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Enhanced recovery after surgery in liver transplantation: Challenges and feasibility

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Abstract

BACKGROUND

Enhanced recovery after surgery (ERAS) started a revolution that changed age-old surgical stereotypical practices regarding the overall management of the surgical patient. In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. One of the last remaining fields, given its significant complexity and intricate nature, is liver transplantation (LT).

AIM

To investigate the existing efforts at implementing ERAS in LT.

METHODS

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical

primary endpoints, namely length of hospital stay.

RESULTS

All studies demonstrated a considerable decrease in length of hospital stay, with no readmission or negative impact of the ERAS protocol applied to the postoperative course.

CONCLUSIONS

ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT.

Key Words: Enhanced recovery; Enhanced recovery after surgery; Recovery; Liver transplantation; Liver

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Core Tip: Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery. The benefits of ERAS in liver transplantation seem promising, and further studies should be conducted to validate its application in properly selected patients.

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INTRODUCTION

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery[1]. Since its introduction in 1997 by Kehlet *et al*[2], initially destined for and subsequently established in colorectal surgery, the concept of ERAS was validated and has since evolved and spread to a multitude of surgical disciplines[3] including solid organ transplantation[4].

Although the concept of enhanced recovery was explored in liver transplantation (LT) before its official introduction by Kehlet *et al*[2] as early as 1990 in the form of early extubation yielding encouraging results[5], it was done so without the classic multimodal approach, focusing and highlighting on the importance of anesthesia management in these patients[6]. Over the years, independent studies have validated the significance and efficiency of other classic ERAS parameters such as preoperative nutrition, early mobilization, early feeding, and optimal analgesia of patients undergoing LT. Nevertheless, the medical literature is scarce in studies that combine all of the above parameters in a classic large-scale ERAS approach specific for LT. This narrative review paper will investigate existing efforts at implementing ERAS in LT, as well as try to identify the existing challenges and future potential developments in the field.

This review paper investigates existing efforts at implementing ERAS in LT and identifies the existing challenges and future potential developments in the field.

MATERIALS AND METHODS

Our goal was to identify the existing studies that evaluate ERAS in orthotopic LT, with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay. Medline, Embase, OVID, and the Cochrane library were searched in the English language using the search terms (ERAS OR “enhanced recovery” OR “fast track” AND “liver transplantation”) from years 1990 to 2021 and after independent assessment from three reviewers, three articles were selected. PRISMA flow chart is presented in [Figure 1](#).

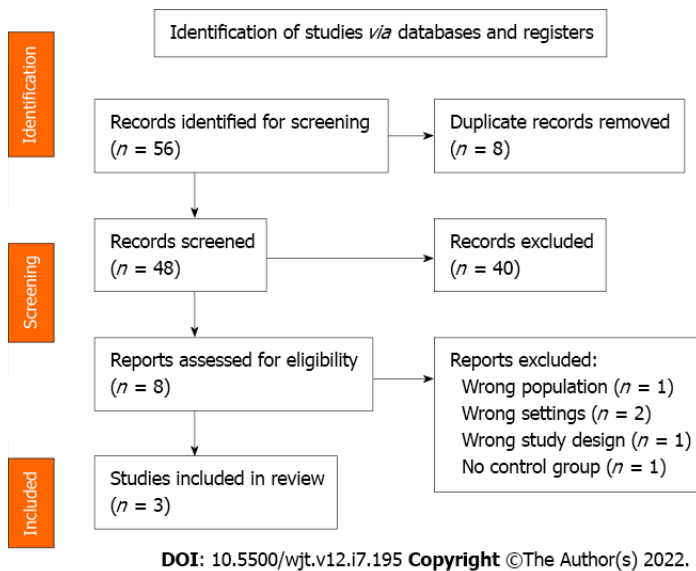


Figure 1 PRISMA flowchart.

RESULTS

There was a small number of studies identified, which were limited scale non-randomized single-center observational studies, with the exception of the work of Rao *et al*[7], who presented a prospective single-blinded randomized study including 128 patients divided in two groups: ERAS ($n = 54$) and control ($n = 74$). The ERAS group was analyzed by logistic stepwise regression analysis and displayed a decreased intensive care unit and hospital stay, without significant difference in the postoperative complication rate between the two groups and no readmissions or postoperative mortality during the follow-up period. Brustia *et al*[8] conducted a small-scale feasibility study with 10 patients treated prospectively with an ERAS protocol who were compared with 20 matched patients treated by the same team in previous years. They designed an elaborate 26-point ERAS protocol and observed a 47% reduction in the total length of stay compared to the control arm. There were no readmissions or postoperative mortality during the follow-up period.

Xu *et al*[9] reported a cohort of 93 patients, 40 in the ERAS group and 53 in the control group, and found a significant reduction of postoperative hospital stay in favor of the ERAS group (14.5 *vs* 16 d; $P < 0.001$). No difference in postoperative complication rate between the two groups and no readmissions or postoperative mortality were noted.

Common inclusion criteria used in the aforementioned studies are presented in Table 1. As expected, patients' Model for End-Stage Liver Disease (MELD) scores were low in all four studies, as they reflect patient status[10]. All studies included patients with a MELD score well below 25. Patients with no previous history of LT were also selected for the ERAS group in all three studies. A considerable number of patients for ERAS LT had a hepatocellular carcinoma (HCC)-related indication in all three studies (Brustia 90%, Xu 42.5%, Rao 33.3%).

Given the lack of a standardized ERAS protocol, each team designed its own protocols, based on previous experience from existing literature on other surgical fields. Table 2 depicts a comparison of the preoperative, intraoperative and post-operative characteristics between the three studies. All of the studies applied multimodal measures in the three distinct phases of classic ERAS protocols: preoperative, intraoperative and postoperative phase. In Table 3, measures applied by all three authors are depicted in capital letters. Of the 26 points proposed by Brustia *et al*[8], 11 (42.3%) were observed by all three authors.

All three studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocol applied in the postoperative course (Table 2). From the above-mentioned publications, we meta-analyzed the primary endpoint, postoperative hospital stay. The variable was continuous, and the results were summarized using median and 25%-75% values (because the data were skewed). The sample mean and standard deviations were calculated using the formula of Wan *et al*[11]. The random-effects model was applied for the meta-analysis, as high heterogeneity was expected among the studies with regard to study populations and diagnostic procedures. The presence of between-study heterogeneity was quantitatively reflected with the I^2 index, considering I^2 of $> 50\%$, indicative of statistically significant heterogeneity. R studio version 4.0.2 software was used to perform all of the statistical analyses, employing the packages "meta" and "metaphor." A comparison of total hospital stay showed a statistically significant difference in both groups ($n = 251$; MD- 5.79; 95% confidence interval (CI), 10.89 to 0.69; $I^2 = 89\%$; $P < 0.01$). Nevertheless,

Table 1 Common inclusion criteria (with incorporation of exclusion criteria)

Inclusion criteria	Brustia <i>et al</i> [8]	Xu <i>et al</i> [9]	Rao <i>et al</i> [7]
Meld score < 25	✓	¹	¹
HCC	✓	✓	✓
The first liver transplantation	✓	✓	✓
Age > 18	✓	> 16	> 16

¹All patients included in the three studies had a MELD score < 25. HCC: Hepatocellular carcinoma; MELD: Model for end-stage liver disease.

great heterogeneity was observed between the samples (Figure 2). A similar meta-analysis of the MELD score showed that there was no statistically significant difference in both groups ($n = 251$, MD -0.25, 95%CI, -1.36 to 0.85; $I^2 0\%$; $P = 0.62$) (Figure 3). As aforementioned, all patients were low MELD patients with a mean MELD well below 20.

DISCUSSION

The scarcity of strong evidence in the widespread application of ERAS programs in LT may reflect the reluctance of teams to implicate such protocols in a cohort of patients that are generally perceived as a frail, high-risk group, undergoing a major surgical procedure of a life-threatening nature. The evolution of LT on the other hand, is a successful story, evolving from an experimental and innovative procedure to a more “standard” one over the last several decades, and especially when performed in high volume centers with experienced multidisciplinary teams. Throughout the years, LT has proved its life saving nature as an operation and the morbidity and mortality plummeted, offering patients excellent survival and quality of life[12]. The major incentives in applying ERAS in LT came from the successful application of Enhanced Recovery Programs in Liver Surgery[13] and the subsequent publication of suggested guidelines for ERAS in Liver Surgery[14]. Although ERAS with its multimodal approach pattern did not appear in the literature until recently, the concept of multimodal clinical pathways in LT was raised as early as 2011 by Pavlakis *et al* of the Beth Israel Deaconess Medical Center team[15], characterizing the transplantation domain as an “*ideal forum for successful implementation of clinical pathways*” and highlighting their importance and potential in reducing length of stay, morbidity, costs, as well as improving patient satisfaction. Piñero *et al*[16] introduced in 2015 the concept of the early discharge from hospital following LT focusing on healthcare costs and proposed an early discharge prediction model based on MELD points (exception MELD points were deemed a favorable prognostic factor), length of surgery (time < 4 h), transfusion of less than 5 units of packed red blood cells, and early respirator weaning. The author concluded that early discharge from the hospital following LT is feasible, without a negative impact on patient or graft survival, nor did it increase short-term rehospitalization. A recent publication of Brustia *et al*[18] in Paris reinforced the basis for further developing ERAS in LT. Although it is a small-scale single-center observational study, the authors reported a 47% reduction of length of hospital stay with no safety issues in a small but well-designed protocol. This conclusion was corroborated by all three publications mentioned above, demonstrating that ERAS in LT could be possible in a larger scale and should be further studied. Rodríguez-Laiz *et al*[17] presented a cohort of 236 patients who were treated with a comprehensive multistep ERAS protocol that is the product of lessons and experiences emanating from liver surgery and other disciplines aiming to evaluate its value as a proof-of-concept. In this study, the authors identified 133 patients who were discharged early and they retrospectively defined them as the ERAS group. However, their study, with extremely short lengths of stay, was inherently flawed, as the authors pointed out, by a lack of a traditional control group; for this reason, their article was not included in our final selection. In 2021 Brustia *et al*[18] drafted the “*Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Society Recommendations*,” after a systematic review by a wide international panel of experts and the application of the Delphi method. The authors of the manuscript recognized the lack of current strong evidence in ERAS in LT but laid a solid foundation and precious scaffold, which can serve as the basis for large studies in the definitive validation of ERAS in LT.

ERAS is a well-validated multimodal approach for almost all types of surgical procedures, and its future in selected LT patients seems promising, as the preliminary results advocate for the safety and efficacy of ERAS in the field of LT. The majority of studies analyzing ERAS in LT use a cohort of low MELD highly selected patients that might not represent the majority of patients that benefit from LT; an issue that has to be addressed. The overall majority of patients in the three studies analyzed were low MELD HCC patients, and this type of selection might harbor an inherent bias in evaluating ERAS in LT. However it is a first step and understandably first steps must be careful. The encouraging results

Table 2 Preoperative, intraoperative, and post-operative characteristics

Preoperative	Brustia <i>et al</i> [8]		Xu <i>et al</i> [9]		Rao <i>et al</i> [7]	
	ERAS group, <i>n</i> = 10	CONTROL group, <i>n</i> = 20	ERAS group, <i>n</i> = 40	CONTROL group, <i>n</i> = 53	ERAS group, <i>n</i> = 54	CONTROL group, <i>n</i> = 74
Gender						
Male	8	17	35	46	40	58
Female	2	3	5	7	1	16
Age, yr	60.1 (52.5-66.1)	58.2 (52.6-65.3)	49.5 (40-56.8)	53 (47-59)	52.4 + 15.2	55.8 + 14.3
Primary cause						
Alcohol	7 (70%)	9 (45%)	7	3	6 (11.1)	10 (13.5)
Viral cirrhosis	7 (70%)	10 (50%)	11	16	30 (55.6)	40 (54.1)
HBV	2 (20%)	4 (20%)	NA	NA	NA	NA
HCV	6 (60%)	8 (40%)	NA	NA	NA	NA
Metabolic syndrome	2 (20%)	4 (20%)	NA	NA	NA	NA
Biliary disease	0	3 (15%)	NA	NA	NA	NA
HCC	9 (90%)	9 (45%)	17	24	18 (33.3)	24 (32.4)
MELD score	7 (6-10)	7 (6-9)	14 (9-22)	17 (14-19)	7.7 + 3.2	7.9 + 4.6
Intraoperative						
Operative time	6.0 (5.9-8.4) h	6.7 (5.7-8.2) h	443.7 + 85.3min	453.5 + 62.3min	265 (215-360) min	325 (275-455) min
Anhepatic period	NA	NA	44.3 + 5.2 min	42.7 + 4.2 min	45 (35-70) min	60 (50-75) min
Blood loss	NA	NA	775 (525-1000) mL	800 (600-1000) mL	1100 (300-4200) mL	2900 (1600-7000) mL
Hypothermia during the operation (<i>n</i> , %)	NA	NA	0	12%	0	0
Postoperative						
Early extubation (h)	2 (0-2)	7.5 (4.5-13.0)	0	6 (5.5-8)	NA	NA
ICU stay (d)	3 (2-4)	4.5 (3.0-8.3)	2 (2-3)	4 (4-5)	2 (1-7)	5 (3-15)
Complications (<i>n</i> , %)	5 (50%)	16 (80%)	9 (22.5%)	26 (49.1%)	10 (18.5%)	20 (27%)
Pain score after operation	3 (1.0-4.0) POD	4.5 (2.7-6.) POD	2.45+ 0.54	3.02+0.44	NA	NA
Postoperative hospital stay (d)	9.5 (9.0-10.5)	18 (14.3-24.3)	14.5 (12-17)	16 (15-18)	18 (15-32)	28 (23-35)
Readmission within 30 d after discharge	NA	NA	0	0	0	0

Categorical variables are reported using percentages; continuous variables are summarized using median and 25%-75% percentiles. ERAS: Enhanced recovery after Surgery; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; ICU: Intensive care unit; MELD: Model for end-stage liver disease.

presented, along with the observed benefit of a well-designed ERAS protocol in these patients mandates further exploration and expansion of inclusion criteria in these types of protocols. After all, an earlier discharge might be the result of a better overall patient management in all aspects of their journey through the hospital and not necessarily the primary endpoint.

One of the key factors in implementing ERAS protocols is the understanding of the philosophy behind ERAS by both patients and caregivers and although this might seem simple or a given, studies indicate that this might not be the case[19,20]. As ERAS is new to the field of LT, similar issues are expected to occur. In the first years of the implementation of ERAS in colorectal surgery, many issues arose concerning patient and physician capability of correctly implementing and accepting what proved to be a validated protocol for better patient recovery[21,22] including the complexity of these multimodal pathways[23], the need for teamwork along with the difficulty of eradicating old surgical stereotypes of traditional care. Agrafiotis *et al*[24], along with the first author of the present review, have

Table 3 Experimental "fast trans" protocol items

Preoperative	Brustia <i>et al</i> [8]	Xu <i>et al</i> [9]	Rao <i>et al</i> [7]
1 Outpatient counseling and information	√	√	√
2 Preoperative carbohydrate loading	√	√	√
3 Absence of preanesthetic medication (anxiolytic)	√		
Intraoperative			
4 Antimicrobial prophylaxis and skin preparation	√		
5 Prevention of intraoperative hypothermia	√	√	
6 Incision	√		
7 Adapted IV filling	√	√	√
8 Temporary portocaval anastomosis	√		
9 No prophylactic nasogastric intubation	√		√
10 No prophylactic abdominal drainage	√		√
11 Prevention of postoperative nausea and vomiting	√		
12 Antithrombotic prophylaxis and/or anti-platelet aggregation	√	√	
13 Early extubation (< 6 h after the end of IT)	√	√	√
Postoperative			
14 Early mobilization (POD1)	√	√	√
15 Patient-controlled analgesia	√	√	
16 Gastric probe removal POD1	√	√	
17 Clear liquid per OS POD1	√	√	√
18 Enteral feeding per OS POD1	√	√	√
19 Stop IV fluids POD1	√	√	
20 Per OS analgesia (POD2)	√	√	
21 Abdominal drain removal POD2	√		
22 Urinary probe removal POD2	√	√	√
23 Stop IV analgesia POD3	√	√	
24 Independent mobilization POD3	√	√	√
25 Daily revision of discharge criteria	√	√	√
26 Audit	√	√	√

ICU: Intensive care unit; IV: Intravenous; LT: Liver transplantation; POD: Post-operative day; PONV: Post-operative nausea and vomiting.

explored in 2013 the efficacy of a "soft" non-strict fast-track protocol in a cohort of 92 patients undergoing colorectal surgery. The conclusion was that even without a strict ERAS protocol, enhanced recovery and accelerated safe patient discharge are possible, pointing out among others[25] that "length of stay should not be an aim in itself within an enhanced recovery protocol. The main object of these programs ought to be the enhancement of patient recovery and not earlier discharge." This statement is endorsed by our team, in the Transplantation Department of a public Medical School part of a public healthcare system with significant challenges, who tried to evaluate the implementation of a non-strict ERAS protocol in selected LT patients in a small cohort of patients trying to replicate the results of Brustia *et al*[8]. In a small feasibility and safety study, we observed a 56% decrease in hospital stay in the ERAS group without any safety issues (unpublished data). These encouraging results might indicate that ERAS, when implemented in the right way, can be beneficial to patients even in small volume transplant centers and their implementation should be encouraged. We also noted the lack of estimation of the importance of every point in the proposed ERAS protocols towards the final endpoint, which hinders the simplification of these protocols, as we do not currently know which one of the steps – if any – could be omitted without a significant compromise in the outcome.

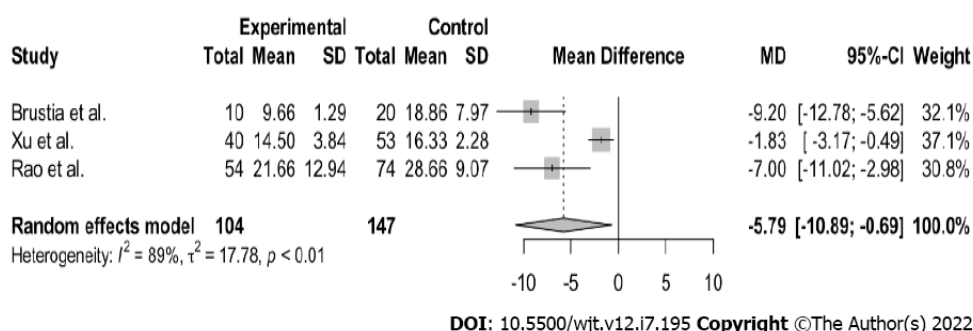


Figure 2 Forest plot of postoperative hospital stay in days.

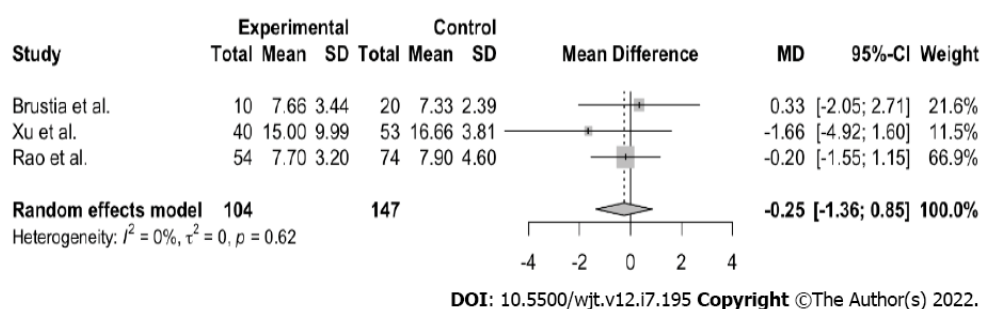


Figure 3 Forest plot of model for end-stage liver disease scores.

Henric Kehlet pointed out the delay of the development of ERAS: “there is an urgent need for better implementation of the current established scientific evidence for ERAS practices in order to fill the still very present gap between knowing and doing” and has been advocating for many years the concept of “stress free, pain free” operations[26], which might seem an impossible task for operations of the magnitude of a LT. However, as the term “fast-track” was gradually replaced by the more correct term “enhanced recovery,” the concept of “first better, then faster” had to be reappraised[27,28].

CONCLUSION

Enhanced recovery means better recovery and its value should be further exploited for liver transplant patients. After all, ERAS is not about the type of operation; ERAS is about the patient.

ARTICLE HIGHLIGHTS

Research background

Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery.

Research motivation

In the last decade, ERAS has gained significant acceptance in the community of general surgery, in addition to several other surgical specialties, as the evidence of its advantages continues to grow. Orthotopic Liver Transplantation (LT) remains one of the last frontiers in the application of ERAS.

Research objectives

To evaluate existing data on the use of ERAS in orthotopic LT.

Research methods

We conducted a systematic review of the existing studies that evaluate ERAS in orthotopic LT with a multimodal approach and focusing on measurable clinical primary endpoints, namely length of hospital stay.

Research results

All studies demonstrated a considerable decrease in length of hospital stay, with no readmissions or negative impact of the ERAS protocols in the postoperative period.

Research conclusions

Enhanced recovery can be safely applied in selected LT patients and its value should be further exploited.

Research perspectives

The future widespread use of ERAS in selected LT patients seems promising.

FOOTNOTES

Author contributions: Katsanos G, Karakasi KE, and Tsoulfas G wrote the manuscript; Morsi-Yeroyannis A and Sinakos E conducted the statistics; Goulis I, Giouleme O, and Vasileiadou S, reviewed the articles; Oikonomou IM and Mochailidou E proofread the manuscript; Tsoulfas G, Katsanos G, and Mouloudi E designed the review; Antoniadis N, Massa E, Tsakiris G, and Evlavis G conducted the bibliographic research and analyzed the results; All authors read and approved the final manuscript.

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