with multimodal analgesia	Moderate	Strong
21. Preventing postoperative nausea and vomiting (PONV)	Multimodal approach to PONV should be used. Patients should receive PONV prophylaxis with 2 anti-emetic drugs	Moderate	Strong
22. Fluid management	The maintenance of low CVP (below 5 cmH2O) with close monitoring during hepatic surgery is advocated. Balanced crystalloid should be preferred over 0.9 % saline or colloids to maintain intravascular volume and avoid hyperchloremic acidosis or renal dysfunction, respectively	Moderate	Strong
23. Audit	Systematic audit improves compliance and clinical outcome in healthcare practice	Moderate	Strong

Recommendations Assessment Development and Evaluation (GRADE) system, in which the level of evidence was classified as high, moderate, low or very low [20]. The research team (EM, MH, ND) made a final decision on inclusion of a study or not and was responsible for drafting the first manuscript.

Items analyzed

The classical 23 ERAS items validated for colorectal surgery were analyzed for liver surgery (Table 1). When only evidence in colorectal surgery was found for an item, it was searched for any evidence or rationale that this item should not be used in liver surgery.

Modified Delphi method

A 3-round Web-based Delphi approach was used in this consensus process [21]. Surgical program directors, chairmen of liver surgery departments, academic surgeons and anesthesiologists with publications involving ERAS and/or liver surgery were identified using PubMed database. They were deemed as “experts” and were separated from the list of authors. To ensure the international standpoint to this consensus, we aimed to recruit a panel of experts from America, Asia and Europe. A recruitment letter in English was sent via e-mail providing a brief outline of the project and its objectives. If invited experts did not respond to the invitation within 2 weeks, a reminder was sent out. Further experts were invited if no answer came in the next 2 weeks or the

Fig. 1 PRISMA flow diagram

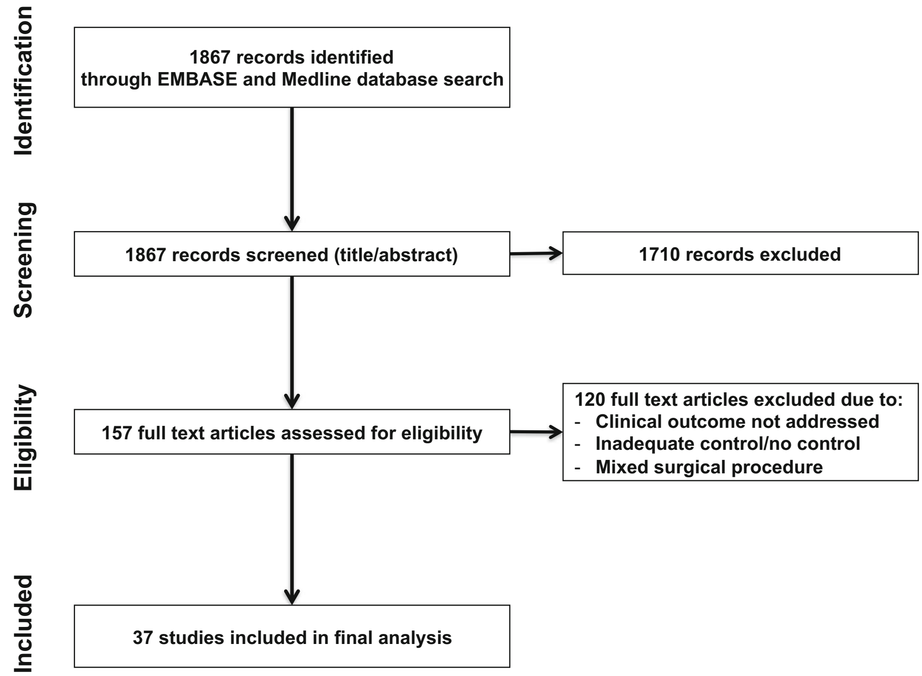

Table 2 RCTs dedicated to liver surgery selected in the systematic review with the level of evidence

Author	Year	Jadad score	Level evidence	Studied items	Morbidity	LOS
Lassen	2008	6	1	Postoperative artificial nutrition	No difference	No difference
Darouiche	2010	4	1	Skin preparation	Preoperative cleansing with chlorhexidine is superior to povidone-iodine for preventing SSI	Not assessed
Hayashi	2011	7	1	Perioperative steroids administration	Positive impact on liver function. No difference in complications	No difference
Wong	2007	5	2	Preventing intraoperative hypothermia	Perioperative warming reduce blood loss and complications	No difference
Okabayashi	2009	3	2	Postoperative glycaemic control	Intensive insulin therapy using a closed-loop system lower SSI	Decreased
Pessaux	2007	5	2	Prophylactic Nasogastric intubation (NGT)	NGT has no advantage. NGT increased the risk of pulmonary complications	No difference
Igami	2011	4	2	Prevention of delayed gastric emptying (DGE)	DGE reduced with omental flap on the cut surface after left-sided hepatectomy	Not assessed
Yoshida	2005	3	2	Prevention of delayed gastric emptying (DGE)	DGE reduced with omental flap on the cut surface after left-sided hepatectomy	Not assessed
Hendry	2010	2	2	Use of postoperative laxatives	Earlier passage of first stool, no change in morbidity	Decreased
Jones	2013	7	1	Goal-directed fluid therapy	Decreased	Decreased

LOS length of hospital stay

expert declined to participate in the study. A positive response to the recruitment letter served as informed consent.

In all 3 rounds, the manuscript was distributed by e-mail via a secured Web link. As previously validated, a modified Delphi process was used [22]. Each expert was asked to comment and edit anonymously the recommendations for each ERAS item using the text editor track change system. The research team served in the role of facilitator, undertaking the synthesis between rounds. The process of synthesis included discussion among the research team, exploring all expert opinions, disagreements and suggestions for change, before synthesized recommendations

Table 3 Items with <75 % expert agreement in rounds 1 and 2 of the Delphi process

Item	Round of disagreement	% of agreement
Perioperative oral immunonutrition	1	42
Perioperative steroids administration	1/2	42/71
Epidural analgesia	1	42
Minimally invasive surgery	1	71
Robotic surgery	1	57
Fluid management	1/2	29/71
Prophylactic abdominal drainage	1	71

were drafted for each subsequent round. Consensus was defined as agreement by >75 % of raters (i.e., 6 of the 7 experts) [23].

Results

The electronic search yielded 1867 potential studies. The selection process according to PRISMA guidelines is displayed in Fig. 1.

Overall 10 RCTs, 3 prospective case series, 5 retrospective case control series, 16 meta-analyses, 2 systematic reviews and one expert opinion study were included in the analysis. The overall quality of RCTs was high (Table 2); 9 RCTs had a Jadad score ≥3. Among the 23 published ERAS items for colorectal surgery, 16 were studied specifically for liver surgery (perioperative oral nutrition, perioperative oral immunonutrition, treatment with carbohydrates, postoperative artificial nutrition, anti-thrombotic prophylaxis, antimicrobial prophylaxis and skin preparation, type of incision, no routine resection site drainage, minimally invasive approach, perioperative steroid administration, postoperative glycaemic control, no prophylactic nasogastric intubation, prevention of delayed gastric emptying, laxatives use, multimodal analgesia and stringent fluid management). Seven items were not studied in liver surgery patients, and data were extrapolated from previous studies in colorectal surgery (preoperative counseling, no preoperative fasting, early mobilization, audit, early oral nutrition, prevention of postoperative nausea and vomiting (PONV) and prevention of postoperative ileus). The summary and grading of recommendations with their respective level of evidence are depicted in Table 1, and the results of the liver-specific studies used for the analysis are summarized in Table 2 (and suppl. Table 1).

Delphi process results

The response rate was 100 % after the first invitation (7 experts invited). Among the experts, one of the 7 was an anesthesiologist (origin UK) and the others were liver surgeon. One expert originates from America, 1 from Japan, 1 from Netherlands, 2 from England, 1 from France and 1 from Switzerland. After 3 rounds, all recommendations were agreed between the experts with a minimum of 75 %. Tables 3 summarize the items with <75 % agreement in rounds 1 and 2.

ERAS recommendations

1. Preoperative counseling

There are no studies evaluating the therapeutic effect of preoperative counseling and patient education before liver surgery. However, it is documented that patient decision aids such as printed documents and online information sources increase the involvement of patients in decision-making process and also increase the value of informed consent [24]. In addition, leaflets or multimedia information regarding the procedure and details of the patients' postoperative tasks improve results of perioperative feeding, mobilization and respiratory physiotherapy, thereby reducing complications after major abdominal surgery [1, 19].

Recommendation: Patients should receive routine dedicated preoperative counseling and education before liver surgery.
Evidence level: moderate
Grade: strong

2. Perioperative nutrition

Malnutrition is an important modifiable risk factor for adverse outcomes after major surgery. Routine nutritional screening should be mandatory for all patients undergoing major surgery [25–27]. Several screening tools are available, and their usefulness in clinical practice is demonstrated. The *Nutritional Risk Score* (NRS), the *Malnutrition Universal Screening Tool* and the *Subjective Global Assessment* (SGA) deserve particular mention [25, 28]. According to the ESPEN guidelines, delaying surgery to allow for preoperative enteral nutrition (for at least 2 weeks) is recommended in patients with at least one of the following criteria: weight loss >10–15 % within 6 months, BMI < 18.5 kg/m^2 and serum albumin <30 g/l (with no evidence of hepatic or renal dysfunction) [25, 28]. Current recommendations suggest 5–7 days of oral supplements before surgery in patients at risk of malnutrition [25, 28]. In severely undernourished patients who cannot be fed adequately orally or enterally, parenteral nutrition is recommended (Grade A) [29].

Recommendation: Patients at risk (weight loss >10–15 % within 6 months, BMI < 18.5 kg/m^2, and

serum albumin <30 g/l in the absence of liver or renal dysfunction) should receive oral nutritional supplements for 7 days prior to surgery. For severely malnourished patients (>10 % WL), surgery should be postponed for at least 2 weeks to improve nutritional status and allow patients to gain weight.
Evidence level: high
Grade of recommendation: strong

3. Perioperative oral immunonutrition

Immunonutrition (IN) contains ω-3 fatty acids, arginine and nucleic acids. So far, the only randomized study on nutrition and liver resection included 26 patients only [30], and no meaningful difference was reported. The ongoing PROPILS trial is likely to deliver a definitive answer: 200 IN patients will be compared to 200 patients receiving isocaloric isonitrogenous nutrition for 7 days before liver resection with overall complications as primary endpoint [31].

Recommendation: There is limited evidence for the use of IN in liver surgery.
Evidence level: low
Grade of recommendation: weak

4. Preoperative fasting and preoperative carbohydrate load

Preoperative fasting no more than 2 h for liquids and 6 h for solid food has proven to be safe and is recommended for digestive surgery [32]. A recent systematic review included 17 randomized trials with 1445 surgical patients [33]. Patients receiving carbohydrates had less perioperative insulin resistance and fewer symptoms like malaise, hunger, thirst, nausea or anxiety. No difference in terms of complications was observed, but one study demonstrated reduced hospital stay [33]. Carbohydrate loading is firmly established in colorectal guidelines [34, 35] and may be recommended in major liver surgery, since some data in the literature support the deleterious effect of insulin resistance on liver regeneration [36].

Recommendation: Preoperative fasting does not need to exceed 6 h for solids and 2 h for liquids. Carbohydrate loading is recommended the evening before liver surgery and 2 h before induction of anesthesia.
Evidence level: No preoperative fasting more than 6 h: moderate; Carbohydrate loading: low
Grade of recommendation: No preoperative fasting more than 6 h: strong; Carbohydrate loading: weak

5. Oral bowel preparation

Mechanical bowel preparation (MBP) may lead to fluid and electrolyte imbalances [37]. There are neither studies nor evidences about MBP before liver surgery.

Recommendation: Oral MBP is not indicated before liver surgery.
Evidence level: low
Grade of recommendation: weak

6. Pre-anesthetic medication

A recent Cochrane review on premedication for day case surgery in adults suggested that patients receiving oral anxiolytics showed impairment of psychomotor function 4 h postoperatively, which reduced the patient's ability to mobilize, eat and drink [38]. This may also hold in patients with impaired liver function after resection, and long-acting sedative premedication should be avoided. In selected cases, short-acting anxiolytics may be administered, to facilitate regional anesthesia prior to general anesthesia induction.

Recommendations: Long-acting anxiolytic drugs should be avoided. Short-acting anxiolytics may be used to perform regional analgesia prior to the induction of anesthesia.
Evidence level: moderate
Grade of recommendation: strong

7. Anti-thrombotic prophylaxis

Major hepatectomy in a normal liver parenchyma is an independent risk factor for postoperative PE [9]. In a large comparative cohort study ($n = 419$), patients treated with postoperative thrombo-prophylaxis beginning at day 1 after major hepatectomy had lower postoperative symptomatic venous thromboembolism (VTE) [39]. LMWH or unfragmented heparin treatment should be initiated 2–12 h before surgery and continued until patients are fully mobile [19]. Of note, possible interference with the use of epidural analgesia still needs to be assessed. The heparin should be administered 12 h prior to insertion of epidural catheter. A Cochrane meta-analysis supports continued treatment for 4 weeks after hospital discharge particularly in oncologic patients [40]. In addition, the use of compressive stockings and intermittent pneumatic compression devices can further decrease this risk [35].

Recommendation: LMWH or unfragmented heparin reduces the risk of thromboembolic complications and should be started 2–12 h before surgery, particularly in major hepatectomy. Intermittent pneumatic

compression stockings should be added to further decrease this risk.
Evidence level: Use of heparin: moderate; Use of intermittent pneumatic compression devices: low
Grade of recommendation: Use of heparin: strong; Use of intermittent pneumatic compression devices: weak

8. Perioperative steroid administration

According to a previous meta-analysis including 5 RCTs' ($n = 379$ patients) comparing preoperative steroid administration to placebo during liver resection, preoperative steroid use was associated with a significant reduction in levels of bilirubin and interleukin 6 (IL-6) on postoperative day 1 [41]. In addition, steroid used was associated with a trend toward lower incidence of postoperative complications. A more recent meta-analysis by Li et al. [42] showed contradictory results, with no impact on postoperative complications after liver resection. Most studies used methylprednisolone at a dosage of 30 mg/kg 30 min to 2 h prior to surgery. The use of steroids in diabetics has not been studied and, since the glycaemic control is impaired after hepatectomy, it is best avoided in this group until further studies are available.

Recommendation: Steroids (methylprednisolone) may be used before hepatectomy in normal liver parenchyma, since it decreases liver injury and intraoperative stress, without increasing the risk of complications. Steroids should not be given in diabetic patients.
Evidence level: moderate
Grade of recommendation: weak

9. Antimicrobial prophylaxis and skin preparation

Liver surgery is classified as clean-contaminated surgery due to bile duct transection. There is no clear evidence for systematic use of antimicrobial prophylaxis in liver surgery [43–45]. In addition, there is no evidence on the benefit of long- or short-term antibiotic therapy in patients with previous bile duct drainage (PBD). Up to 70 % of PBD patients have positive bile cultures (4 % with MRSA) and are associated in up to 30 % of cases with surgical site infection (SSI), but without increased mortality or postoperative hospital stay compared to patients with negative bile cultures [46].

Based on the Advisory Statement from the National Surgical Infection Prevention Project, antibiotics should be administered before skin incision less than 1 h before surgery [47]. In a recent Cochrane meta-analysis including 7 RCTs' ($n = 521$ patients), no antimicrobial method (i.e., perioperative antibiotic therapy, pre- and probiotics through enteral feeding catheter) could improve outcomes after liver surgery [43]. Hirokawa et al. [44] demonstrated that postoperative antibiotic therapy with flomoxef sodium third-generation cephalosporin) every 12 h for 3 days did not prevent postoperative infectious complications compared to single preoperative administration. The administration of antibiotics for 2 or 5 days after hepatectomy without biliary reconstruction did not modify SSI and systemic infections [45].

Recommendation: Single dose intravenous antibiotics should be administered before skin incision and less than 1 h before hepatectomy. Postoperative "prophylactic" antibiotics are not recommended.
Evidence level: moderate
Grade of recommendation: strong

Regarding skin preparation, one single RCT ($n = 100$ patients) assessed the efficacy of chlorhexidine gluconate for pre-hepatectomy skin cleansing [48]. According to this study, SSI (primary outcome measure) was not different compared to control with saline solution only. On the other hand, a recently published large RCT ($n = 849$ patients) including abdominal (and liver surgery) and non-abdominal types of surgery demonstrated that preoperative cleansing with chlorhexidine–alcohol 2 % was superior to povidone-iodine to prevent SSI [49].

Recommendation: Skin preparation with chlorhexidine 2 % is superior to povidone-iodine solution.
Evidence level: moderate
Grade of recommendation: strong

10. Incision

There are four major types of incision: median incision, right transverse incision with vertical extension to the xiphoid (J-shaped), subcostal incision extending to the left and bilateral transverse incision with vertical extension (Mercedes-type). According to the two largest retrospective cohort studies ($n = 1426$ and 626 patients, respectively) including one or multiple control groups, Mercedes-type incision had the highest incisional hernia risk at one year [50, 51]. Of note, perioperative morbidity and pulmonary complications were similar whatever the shape of the incision. For a better exposure of the hepato-caval junction, the inverted "L incision" (modified Makuuchi) can also be used [52].

Recommendation: The choice of incision is at the surgeon's discretion. It depends on the patient's

abdominal shape and location in the liver of the lesion to be resected. Mercedes-type incision should be avoided due to higher incisional hernia risk.
Evidence level: moderate
Grade of recommendation: strong

11. Minimally invasive approach

The Second International Consensus Conference on Laparoscopic Liver Resections in Morioka 2014 (Japan) concluded that minor laparoscopic liver resections (LLRs) had become standard practice, while major LLRs still remain innovative procedures and deserved further investigations [53]. One single retrospective study assessed LLRs in patients within ERAS protocol and suggested its feasibility with acceptable risk and possible additional accelerate recovery with reduced length of stay [54]. The results of the ongoing multicenter Orange-II trials assessing open versus laparoscopic left lateral hepatic sectionectomy within an enhanced recovery ERAS program may provide further evidence [55]. Twelve other systematic reviews were identified [56–67], 9 included meta-analysis comparing open versus laparoscopic liver surgery [58–60, 62–67]. These meta-analyses concluded that LLR was associated with lower intraoperative blood loss, blood transfusion, postoperative complications and shorter hospital stay. In addition, LLR reduced the incidence of liver failure and lowered postoperative ileus, while decreasing overall cost [60, 63, 68]. Moreover, it seems that patients with LLR had a faster oral intake and required less intravenous narcotic use [66]. LLR achieved similar short- and long-term oncologic outcomes for HCC or colorectal liver metastases (CLM) [59, 62, 69]. Finally, some authors advocated the systematic use of LLR for left lateral resection in benign liver lesions and in living donors for pediatric liver living donor transplantation [70, 71].

Recommendation: LLR can be performed by hepato-biliary surgeons experienced in laparoscopic surgery, in particular left lateral sectionectomy and resections of lesions located in anterior segments.
Evidence level: moderate
Grade of recommendation: strong

There were no studies assessing the safety of robotic liver surgery in patients within an ERAS protocol. Robotic liver resection seems to be feasible by hepato-biliary surgeons with advanced training, especially for lesions located in the postero-superior segments [72, 73]. However, according to a recent large series comparing robotic versus laparoscopic hepatectomy, significant benefits were not demonstrated yet [74].

Recommendation: There is currently no proven advantage of robotic liver resection in ERAS. Its use should be reserved for clinical trials.
Evidence level: low
Grade of recommendation: weak

12. Prophylactic nasogastric intubation

Two recent Cochrane systematic reviews demonstrated that prophylactic nasogastric intubation after abdominal surgery should be abandoned in favor of selective use. Increased pulmonary complications and longer time to return of bowel function were observed in patients with routine nasogastric tube [75]. One RCT (including 200 patients) confirmed those results after hepatectomy [76].

Recommendation: Prophylactic nasogastric intubation increases the risk of pulmonary complications after hepatectomy. Its routine use is not indicated.
Evidence level: high
Grade of recommendation: strong

13. Prophylactic abdominal drainage

The strongest evidence to omit routine prophylactic drainage after major abdominal surgery arises from a meta-analysis published in 2004 [77]. This meta-analysis, however, included 3 RCTs on liver resection only, with low sample size [78, 79]. Kyoden et al. [80] assessed the value of prophylactic drainage in a retrospective cohort study including 1269 consecutive elective liver resections. Prophylactic drainage reduced the frequency of subphrenic abscess and biliary fistula or biloma formation.

Recommendation: The available evidence is non-conclusive and no recommendation can be given for the use of prophylactic drainage or against it after hepatectomy.
Evidence level: low
Grade of recommendation: weak

14. Preventing intraoperative hypothermia

Normothermia (>36°) during surgery is recommended to reduce postoperative cardiac and non-cardiac complications [81–86]. However, no study specific to liver surgery investigating this point could be found. According to one RCT and one recent meta-analysis, even mild hypothermia increased significantly the risk of blood loss and transfusion [82, 86]. One meta-analysis suggested that circulating water garments offer better temperature control than forced air warming systems [87].

Recommendation: Perioperative normothermia should be maintained during liver resection.
Evidence level: moderate
Grade of recommendation: strong

15. Postoperative nutrition and early oral intake

Lassen et al. [88] conducted a multicenter randomized trial with 427 digestive surgery patients, who received either normal food from postoperative day 1 or a conservative regimen with *nil* by mouth and enteral tube feeding. There was no difference in complications, reoperations or mortality, but resumption of bowel function was faster in the "early food" group. Sixty-six patients in this study had either liver resection or hepatico-jejunostomy, confirming safety and benefits of early oral intake. Hendry et al. [89] demonstrated the benefits of the routine use of oral laxatives combined with oral nutritional supplements in liver surgery patients within enhanced recovery pathway. Postoperative supplemental nutrition is only indicated in malnourished patients or in prolonged postoperative fasting (>5 days) such as when severe complications arise [25–27]. A systematic review confirmed that enteral nutrition should be preferred over parenteral nutrition after liver resections for better immune function and lower rates of infectious complications [90].

Recommendation: Most patients can eat normal food at day one after liver surgery. Postoperative enteral or parenteral feeding should be reserved for malnourished patients or those with prolonged fasting due to complications (e.g., ileus >5 days, delayed gastric emptying).
Evidence level: Early oral intake: moderate; Oral nutritional supplements: moderate; No routine postoperative artificial nutrition: high.
Grade of recommendation: Early oral intake: strong; Oral nutritional supplements: weak; No routine postoperative artificial nutrition: strong.

16. Postoperative glycaemic control

Perioperative hyperglycemia is frequently observed after major surgery [91, 92]. These changes result from a transient insulin resistance with a compromised peripheral insulin-dependent glucose uptake [93]. Hyperglycemia induced by surgical stress results in deregulation of liver metabolism and immune function, impairing postoperative recovery. In colorectal and pancreatic surgery, early postoperative hyperglycemia was associated with adverse outcomes [19, 94, 95]. Postoperative insulin sensitivity is significantly reduced in patients not treated with insulin during surgery [96]. In addition, there is a rapid change in glucose concentration during hepatectomy with Pringle maneuver, reflecting glycogen breakdown within hepatocytes because of hypoxia [97]. According to one RCT ($n = 88$), patients who received insulin therapy using a closed-loop glycemic control system (i.e., an artificial pancreas) during hepatectomy had reduced total hospital costs and SSI compared to the commonly used sliding-scale method [98]. There is evidence that preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient decreased insulin resistance in patients undergoing hepatectomy [99]. A raised blood lactate after liver surgery, which correlates with postoperative morbidity [100], can be related to insulin resistance or to a mix between insulin resistance and ischemia–reperfusion injury. Therefore, insulin therapy should be initiated early during liver surgery to maintain normoglycemia (80–120 mg/dL). Programmed infusion of insulin administered as determined by the control algorithm of a closed-loop artificial endocrine system seems to be superior than manual injection of insulin according to the commonly used sliding-scale method [98].

Recommendation: Insulin therapy to maintain normoglycemia is recommended.
Evidence level: moderate
Grade of recommendation: strong

17. Prevention of delayed gastric emptying

Left-sided liver resection may be associated with a higher risk of DGE due to disruption of normal gastrointestinal movement at the point of contact between the stomach and the cut liver surface. According to 2 RCTs, the use of omentum flap to cover the liver cut surface after left-sided hepatectomy reduced the incidence of DGE [101, 102].

Recommendation: An omentum flap to cover the cut surface of the liver reduces the risk of DGE after left-sided hepatectomy.
Evidence level: high
Grade of recommendation: strong

18. Stimulation of bowel movement

According to 2 recent meta-analyses, the use of ERAS protocol significantly shortened the time to first flatus, hence reducing the postoperative ileus period [12, 103]. In the study by Hendry et al. [89], the routine use of postoperative laxatives resulted in an earlier first passage of stool, but the overall rate of recovery was unaltered in liver surgery patients. The use of chewing gum (CG) after surgery has been addressed in a large Cochrane review [104]. This meta-analysis showed no clear benefit of CG in ERAS patients and included few patients with liver surgery. The use of laparoscopic surgery and aiming for a neutral fluid balance by avoiding salt and fluid overload in the postoperative period have been shown to reduce the risk of postoperative ileus [12, 63].

Recommendation: Stimulation of bowel movement after liver surgery is not indicated.
Evidence level: high
Grade of recommendation: strong

19. Early mobilization

Bed rest is associated with multiple documented deleterious effects [105, 106]. Bed rest favors diffuse muscle atrophy, thromboembolic disease and insulin resistance [107]. There was no evidence that early mobilization is deleterious after liver surgery. Further studies are needed to determine the frequency and the number of hours required to improve patients outcome.

Recommendation: Early mobilization after hepatectomy should be encouraged from the morning after the operation until hospital discharge.
Evidence level: low
Grade of recommendation: weak

20. Analgesia

In one RCT using thoracic epidural analgesia (TEA), a short length of stays of 4 days after major liver resection was achieved with low complication rate [13]. A concern using TEA is the possible prolongation of prothrombin time after hepatectomy, which may delay epidural catheter removal and increase administration of corrective blood products [108]. A recent RCT showed that epidural analgesia in open liver resection might be a risk factor for postoperative kidney failure due to hypotension [109]. Several studies have suggested that intrathecal opiates are a suitable alternative to epidural analgesia and traditional morphine PCA [110, 111]. One recent RCT compared the role of local anesthetic wound infusion catheter plus patient-controlled opiate analgesia to standard epidural analgesia after open liver resection within an ERAS protocol [112]. Wound infusion reduced the length of time required to fulfill criteria for hospital discharge; however, epidural analgesia conferred better analgesia control. A meta-analysis of 4 studies ($n = 705$) with open liver resections has shown lower pain scores on day 1 postoperatively with epidural, but similar outcome compared to local anesthetic infiltration via wound catheters [113]. There was no difference in hospital length of stay, and the overall complication rate was higher in the epidural group.

Recommendations: Routine TEA cannot be recommended in open liver surgery for ERAS patients. Wound infusion catheter or intrathecal opiates can be good alternatives when combined with multimodal analgesia.
Evidence level: moderate
Grade of recommendation: strong

21. Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is common after major surgery, but the multimodal approach within ERAS pathway enables most patients after liver resection to eat on postoperative day 1 [13]. Risk factors are assessed preoperatively and include: previous PONV, female gender, younger age, non-smoker and use of volatile anesthetic agents and opioids [114]. 5HT3 antagonists remain the first-line therapy due to their good side effect profile. Low-dose dexamethasone improves liver regeneration (with no additional benefit at higher doses) [115]. As dexamethasone can worsen glycemic control, it should be used with caution in diabetics. Other secondary drugs are antihistamines, butyrophenones and phenothiazines [115]. According to the recommendations from the international consensus group on PONV, 2 antiemetic drugs are advocated to reduce postoperative PONV [116].

Recommendations: A multimodal approach to PONV should be used. Patients should receive PONV prophylaxis with 2 antiemetic drugs.
Evidence level: moderate
Recommendation Grade: strong

22. Fluid management

The reduction in hepatic venous congestion by careful control of central venous pressure (CVP) during hepatic resection is associated with a reduction in intraoperative blood loss [117–119]. A Cochrane review evidenced that a lower CVP reduced blood loss, but there was no difference in red cell transfusion requirements, intraoperative morbidity or long-term survival benefits [120]. In a recent meta-analysis by Hughes et al., the maintenance of a low CVP is associated with reduced blood loss and blood transfusion rates [121]. The goals of intraoperative fluid management are to maintain central euvolemia and to avoid excess salt and water. To achieve this, patients undergoing surgery within an ERAS protocol should have an individualized fluid management plan. As part of this plan, excess crystalloid and blood loss should be avoided in all patients. Although the measure of stroke volume variation (SVV) has been proposed as appropriate replacement for CVP monitoring [122], it is more likely that a synergistic combination of CVP monitoring and SVV methods will become the standard form of hemodynamic monitoring in liver surgery.

One recent study has demonstrated that goal-directed fluid therapy at the end of hepatic resection and during the first 6 h enabled a faster restoration of circulating volume with reduction in complications [13]. The use of balanced crystalloid solution rather than 0.9 % normal saline to maintain intravascular volume is recommended to avoid hyperchloremic acidosis and other causes of postoperative morbidity [123, 124]. The role of colloids remains controversial, and the use of hetastarches increases the risks of renal dysfunction when SIRS response and sepsis are present, and should be avoided in liver resection [125].

Recommendations: The maintenance of low CVP (below 5 cmH_2O) with close monitoring during hepatic surgery is advocated. Balanced crystalloid should be preferred over 0.9 % saline or colloids to maintain intravascular volume and avoid hyperchloremic acidosis or renal dysfunction, respectively.
Evidence level: moderate
Recommendation Grade: strong

23. Audit

The effectiveness of audit in improving health care has been demonstrated in a recent Cochrane systematic review [126]. Feedback was more efficient when baseline performance was low, when the source was a supervisor or a colleague, and when it was provided more than once, delivered in verbal and written formats, and when it included both explicit targets and action plan. Since strict adherence to the protocol is paramount for the success of ERAS implementation, auditing compliance has become *per se* a key element [34].

Recommendation: Systematic audit improves compliance and clinical outcome in healthcare practice
Evidence level: moderate
Grade of recommendation: strong

Conclusions

This systematic review highlights that the current available data on enhanced recovery pathways in liver surgery are scarce and lacks standardization. Although 16 out of the 23 standard items of ERAS were studied for liver surgery, the quality and level of evidence of the studies remain low. The highest level of evidence (level 1 or 2) was available for only 5 items. Though the value of enhanced recovery pathways has now been demonstrated in colorectal surgery, with a significant reduction in morbidity, cost and hospital stay, there is a need to perform high-quality studies to confirm the benefit of ERAS pathways in liver surgery. In conclusion, the proposed ERAS pathway for liver surgery is based on the best available evidence, but it needs to be further investigated. In addition, a very important aspect of ERAS pathways is the assessment of adherence to the protocol (compliance). Compliance with the new proposed liver ERAS protocol should be documented as part of further trial to allow benchmarking.

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Compliance with ethical standards

Conflict of interest EM, MH, CS, JP, CHCD, OF, JNV, PAC declares that they have no conflicts of interest. MS Grants, consulting and travel: Merck, Deltex, Baxter, LIDCO, not related to present work. OJG Educational grant: Ethicon (Johnson and Johnson), not related to present work. NK Research grants from Dainihon Sumitomo, Bristol Mayers, and Taiho Yakuhin, not related to present work. ND Grants and consulting: Nestlé Scientific, MSD, Covidien, Johnson and Johnson, not related to present work.

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