Textbook Outcome Among Patients Undergoing Enhanced Recovery After Liver Transplantation Stratified by Risk. *A Single-Center Prospective Observational Cohort Study*

1. INTRODUCTION

The analysis of surgical outcomes usually focuses on the achievement of one or more parameters related to complications, cure of the disease, or survival. More rarely, the analysis focuses on quality of life, and exceptionally on parameters related to patient perception, the so-called patient-centered outcomes. From a patient's perspective, leaving the hospital uncomplicated after undergoing a complex life-threatening surgical procedure is considered a desirable goal. Liver transplantation (LT) --one of the most complex surgical procedures-- is applied to patients who are at very high risk of postoperative complications as a consequence of the advanced stage of their liver disease and secondary multi-organ involvement.

Enhanced recovery after surgery (ERAS) aims to reduce the risk of postoperative complications through the coordinated implementation of a set of measures in order to minimize the impact of surgical aggression and facilitate the rapid return of the patient to normal life. ERAS has been applied in few LT centers in the world.[1–5] It should meet non-inferiority criteria in terms of morbidity and mortality when compared to other well-established LT programs.[6] Furthermore, the comparison should be established based on objective criteria that group patients into cohorts of similar risk.

When patients have no complications, no prolonged length of hospital stay, no readmission and no mortality after a procedure, they are considered to have experienced a textbook outcome (TO). This concept is gaining acceptance as a metric that encompasses the most relevant adverse events that can occur as a result of a surgical procedure. In fact, TO has recently been examined after complex surgical procedures, some related to hepato-pancreatic-biliary surgery.[7–14] However, there is not yet a broad

agreement on which components and cut-off levels should be applied to define TO. But most studies include the absence of relevant intraoperative complications, the non-prolonged length of hospital stay (defined as the 50th or 75th percentile of the median length of hospital stay), and the absence of readmission within 30 days of the index procedure, mortality, and complications requiring reoperation or an invasive procedure within 30 to 90 days of the index procedure.

To date, TO has been examined in two studies of patients undergoing LT.[15,16] Our study is the first in patients undergoing ERAS after LT, and the first to stratify patients into cohorts according to the risk of complications. Our hypothesis was that including all relevant adverse events that occur during the first 90 postoperative days would best serve the genuine interest of patients.

1. PATIENTS AND METHODS

2.1. Study Design

This is a prospective, observational cohort study conducted in a single center, aimed at evaluating the quality of care for patients undergoing ERAS after LT. The medical Ethics Committee judged that no informed consent from the patients was necessary because of the observational nature of the study without additional burden for the patient. Analysis of data for the present study was subsequently approved (Ref CEIm PI2018/132) by the Ethics Committee. The study is a post hoc secondary analysis of data collected in a previous study registered in www.researchregistry.com/ with the unique identification number (UIN) 5999.[17] The work has been reported in line with the STROCSS criteria.[18]

2.2. Setting

In September 2012, a new liver transplant program was launched at our hospital in Spain. From the beginning, a decision was made to implement ERAS as an essential part of the program and offer it to all patients to be included in the waiting list. The main objective of an ERAS protocol is to accelerate recovery after surgery by applying a multimodal and standardized program to all phases of the care process, which includes stress reduction and prevention of complications. Our ERAS protocol followed all recommendations designed for liver surgery by the ERAS Society, except those specific for preoperative nutrition, not applicable to LT.[19] It was based on recent descriptions.

The detailed protocol and its compliance have been described elsewhere.[17] Briefly, the protocol included: a) structured preoperative counseling; b) perioperative actions such as antibiotic prophylaxis before skin incision, normothermia during the procedure, intraoperative fluid restriction, thromboelastometry, temporary porto-caval shunt, duct-to-duct biliary reconstruction, no use of T-tube, no abdominal tubes or drains, and extubation in the operating room; and c) postoperative course with no nasogastric tube, no antiemetic medications, early postoperative oral intake, early removal of the urinary catheter, ambulation initiated the same day of surgery, no antithrombotic medication, postoperative analgesia given orally, and no use of opioids.

The following criteria for hospital discharge had to be fulfilled: pain control with oral analgesics, independent ambulation, oral tolerance to solid food, good biochemical function of the graft, good compliance with the immunosuppressive regimen, and absence of adverse events or renal failure. Outpatient follow-up was initially twice a week and attended simultaneously by a hepatologist, surgeon and pharmacist. Patients were followed-up until August 2020.

2.3. Population

Patients were selected from a database maintained and audited prospectively during the study period (September 2012 to August 2017). The database included all consecutive patients who received a LT during the study period. From there, the study cohorts were selected.

2.4. Variables and Data Collection

Donor and recipient age, raw MELD score before LT, underlying liver disease, cold ischemia time, relevant intraoperative events, and postoperative events during 90 days after index procedure were recorded. Postoperative complications were recorded according to the Clavien-Dindo grading system.[20]

For cost analysis, operative time, length of ICU and hospital stay, radiology and endoscopy procedures following index procedure, as well as length of stay and any procedures during a 30-day readmission were recorded. Data was censored on postoperative day 30, and patients who died within the first month were excluded from cost analysis. Fees for the provision of health care were obtained from the hospital administration and the government agency for health economics.[21]

Estimated Glomerular Filtration Rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration, [CKD-EPI $_{(crea)}$].[22] Recipients who survived more than 3 months and had at least two separate eGFR measurements within a 3-month interval were included. Recipients were followed for two years or until death if it occurred earlier. The eGFR measurements for each patient were grouped into time intervals (i.e., 0 - 15 days, 2 – 3 months) and the 25th percentile eGFR for each time interval was obtained. A final value ≥60 mL/min per 1.73 m^2 indicated that the patient was considered as not having CKD during that time interval.[23] The percentage of patients with eGFR ≥60 out of the total number of patients in each time interval was recorded. Furthermore, to assess the variability of kidney function over time, pre-transplantation eGFR was chosen as the baseline value. The area under the eGFR curve

(AUC) was calculated during the 2 years post-LT for each patient. An AUC <100% indicated a decrease in eGFR, while an AUC >100% indicated an increase in eGFR.[24]

Immunosuppression consisted of a regimen based on tacrolimus (Advagraf), mycophenolate mofetil and steroids. An intensive pharmacokinetic monitoring program was implemented from day one of treatment. The dose of tacrolimus to achieve a given target steady plasma level of the immunosuppressant was calculated using a Bayesian estimation methodology, based on individual pharmacokinetic parameters, and tailored for each patient according to kidney function, etiology of cirrhosis (i.e., hepatitis C virus, alcohol), and biochemical liver function tests post-transplantation.[25] Target trough levels of tacrolimus were 6 to 8 ng/mL.[17] Tacrolimus doses and trough levels for each patient were grouped into time intervals (i.e., 0 – 15 days, 2 – 3 months) and the median dose and trough level were obtained for each time interval.

2.5. Exposure Assessment

Our main exposure was individual risk prediction based on combined donor and recipient characteristics. To define the low and medium risk cohorts, exclusion criteria were adopted in the recipient: acute liver failure, on mechanical ventilation at the time of surgery, receiving a graft from donors after circulatory death, portal vein thrombosis, previous major abdominal surgery (hepato-biliary surgery and extensive colorectal surgery), partial graft implantation or re-transplantation. The donor/recipient match was selected according to the balance of risk (BAR) score, which includes donor age, recipient Model for End-Stage Liver Disease (MELD) score, recipient age, re-transplant status, the need for mechanical ventilation and cold ischemia time.[26] Patients who

received a donor liver after brain death and with a BAR score of 9 points or less were identified. The raw MELD score at the time of transplantation was used to stratify these patients into low-risk (MELD ≤ 20) and medium-risk (MELD 21-30) cohorts. All patients outside the selection criteria who were transplanted over the same study period were analyzed separately. Patients were listed with hepatocellular carcinoma (HCC) weighting.

2.6. Outcome Definition

The TO was defined based on the absence of all of the following: intraoperative pRBC transfusion, postoperative renal replacement therapy, prolonged length of hospital stays (a length of hospital stays ≥75th percentile of the total cohort), 30-day readmission, 90-day hepatic artery thrombosis, 90-day biliary complications, 90-day Clavien-Dindo grade ≥III complications, and 90-day mortality. When all these eight components together did not occur, the patient was labeled as having achieved a TO.

2.7. Statistical Analysis

Descriptive statistics were used for intra- and postoperative parameters. Quantitative variables are reported as median and interquartile range (IQR), and categorical variables as absolute and relative frequencies. Statistical differences between groups were analyzed using the chi-squared test for categorical data and the t-test or Mann-Whitney U test for quantitative data. Multivariable logistic regression analysis was used to determine whether there is an association between patient and transplant characteristics, and the achievement of a TO. Following similar studies on liver surgery and LT,

demographic variables (age, gender), as well as variables related to the underlying liver disease (i.e., hepatocellular carcinoma, hepatitis C virus [HCV]) and the risk of transplantation (summarized in the previously defined low-, medium-, and outside the selection criteria cohorts) were included in the model.[6,17] In addition, the final variables in the model were selected based on the lowest Akaike information criterion value. The Kaplan-Meier life-table analysis was used to study overall survival, defined as the timeframe between LT and death or end of follow-up, because precise dates of death or termination of follow-up were known. Log-rank test was performed to compare survival curves. *P* values of less than .05 were considered to indicate significance. All analyses were carried out using RStudio, version 1.2.5001.

3. RESULTS

3.1. Patient and Transplant Characteristics

During the study period, 181 patients received a liver transplant (**Table 1**). Most were male (83.4%) and the median age (IQR) was 57 (52 – 64) years. Alcohol (56.9%) and hepatocellular carcinoma (55.8%) were the most frequent causes of the underlying liver disease, followed by HCV (33.1%). Ascites was found in about half of the patients (47%) at the time of transplantation. Cold ischemia time reached a median (IQR) of 272 (223 - 341) min, and operative time a median of 309 (275 - 350) min. More than half of the patients belonged to the low-risk cohort (55.8%), a minority to the medium-risk cohort (8.3%), and just over a third of the patients to the cohort outside the selection criteria (35.9%). The median (IQR) for intraoperative pRBC transfusion and length of hospital stay was 0 (0 - 0) units and 4 (3 - 6) days, respectively. Therefore, the absence of intraoperative transfusion of pRBC was considered a component of TO, and the 75th percentile (≤6 days) was selected as the cutoff for non-prolonged length of hospital stay.

3.2. Textbook Outcome After Transplantation

When looking at each individual component in the entire cohort (**Fig 1**), the majority of patients did not need postoperative renal replacement therapy (92.8%) or did not have 90-day hepatic artery thrombosis (95%). The percentage of patients who achieved TO was lower when considering other components individually: no intraoperative pRBC transfusion (84.5%), no 90-day biliary complications (88.4%), no 90-day mortality (89%), no prolonged length of hospital stay (78.4%) or no 30-day readmission (76.1%).

Finally, the absence of 90-day Clavien-Dindo complications grade ≥III had the lowest association with TO (55.2%). The contribution of each of the eight components to the achievement of the TO was likewise calculated separately for each of the three risk cohorts (**Fig 1**). In addition, the cumulative TO achievement was then calculated by combining the individual contributions. Overall, TO was finally achieved in 59 patients (32.6%) (**Table 1**), a figure that varied according to the risk of transplantation; it reached 42.6% in the low-risk cohort, decreased to 26.7% in the medium-risk cohort, and was 18.5% in the cohort outside the selection criteria (**Fig 1**).

3.3. Variables Associated with Textbook Outcome

Patients most likely to experience TO were older (patients who achieved TO, 60 years [54 – 66]; patients who did not achieve TO, 56 years [50.2 – 62]; *P*=.003). Patients most likely to experience TO had less advanced liver disease (**Table 1**). Specifically, patients who achieved TO were more likely to have hepatocellular carcinoma (patients who achieved TO, 45 of 59 [76.3%]; patients who did not achieve TO, 56 of 122 [45.9%]; *P*<.001), more likely to belong to a Child A stage (patients who achieved TO, 25 of 59 [42.4%]; patients who did not achieve TO, 24 of 122 [19.7%]; *P*=.003), more likely to not have ascites in surgery (patients who achieved TO, 41 of 59 [69.5%]; patients who did not achieve TO, 55 of 122 [45.1%]; *P*=.003), more likely to have a lower MELD score (patients who achieved TO, 11 [8.5 – 16]; patients who did not achieve TO, 16 [12 – 20.9]; *P*<.001), more likely to have a lower BAR score (patients who achieved TO, 4 [2 – 7]; patients who did not achieve TO, 6 [2.3 – 8]; *P*=.006), and more likely to belong to the low-risk cohort (patients who achieved TO, 43 of 59 [72.9%]; patients who did not achieve TO, 58 of 122 [47.6%]; *P*=.005). Furthermore, patients with a

higher probability of experiencing TO required less surgical time (**Table 1**). In this sense, patients who achieved TO were more likely to need a shorter cold ischemia time (patients who achieved TO, 254 min [220 – 292]; patients who did not achieve TO, 282 min [224 – 348]; *P*=.045), and more likely to need a shorter operative time (patients who achieved TO, 295 min [260 – 341]; patients who did not achieve TO, 312 min [279 – 357]; *P*=.04).

In contrast, patients less likely to experience TO had more advanced liver disease (**Table 1**). Specifically, patients who did not achieve TO were more likely to have acute liver failure (patients who achieved TO, 0 [0%]; patients who did not achieve TO, 9 of 122 [7.4%]; *P*=.03), more likely to belong to a Child C stage (patients who achieved TO, 14 of 59 [23.7%]; patients who did not achieve TO, 53 of 122 [43.4%]; *P*=.003), more likely to have ascites in surgery (patients who achieved TO, 18 of 59 [30.5%]; patients who did not achieve TO, 67 of 122 [54.9%]; *P*=.003), and more likely to belong to the cohort outside selection criteria (patients who achieved TO, 12 of 59 [20.3%]; patients who did not achieve TO, 53 of 122 [43.4%]; *P*=.005).

On multivariable analysis, age (odds ratio [OR], 1.05 [95% CI, 1.01 – 1.09]; *P*=.02), and having hepatocellular carcinoma (OR, 2.83 [95% CI, 1.37 – 6.03]; *P*=.005) were individually associated with a greater probability of achieving a TO (**Table 2**). On the contrary, belonging to the cohorts of medium risk or outside the selection criteria was associated with a lower probability of achieving a TO (OR, 0.46 [96% CI, 0.22 – 0.93]; *P*=.03).

3.4. Quality Outcomes

The cost of transplantation, ICU and hospital stays and procedures during the first month reached a median (IQR) of € 13.8 thousand (11.4 – 18.1) (**Table 3**), a figure that varied according to the risk of transplantation; it decreased to € 12.1 thousand (10.8 – 16.3) in the low-risk cohort, and increased to € 14.2 thousand (12.2 – 15.9) in the medium-risk cohort, and to € 16.2 thousand (13.8 – 22.1) in the cohort outside the selection criteria. Patients less likely to experience TO required more hospital resources. Specifically, patients who did not achieve TO were more likely to have an increased cost (patients who achieved TO, € 11.3 thousand [10.1 – 12.4]; patients who did not achieve TO, € 16.3 thousand [13.0 – 21.4]; *P*<.001). A similar pattern was observed for each risk cohort (**Table 3**).

Over the first two years after LT, including hospitalization and outpatient follow-up, a total of 7,083 eGFR measurements were obtained from the 159 patients who survived more than 3 months. Fewer eGFR measurements were counted in patients more likely to experience TO (patients who achieved TO, 33 [29 – 41]; patients who did not achieve TO, 45 [35 – 57]; *P*<.001). During the two-year post LT follow-up, the EGFR variability of patients who experienced TO was similar to that of patients who did not achieve TO (patients who achieved TO, 92.4% [82.8 – 98.5]; patients who did not achieve TO, 90.8% [76.4 – 100]; *P*=.56). Patients more likely to experience TO maintained better kidney function in the short and medium term. Specifically, patients who achieved TO were more likely to remain free of CKD (patients who achieved TO, 83.8% [82.7 – 85.6]; patients who did not achieve TO, 67.9% [66.9 – 70.2]), a trend that reached statistical significance for eighteen months after LT (**Fig 2**).

Induction with Basiliximab was used in 18 out of 59 patients who experienced TO and in 35 out of 122 patients who did not achieve TO (*P*=.94). The proportion of patients who had to discontinue tacrolimus, for some time or permanently during the study period, and switch to another immunosuppressant was lower in those who experienced TO than in those who did not achieve TO (6.8% vs 22.2%; *P* = .02). During the first 15 days after LT, the median dose of tacrolimus was identical for all patients (patients who achieved TO, 10 mg/day [7.75 – 13]; patients who did not achieve TO, 10 mg/day [7 – 12.6]; *P*=.58). The tacrolimus dose progressively decreased throughout the first year and a half after LT, and no significant differences were found between the two groups (**Fig 3**). From month 19 to month 24 post-LT, patients who experienced TO received a lower dose of tacrolimus (patients who achieved TO, 2 mg/day [1.5 – 3]; patients who did not achieve TO, 3 mg/day [2 – 3.5]; *P*=.49).

Over the first two years after LT, including hospitalization and outpatient follow-up, a total of 4,510 tacrolimus trough level measurements were performed in the patients who survived more than 3 months. Fewer tacrolimus trough level measurements were performed in patients more likely to experience TO (patients who achieved TO, 25 [22 – 29.5]; patients who did not achieve TO, 29 [24 – 35]; *P*=.01). The tacrolimus trough level was 7.9 ng/mL (6.6 – 9.4) during the first 15 days post-LT, it increased to 9.4 ng/mL (8 – 11) during the second 15-day period, and progressively decreased to 5.4 ng/mL (4.6 – 6.5) at the end of the second year (**Fig 3**). There were no statistically significant differences between patients who did not achieve TO and those who experienced TO **(Fig 3**).

Median follow-up of patients who experienced TO (4.5 years [3.4 – 6.1]) was similar to that of patients who did not achieve TO (4.6 years [3.1 – 5.9]; *P*=.51). On long-term follow-up, the survival of patients who experienced TO was similar to that of patients who did not achieve TO (*P*=.2) (**Fig 4**), a finding that held for each risk cohort separately.

4. DISCUSSION

The achievement of TO is based on the absence of a set of adverse events resulting from a specific treatment. Our program is characterized by low intraoperative pRBC transfusion requirements, such that the median is 0 units and the 75th percentile is also 0 units. Consequently, we have chosen the requirement of no pRBC transfusion to define TO. Something similar occurs with no need for postoperative renal replacement therapy. Another relevant component in the definition of TO achievement is the length of hospital stay. A characteristic of our program is that hospital stays reach a median of 4 days for the entire series. Therefore, we have introduced the 75th percentile (≤6 days) as the cut-off level to define TO achievement in the three risk cohorts. The percentage of readmission at 30 days is high in our program at the expense of the short hospital stay, a circumstance that our patients are aware of before their enrollment in the transplant waiting list.[6] Finally, we have selected the 90-day period to determine compliance with the four remaining components of TO achievement, namely, hepatic artery thrombosis, biliary complications, Clavien-Dindo grade ≥III complications, and mortality. The first two have been individualized due to their relevance and impact on the postoperative period of LT. It is true that they would have been included in grade ≥III complications, but we wanted to highlight them separately. Despite using expanded criteria, one in three patients undergoing LT in our center experiences TO, a figure similar to that of other studies that apply the concept of TO to complex liver surgery procedures, including LT.[7–16]

The present study examines data from a single center, whose experience is focused on applying an ERAS protocol to LT.[17] Our study is the first to provide data on the

achievement of TO in patients undergoing ERAS after LT stratified by risk. Low-risk patients achieved TO in a higher proportion (42%) than medium-risk patients (26%). Obviously, this proportion was lower in patients who fall outside the selection criteria (18%).

It is not a contradiction in our findings that the likelihood of achieving TO in LT increases with age. Underlying liver diseases with more severe potential, such as acute liver failure, usually occur at a younger age. It is also not surprising to find that hepatocellular carcinoma increases the likelihood of experiencing TO. Firstly, because hepatocellular carcinoma confers priority for transplantation due to its malignant nature. Secondly, because the tumor develops in a liver that is more likely to be in a less advanced stage of underlying disease when faced with transplantation. It also makes sense that patients in the medium risk cohort or who fall outside the selection criteria are less likely to achieve TO since they are carriers of conditions that pose a higher risk of complications.

The liver transplantation program in our country is run by the national health service. This health provider updates a scale for estimating costs based on operating room time, days of stay in ICU and hospital, and specific procedures performed on the patient.[21] Therefore, the costs reflect average activity but do not come from analytical accounting. This may explain the downward estimate of our prices compared to other healthcare providers or countries. However, the lower consumption of ICU and hospital stays has an impact on the total cost for any healthcare provider. Furthermore, the achievement of TO entails a reduction in costs, a pattern that remains for each risk cohort.

Favorable outcomes are usually associated with less laboratory testing and fewer follow-up outpatient visits. Compared with patients who did not achieve TO, those who achieved TO in our study required 25% fewer eGFR measurements during their hospitalization and throughout the first two years of follow-up after LT. It is interesting to note that, after LT, the proportion of patients who maintained eGFR levels within normal values (≥60 mL/min per 1.73 m^2) was higher in those who achieved TO than in those who failed TO (83.8 % vs 67.9%). And that this beneficial effect was significantly maintained during the first year and a half after LT.

Long-term renal function after LT is considered to depend on the degree of renal impairment prior to transplantation, the injury caused by the transplant itself, and the adverse effects of immunosuppressive medication.[23] Our data show that TO and non-TO patients received similar doses to achieve similar target trough levels of tacrolimus. Therefore, the better renal function of the patients who experienced TO in our study cannot be attributed to tacrolimus.

The patients who experienced TO in our study showed a trend towards better long-term survival, but this difference did not reach statistical significance. Interestingly, a previous study came to a similar conclusion.[15] Both series are unicentric and include a limited number of patients. Perhaps future multicenter studies will provide a different view.

4.1. Limitations

The small number of patients and the single-center nature of the study prevent us from reaching conclusions applicable to a broader population. Furthermore, stratification of patients into risk cohorts entails the analysis of an even smaller sample of the population. On the other hand, the use of ERAS has been established in few LT centers, which makes it difficult to establish comparisons.[1–5] The severity of the patients included in our waiting list and the management of the list in our country differ substantially from the usual conditions found in many LT centers around the world. The greater availability of organs in our geographic area may explain these differences, at least in part. However, our patients have been stratified according to reference values defined in an international multicenter study.[6] On the other hand, the metric we have used is reproducible and is available to any LT center interested in examining this topic in depth. Although the TO concept incorporates a set of desirable aspects from the medical perspective, it has not yet introduced the so-called patient-centered outcomes.

5. CONCLUSIONS

One third (32.6%) of patients who undergo ERAS after LT experience a TO, a proportion that reaches 42.6% in low-risk patients. Age and having a hepatocellular carcinoma are independently associated with a greater probability of experiencing a TO in this setting. Patients in the medium risk cohort or those who fall outside selection criteria are less likely to experience a TO. A composite metric defined as TO can become a useful tool to guide individualized improvement strategies according to risk in the management of a complex procedure such as LT, with a high impact on resource consumption and quality of life of patients. A novel finding of our study is that patients

who experience TO are more likely to maintain normal kidney function in the short and medium term after LT.

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Table 1. Demographic and Clinical Characteristics for Patients Undergoing Enhanced Recovery After Liver Transplantation, Ranked by Textbook Outcome Achievement

Variable	Total	T
		Failed
Patients, n (%)	181	122 (67.4)
Age, years, median (IQR)	57 (52 – 64)	56 (50.2 – 62)
Gender, n (%)		
Male	151 (83.4)	99 (81.1)
Female	30 (16.6)	23 (18.9)
Underlying liver disease, n (%)†		
Hepatocellular carcinoma	101 (55.8)	56 (45.9)
Hepatitis C	60 (33.1)	35 (28.7)
Alcoholic cirrhosis	103 (56.9)	71 (58.2)
Hepatitis B	12 (6.6)	8 (6.6)
Acute liver failure	9 (5.0)	9 (7.4)
Other	34 (18.8)	27 (22.1)
Platelets count, $x10^3$ µL, median (IQR)	85 (57 – 128)	84.5 (56.2 – 132)
Child score, n (%)		
A	49 (27.1)	24 (19.7)
B	65 (35.9)	45 (36.9)
C	67 (37.0)	53 (43.4)
Ascites, n (%)		
No	96 (53.0)	55 (45.1)
Yes	85 (47.0)	67 (54.9)
Cold ischemia time, min, median (IQR)	272 (223 – 341)	282 (224 – 348)
Operative time, min, median (IQR)	309 (275 – 350)	312 (279 – 357)
MELD score at transplant, median (IQR)	15 (10 – 19)	16 (12 – 20.9)
BAR score at transplant, median (IQR)	4 (2 – 7)	6 (2.3 – 8)
Risk cohorts, n (%)		
Low	101 (55.8)	58 (47.6)
Medium	15 (8.3)	11 (9.0)
Outside the selection criteria	65 (35.9)	53 (43.4)

IQR: interquartile range. (†) Some patients had more than one underlying liver disease. MDRD6: Modification of Diet in Renal Disease calculated on 6 variables (age, sex, ethnicity, serum creatinine, urea, and albumin). MELD: model for end-stage liver disease. BAR: balance of risk.

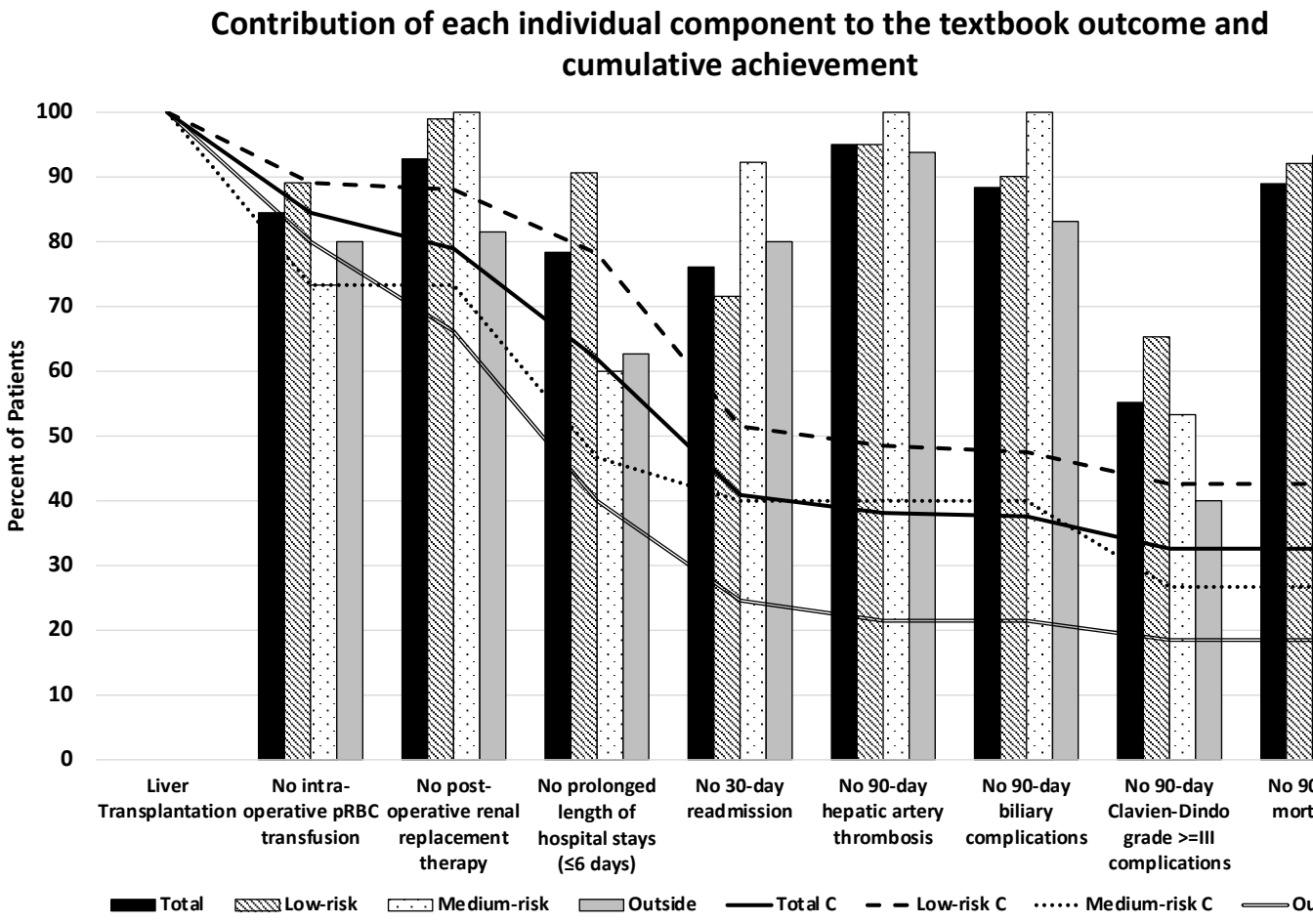

Figure 1. Textbook outcomes of patients undergoing enhanced recovery after liver transplantation stratified into low-risk, medium-risk, and high-risk (outside the selection criteria) cohorts. The contribution of each individual component (horizontal axis) to the textbook outcome (bars) and the cumulative (C) achievement (lines) are depicted in percentages (vertical axes).

Table 2. Logistic Regression Analysis of Characteristics Associated with Textbook Outcome

Characteristics	Univariable analysis		Multivariable an
	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)
Age, years	1.06 (1.02 – 1.10)	.005	1.05 (1.01 – 1.09)
Gender			
Male	1 [Reference]		
Female	0.58 (0.22 – 1.38)	.24	
Underlying liver disease			
Hepatocellular carcinoma	3.79 (1.92 – 7.82)	<.001	2.83 (1.38 – 6.03)
Hepatitis C	1.83 (0.95 – 3.50)	.07	
Alcoholic cirrhosis	0.85 (0.46 – 1.60)	.6	
Hepatitis B	1.04 (0.27 – 3.44)	.96	
Other	0.47 (0.18 – 1.11)	.1	
Risk cohorts			
Low	1 [Reference]		1 [Reference]
Medium + Outside selection criteria	0.34 (0.17 – 0.65)	.002	0.46 (0.22 – 0.93)

Table 3. Cost Assessment for Patients Undergoing Enhanced Recovery After Liver Transplantation, Ranked by Textbook Outcome Achievement

Population	Total	Textbook Outcome	
		Failed	Achieved
All patients, x10^3 €, median (IQR) ¶	13.8 (11.4 – 18.1)	16.3 (13.0 – 21.4)	11.3 (10.1 – 12.4)
Risk cohorts, x10^3 €, median (IQR) ¶			
Low	12.1 (10.8 – 16.3)	15.8 (11.9 – 20.5)	11.2 (9.9 – 12.1)
Medium	14.2 (12.2 – 15.9)	15.1 (13.9 – 16.9)	11.8 (11.1 – 12.2)
Outside the selection criteria	16.2 (13.8 – 22.1)	18.2 (15.0 – 24.0)	13.3 (11.0 – 14.1)

(¶) Operative time, length of ICU and hospital stay, radiology and endoscopy procedures following index procedure, as well as length of stay and any procedures during a 30-day readmission were included. Data was censored on postoperative day 30; and patients who died within the first month were excluded from cost analysis. Fees for the provision of health care were obtained from the hospital administration and the government agency for health economics.

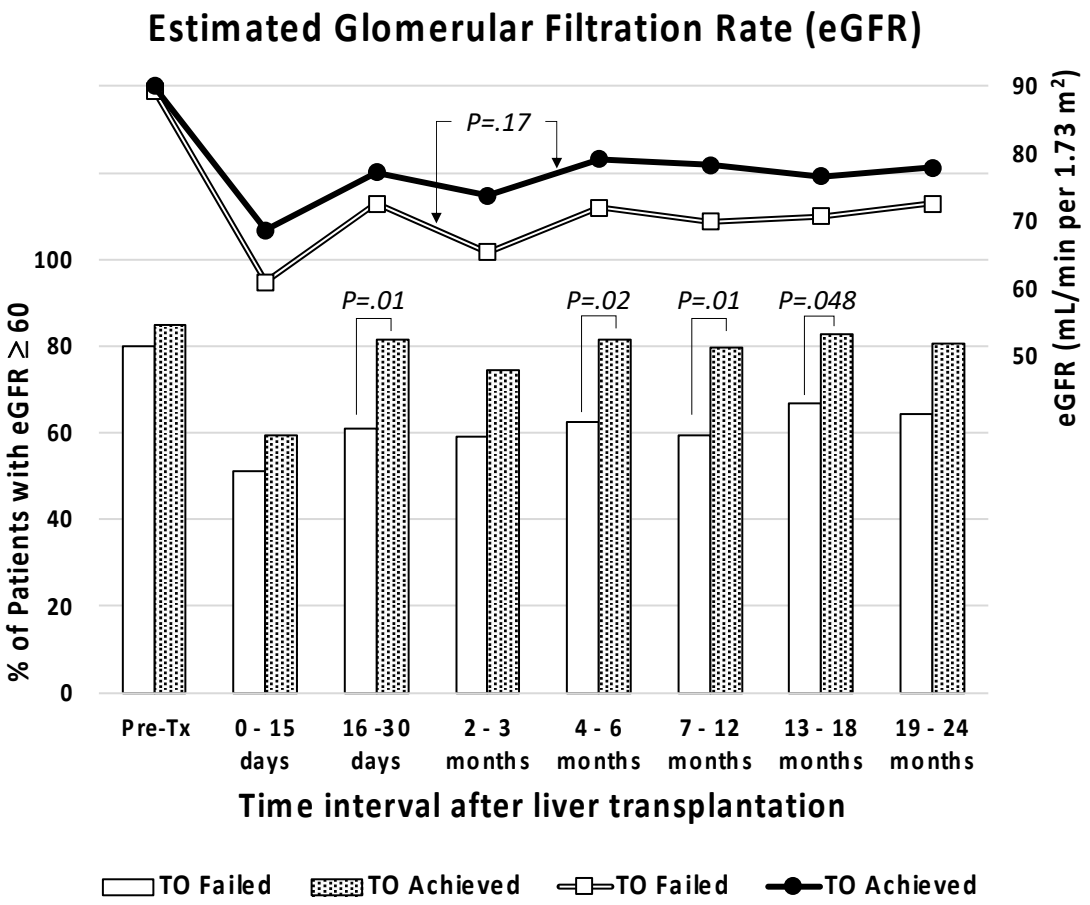

Figure 2. Percentage of patients with estimated Glomerular Filtration Rate (eGFR) ≥60 mL/min per 1.73 m^2 (left scale, bars), and eGFR (right scale, lines) at time intervals after Liver Transplantation, ranked by Textbook Outcome (TO) achievement. Patients who died during the first 90 days were excluded from the analysis

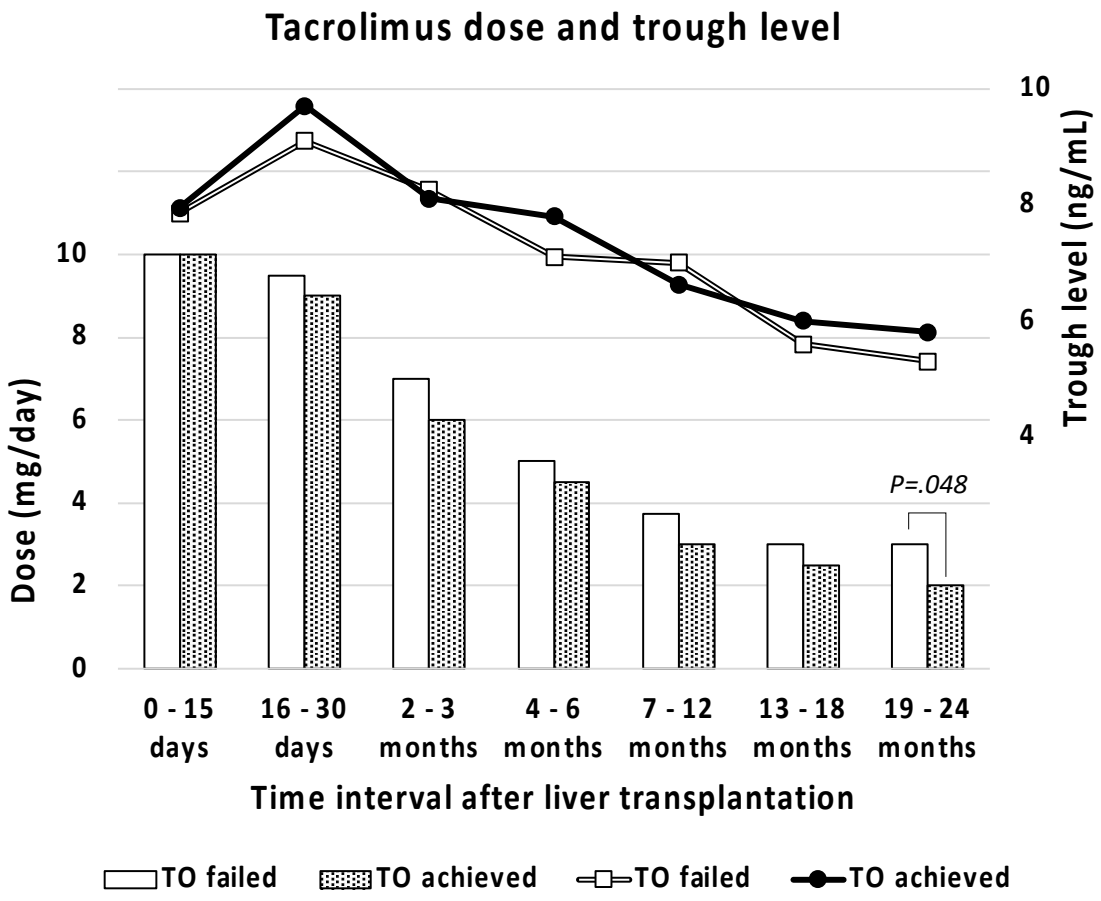

Figure 3. Doses of tacrolimus (left scale, bars), and tacrolimus trough level (right scale, lines) at time intervals after Liver Transplantation, ranked by Textbook Outcome (TO) achievement. Patients who died during the first 90 days were excluded from the analysis

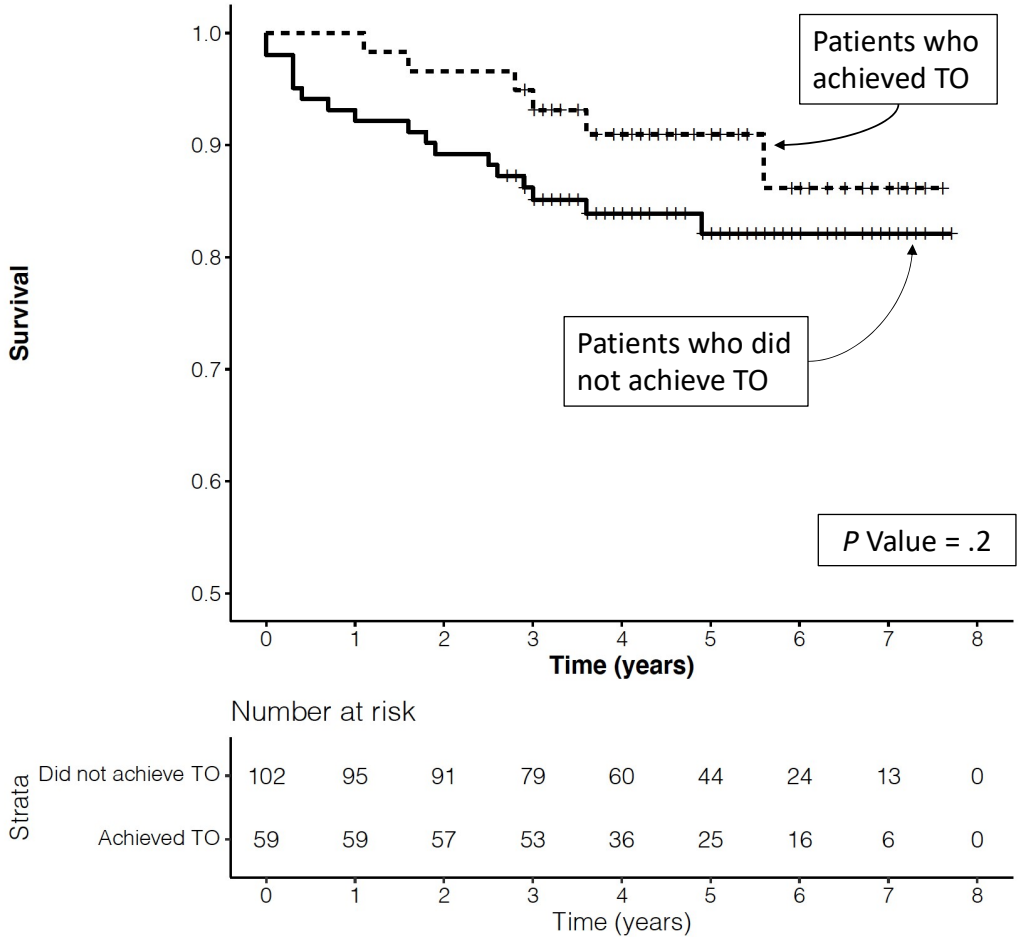

Figure 4. Overall survival according to Textbook Outcome (TO) in patients undergoing Enhanced Recovery After Liver Transplantation. Patients who died during the first 90 days were excluded from the analysis