**Optimal results through Enhanced Recovery: Achieving Textbook Outcomes with High Compliance in Elective Liver Surgery.**

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**ABSTRACT**

**BACKGROUND:**

Existing studies suggest a positive correlation between high compliance with enhanced recovery programs (ERP) and improved outcomes. While individual outcome measures have advantages, composite benchmarks, such as textbook outcome (TO), offer a more comprehensive assessment of healthcare performance. Given the link between ERP and postoperative outcomes, this study aims to investigate the impact of ERP on TO attainment after Liver Surgery (LS).

**METHODS**

A prospective multicenter cohort of patients undergoing LS and exposed to ERP from 2016 to 2022 in France was analyzed. The primary outcome was to compare the rates of TO achieved between patients with high ERP compliance (>70%) and those with low ERP compliance (<70%) after LS.

**RESULTS**

A total of 706 patients were included in the study, and 217 (30.7%) achieved TO: 170 patients with high ERP compliance (24%) versus 47 patients (6.6%) with low ERP compliance attained TO (p<0.001). High ERP compliance was associated to an increased likelihood of achieving TO [OR = 1.49 (95% CI: 1.01, 2.24); P = 0.049], while cholangiocarcinoma [OR = 0.11 (95% CI: 0.02, 0.39); P = 0.003], high complexity liver surgery [OR = 0.22 (95% CI: 0.13, 0.36); P < 0.001], intraoperative hypotension requiring vasopressors [OR = 0.29 (95% CI: 0.10, 0.68); P = 0.010], and post-operative ileus [OR = 0.08 (95% CI: 0.00, 0.37); P = 0.013] were negatively associated to TO.

**CONCLUSIONS**

Patients with high ERP compliance after LS experience elevated rates of TO, compared to those with low ERP compliance.

**BACKGROUND**

While there have been notable advancements in the management of patients undergoing liver surgery (LS)1,2 postoperative morbidity, prolonged hospital-stays (LOS), and increased hospital costs3–7continue to be observed on a daily basis.

The enhanced recovery program (ERP) is an evidence-based multimodal care program developed to minimize the response to surgical stress8–10, with updated recommendations focusing on LS in 202211. Studies exploring the impact of ERP in LS suggest a strong dose-response relationship between high compliance to the protocol and improved outcomes (morbidity and LOS)12–14, even when stratified for LS complexity12.

While analyzing individual outcome measures (morbidity, LOS or readmission) offers advantages, composite benchmarks integrate information from multiple domains into a single summary measure providing a comprehensive and readable assessment of healthcare journey performance, compared to individual measures15–18. One composite measure is the textbook outcome (TO), providing a comprehensive summary of hospital performance19: this includes different desirable postoperative outcomes that represent, one achieved, the ideal (so called textbook) hospitalization18. Achievement of TO after LS is heterogeneous across studies, ranging from 6% to 66% according to the use of laparoscopy20 and underlying diseases20–24span style="font-family:'Calibri Light'">.

Given the association between ERP and postoperative outcome measures, the aim of this study was to explore the impact of an ERP on TO achievement after LS.

**METHODS**

***Study design***

This study exploring TO was designed as an open-label, prospective multicenter cohort of patients undergoing elective LS, and exposed to an ERP within the Francophone Group for Enhanced Recovery After Surgery (*Groupe francophone de Réhabilitation Ameliorée après Chirurgie* [GRACE]).

Data reporting was structured according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement25 and the Reporting on ERAS® Compliance, Outcomes, and Elements Research (RECOVER) Checklist26.

***Textbook outcomes***

The composite TO were defined by the simultaneous presence of the six following variables: microscopically negative margins (R0), no perioperative transfusion (intra- or postoperative), no postoperative surgical complications (any complication from Clavien-Dindo>I to Clavien-Dindo<IV), no prolonged length of stay (LOS≤50th percentile of the whole cohort), no readmissions to any hospital or facility within 30 days after discharge, and no postoperative mortality (Clavien-Dindo V) within 30 days after surgery18.

***Patient population***

Adult (>18 y old) patients treated by LS within the twenty participating French or Belgian hospitals between June 2016 and August 2022 were eligible to participate. The ERP was based on a multimodal approach addressing a bundle of preoperative, intraoperative, and postoperative elements of care tailored for LS10,11,27.

***Data source and collection***

A central online database adapted to LS guidelines10 and designed for interactive tool, GRACE-Audit ([www.grace-audit.fr](http://www.grace-audit.fr)), was used for data collection. For each patient were available approximately 180 different demographics, pre-, peri- and postoperative variables, including complications and follow-up. The audit tool was declared to the French data protection authority (*Commission Nationale de l'Informatique et des Libertés*) in 2014 (#1817711). Each patient’s data was prospectively collected up to 90 days after surgery. The IRB approval was not required for his study.

Each Center’s investigator was asked to extract from each patient’s file all the supplementary variables required to calculate TO and update the follow up. A working database was extracted from the GRACE Audit system and enhanced with TO variables in March 2023.

***Variables***

LS were grouped into 3 levels (classes) according to their complexity, as defined by the Institut Mutualiste Montsouris (IMM) classification 28,29 as follows: Class I included wedge resection and left lateral sectionectomy; Class II included the removal of anterolateral segments and left hepatectomy; Class III included the removal of posterosuperior segments, right posterior sectionectomy, right hepatectomy, central hepatectomy, and extended left/right hepatectomy.

Overall compliance was calculated as the number of ERP elements fulfilled out of 21 (the total number of ERP elements) for each patient. According to previous studies on ERP in colorectal 30,31, or LS 13,14, the threshold considered for high compliance was 15 out of 21 items fulfilled (corresponding to 70%).

***Comparison***

Patients with high compliance to ERP (>70%) were compared to those with low compliance to ERP (<70%).

***Outcomes***

We formulated the hypothesis that patients with high ERP compliance (>70%) after LS could experience a higher rate of TO compared to those with low ERP compliance (<70%).

For this reason, the primary outcome was to compare the rate of patients achieving TO after LS in the high ERP compliance group versus those in the low ERP compliance group.

Secondary outcomes were to define the compliance to each ERP element in the general cohort and in the subgroup of patients fulfilling TO. Moreover, predictors of TO were explored.

***Statistical methods***

*Statistical software*

Data managing, visualization, statistical evaluation and analysis were performed with R software (version 4.0.2 or higher. The R Foundation for Statistical Computing. [www.cran.r-project.org](http://www.cran.r-project.org), Vienna, Austria).

*Descriptive statistics*

Categorical variables were reported as percentages, while continuous variables were summarized as means and standard deviation (SD) or median and range for discrete variables, as appropriate. The Student’s t-test or Mann-Whitney U test were used for comparisons of quantitative variables as appropriate, whereas a χ² test or Fisher’s exact test was used to compare categorical data. Data were compared before and after matching.

*Definition of variables predicting TO achievement*

Unadjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for variables associated with TO by a logistic regression univariable model. Variables with a P value < than 0.05 or clinically significant were entered in a multivariable logistic regression model to identify factors independently associated with TO. The final model expressed the adjusted ORs and 95% CI. All tests were two tailed, and P values < 0.05 were considered significant.

**RESULTS**

During the study period, 856 patients undergoing elective liver surgery at 20 centers were prospectively enrolled in the GRACE-Audit Interactive System. After excluding 150 records with incomplete or no data (preventing ERP compliance and/or TO definition), a total of 706 patients (82%) comprised the study cohort (Supplementary Figure 1). Among them, 384 patients (54.4%) were male, with 20.1% having a BMI greater than 30 kg/m², and the mean age was 60.04 ± 14.18 years. The majority of patients were treated for cancer (n=560, 79.3%): colorectal metastasis (n=230, 32.6%), non-colorectal metastasis (n=148, 21%), hepatocellular carcinoma (n=134, 19%), and cholangiocarcinoma (n=43, 6.1%), with R0 resection achieved in 88.5% (n=622) of patients.

According to the 3-level classification of LS complexity32,33 49.7% (n=351), 27.8% (n=196), and 22.5% (n=159) of patients underwent low- (I), mid- (II), and high-complexity (III) procedures, respectively. Among those who underwent a minimally invasive approach (laparoscopic or robotic approach, n=363, 51.4%), the open-conversion rate was 6.5%, although the rationale was not recorded. The mean length of stay (LOS) was 6.45 ± 6.71 days, and complications were observed in 58.6% (n=413) of cases, with 49.1% (n=313) classified as severe (Clavien III or higher). The characteristics of the patients and operative factors are detailed in Table 1 and Table 2, respectively.

**Primary outcome: rates of Textbook Outcomes according to ERP compliance.**

Overall, 217 out of 706 patients, constituting 30.7% of the study cohort, achieved TO.

Among them, 170 patients with high ERP compliance (24% of the whole cohort) achieved TO, whereas only 47 patients with low ERP compliance (6.6% of the whole cohort) attained TO (p<0.001).

**Secondary outcomes**

Enhanced Recovery Protocol Compliance.

The overall compliance with the ERP was 52% (median = 12 items, IQR 11-14), with individual element compliance rates ranging from 3% to 100% (Figure 1).

High compliance (>70%) was observed in 484 patients (68.6% of the cohort), with a median of 16 items (IQR 15-17). Compared to low compliance (< 70%), high compliance patients were younger, with lower rates of stay in ICU and shorter LOS (Table 1).

Supplementary Figure 2 provides a summary of the cumulative number of patients per compliance class.

Textbook outcome distribution

Details of each TO distribution by its definition is illustrated in the Figure 2 and Table 3. Among the subgroup of patients achieving TO, the distribution of ERP individual elements is illustrated in the Supplementary Figure 3.

Even in case of mid- and high- surgical difficulty (class II and III of the IMM classification), patients who successfully achieved TO exhibited a significantly higher number of ERP items compared to those who did not attain TO (Figure 3).

Predictors of Textbook outcomes achievement.

The results of univariable and multivariable logistic regression analyses on complications are summarized in Table 4. In the univariable analysis, factors such as age at surgery, malignant disease, high complexity surgery (IMM III), hypotension, the use of vasopressors during liver surgery, and postoperative ileus were associated with a decreased likelihood of achieving TO, while high compliance with the ERP was associated to an increased likelihood of achieving TO.

Upon adjusting for these variables in the multivariable logistic regression, cholangiocarcinoma [OR = 0.11 (95% CI: 0.02, 0.39); P = 0.003], high complexity liver surgery [IMM III, OR = 0.22 (95% CI: 0.13, 0.36); P < 0.001], intraoperative hypotension requiring vasopressors [OR = 0.29 (95% CI: 0.10, 0.68); P = 0.010], and post-operative ileus [OR = 0.08 (95% CI: 0.00, 0.37); P = 0.013] were independently associated against achieving TO.

Conversely, high ERP compliance (>70%) was independently associated with an increased likelihood of achieving TO [compliance >70% OR = 1.49 (95% CI: 1.01, 2.24); P = 0.049].

**DISCUSSION**

Both ERP and TO share a parallel significance, each warranting consideration as a comprehensive bundle. ERP, intended as a multimodal care program, showed greater efficacy than the implementation of singular elements in isolation (e.g., minimally invasive LS or a no-drain policy)8–10. To measure the impact of ERP, postoperative complication rates or length of hospital stay (LOS) have been commonly proposed as straightforward proxies, but they have faced considerable criticism. Conversely, TO represents a composite measure offering a comprehensive overview of favorable postoperative outcomes, thereby more accurately reflecting hospital performance compared to individual outcomes18,34.

Utilizing TO as a metric to assess the impact of ERP aligns with logical reasoning, and to the best of our knowledge, this was the first prospective multicenter study focusing on this point.

We supposed that patients exposed to better perioperative care (high ERP compliance) were more likely to experience favorable outcomes (TO). This hypothesis was confirmed by the observation that higher rates of patients with high ERP compliance achieved TO after LS, compared to those with low ERP compliance (TO 35.1%, n=170 high ERP compliance, versus TO 21.2%, n=47 with low ERP compliance, p<0.001).

Nevertheless, the rates of TO achievement were surprisingly low in whole cohort (n=706) as well (30.7%, n=217), without any clear hypothesis explaining this observation. Both the “LOS outcome” (n=401, 56.9%) and “postoperative complications”  (n=413, 58.6%) were the two more difficult outcomes to be achieved, similarly to previously published literature20–24,34.

High ERP compliance was an independent and strong predictor of achieving TO, which aligns with the hypothesis of this study: better perioperative care might be associated to better postoperative outcomes. Together with high ERP, indication for LS other than cholangiocarcinoma, low and mid-complexity procedures (IMM I-II), absence of intraoperative hypotension requiring vasopressors, and no post-operative ileus were predictors of TO.

Previous studies pointed out high rates of postoperative complications, length of stay35,36 and readmission37 among patients affected by cholangiocarcinoma, compared to HCC or liver metastasis3. Patients with postoperative complications are less likely to experience early discharge, and are exposed to high risk of hospital readmission. This sort of domino-effect within inter-dependent outcomes may explain the lower rates of TO in cholangiocarcinoma when compared to other malignancies, as reported by studies focusing on TO after LS18,38,39.

The inverse relationship between increasing surgical complexity and worst postoperative outcomes is clearly established29,32,40,41, even in case of ERP12, translating in lower rates of TO34,42.

The impact of hypotension during LS has been a subject of prolonged debate, marked by evolving perspectives. Blood loss, a well-established factor contributing to hypotension, has long been recognized as influential in the peri-operative outcomes of patients undergoing liver resection1,43, as indicated by previous studies focusing on perioperative strategies to minimize blood loss44. Conversely, alternative approaches, such as maintaining low central venous pressure (CVP), employing controlled hypotension, and utilizing vasopressors, have been considered reliable solutions to mitigate blood loss during LS45–47.

Controlled hypotension, inclusive of vasopressors, emerges as a potentially favorable option during LS, aiming to minimize blood loss with purportedly limited repercussions on overall outcomes48,49. This perspective contrasts with the findings of the present study. Unfortunately, the available data within the cohort lacked granularity, impeding the differentiation of whether hypotension and vasopressor use were consequences of excessive blood loss or deliberate measures to sustain a low CVP.

Postoperative ileus has the potential to extend the duration of postoperative hospitalization, thus preventing from TO achievement. ERAS® recommendations in Liver Surgery, as outlined in prior literature10 and subsequent updates11, have delved into strategies aimed at reducing the delay in gastric emptying and promoting bowel movements.

Despite its prospective design, this study is subject to typical limitations associated with multicenter prospective registries. These limitations encompass incomplete data, such as the administration of neoadjuvant chemotherapy, preoperative biliary drainage, preoperative assessments including prior hepatic volumetry, and subsequent peri-operative strategies implemented for major hepatectomies, absence of long-term oncologic follow-up, and a notable heterogeneity in the realm of expertise. Some variables are not captured by the registry, such as the socioeconomic status of patients.

It should be noted that not all participating centers handle comparable frequencies of benign lesions, hepatocellular carcinoma, cholangiocarcinoma, colorectal, and non-colorectal metastases. Additionally, there exists variability in the volume of cases contributed by individual centers over the course of the study period. As already reported on a previous study on ERP and LS12, in France the implementation of ERPs is not institutionally based and relies on each surgeon responsible for the local ERP, thus introducing the possibility of selection bias fothe most suitable patients. The sole ERP variable with an exceedingly low rate of application was Perioperative Nutrition. The underlying reasons are missing, but probably rely on a combination of logistical limitation and absence of anticipation by the medical team.

This study suggested that patients with high compliance tend to achieve ideal (textbook) outcomes (TO), mirroring the overall quality across various performance domains, and highlighting the importance of consistently applying ERPs in clinical practice. The use of a single and consensual metric can simplify the interpretation of ERP results rather than scattered outcomes (e.g. reduction in LoS and overall complications but not severe complications). In other words, analyzing quality trends through TO may be more straightforward for both patients and clinicians, as opposed to interpreting disparate individual performance indicators.

Additionally, the use of textbook outcomes as an assessment criterion appears to be reproducible and could standardize the presentation of results in future studies, enabling for continuous quality monitoring and increasing comparability for future meta-analysis.

**CONCLUSIONS**

Patients exhibiting high compliance with Enhanced Recovery Program experience elevated rates of achieving TO after LS. Subsequent research endeavors will delve into the correlation between TO and oncologic outcomes, including time-to-chemotherapy, disease-free survival, and overall survival.

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**TABLES**

1. **Baseline characteristics of the study population**
2. **Postoperative outcomes of the study population**
3. **Textbook Outcome Distribution by Its Definition.**
4. **Logistic Regression Analysis of Preoperative and Intraoperative Factors Associated With the Textbook Outcomes**

**FIGURES**

1. **Individual element compliance, study population**
2. **Textbook Outcome Distribution by Its Definition. The symbol \* indicates p<0.05.**
3. **IMM Surgical difficulty, TO achievement and ERP compliance.**

**SUPPLEMENTARY**

1. **Flowchart of the study population**
2. **Cumulative number of patients per compliance class**
3. **Individual element compliance, subgroup of patients having experienced TO**

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