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# Outcome of Liver Retransplantation in a Combined Pediatric and Adult Transplant Program —An Initial Experience in Copenhagen—

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**Abstract**：Background：Despite generally poor outcomes for liver retransplantation, this is still the only therapeutic option in recipients whose primary graft has failed. The purpose of this study was to analyze the outcome of liver retransplantation performed at a single center in an attempt to identify risk factors associated with patient survival and to assess both morbidity and the causes of death.

Materials and methods：Between October 1990 and December 2002, 46 patients underwent 54 liver retransplantations at Rigshospitalet, University of Copenhagen. The survival data were stratified and multivariate analyses were conducted to identify variables associated with the outcome after retransplantation.

Results:The 90–day, 1－, and 5–year patient survival rates after retransplantation were 60.4%, 55.4% , and 43.8% , respectively, with the biggest drop in survival probability occurring 90 days after retransplantation. These survival rates were significantly worse than those following single transplantation during the same period. However, the results tended to improve in the latter phase of our program, especially when considering an urgent retransplantation. A multivariate analysis identified only two variables that demonstrated an independent prognostic value when estimating the long–term survival after retransplantation: namely, the operation time and the preoperative coagulation factor. The Cox model was highly predictive of subgroups of patients with little chance of surviving.

Conclusions:Our findings stress the importance of the preoperative levels of coagulation factor and the operative duration on the results after retransplantation. We believe that these findings should assist in the rational selection of patients suitable for retransplantation.

**Key words：Liver retransplantation, Patient survival, Multivariate analysis, Cox model**

## Introduction

Since the liver transplant program in Rigshospitalet was initiated in October 1990, liver transplantation (LT) is now offered routinely to patients with advanced liver failure in Denmark.[1)] As more patients have survived long after their primary LT, eventual graft failure has occurred and liver retransplantation (re–LT) is now being required increasingly more often. Re–LT has been reported to be necessary in 9% to 29% of patients who receive primary grafts.[2)–5)] The overall results after re–LT are inferior to those following the primary allograft.[4)5)] Although recent reports have showed an improved survival after re－LT, especially when considering "non–urgent" re–LT,[5)] it remains unclear regarding whether re–LT

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should be performed without any restrictions for the optimal utilization of limited donor organs.

In order to clear up these questions, several studies have addressed the indications for re-LT.[5)-7)] In Denmark donor availability has until now not been considered a great problem, thus resulting in short waiting times and consequently, a low mortality of recipients on the waiting list.[2)8)] For this reason, despite inferior results in patients receiving multiple grafts, re-LT has liberally been considered an appropriate clinical option in our program. However, the number of patients requiring re-LT is expected to grow as the patients who received their primary grafts survive long enough to develop graft dysfunction, resulting in a reduced access to LT for patients awaiting their first LT. Therefore, current liberal re-LT provisions should be reconsidered to maximize the benefits of organ allocation. The aim of this study was to assess the short- and long-term outcomes of our approach to re-LT. To this end, we attempted to define a mathematical model that would help improve the survival of retransplanted patients.

## Materials and methods

**Population**：Between October 1990 and December 2002, 402 consecutive LT were performed on 348 patients at Rigshospitalet, University of Copenhagen. Forty-six patients (27 males and 19 females) were retransplanted with 54 liver allografts and constitute the basis of this study. The median age at re-LT was 44 years (range, 0 to 66 years). Six patients required multiple re-LTs (third graft, n=4; fourth graft, n=2). Seventeen patients who underwent a multi-organ transplantation (combined with kidney, lung, or heart) were excluded.

The median follow-up time after the re-LT was 8.5 months (range, 1 day to 9.2 years). Adult patients (18 years of age or older) comprised 78.3% (n=36) and child patients (under 18 years) comprised 21.7% (n=10) of the series. Forty-one of the second allografts were full-size livers, and five were reduced-size livers from cadavers.

**Study design**：The entire cohort was further divided into two different time periods：phase Ⅰ re-LT (between October 1990 and December 1996, n=18); and phase Ⅱ re-LT(between January 1997 and December 2002, n=28). All candidates for re-LT were categorized as urgent (n=19) or elective (n=27) recipients. Patients listed as urgent in the Nordic Liver Transplant Registry had absolute priority for any donor liver for 72 hours following listing.[9)] The following variables for the 46 retransplanted patients were studied：age group (adult vs. child), sex, primary diagnosis, indication for re-LT, interval to re-LT, urgency (urgent vs. elective) of re-LT, status (at home vs. hospitalization) at re-LT, requirement of respiratory support before re-LT, immunosuppression (cyclosporine-base vs. taclorimus-base) after the re-LT, and preoperative laboratory parameters including the levels of serum coagulation factor (Ⅱ, Ⅶ, Ⅹ) which is the parameter of the synthetic ability of liver, total bilirubin, creatinine, and thrombocyte. Donor variables were age, sex, ABO-matching, and length of stay in the intensive care unit (ICU) before procurement. Factors concerning the surgical technique were the operation time, blood loss during operation, cold ischemic time, and type of allograft (full-size vs. reduced-size).

**Patient morbidity and death**：The incidence of various complications after re-LT were assessed, including biliary complications, vascular complications, bleeding complications, infectious complications, rejection, sepsis, and organ failure. Biliary complications included bile leakage and biliary strictures (anastomotic or ischemic type non-anastomotic biliary lesion). Vascular complications included hepatic artery thrombosis, portal vein thrombosis, and venous outflow obstruction. Bleeding complications were defined as any postoperative bleeding that necessitated reoperation. Infectious complications included cholangitis, liver abscess, and pulmonary infection. Sepsis was distinguished from infectious complications and confirmed by a positive blood culture. Rejection included episodes of acute or chronic rejection. Organ failure was defined as organ insufficiency requiring an auxiliary organ support system. The assignment for cause of patient death was made based on the determination of the most likely precipitating event.

**Statistic analysis**：Comparison of variables was performed using the chi-squared test, Fisher's exact test, or the Mann-Whitney *U* test where

appropriate. Survival analyses were performed using the Kaplan–Meier method and compared by means of the log–rank test. All variables with *p* less than 0.1 were entered into the Cox proportional hazard model for time–dependent analysis and logistic regression analysis for binary outcomes, using forward and backward stepwise selection to identify independent risk factors. Missing variables were not included. For all tests, a *p* value of $<0.05$ was considered significant. All analyses were carried out using SPSS Ⅱ version 11.0.1 for Windows (SPSS Inc., Chicago IL).

## Results

The leading indication for re–LT was chronic rejection (n=12, 28%), followed by vascular complications (n=8, 19%), primary non–function (PNF) (n=7, 16%), biliary complications (n=6, 14%), liver abscess (n=4, 9%), and acute rejection (n=2, 5%). The incidence of re–LT was 13.4%. Ninety–day, 1–, and 5–year survival rates of patients who underwent the first re–LT were 60.4, 55.4, and 43.8% , respectively (Fig. 1). These survival rates were significantly lower than those of patients undergoing single LT during the same period, with 90 –day, 1–, and 5–year patient survival rates of 85.3, 77.2, and 70.1%, respectively. ($p<0.0001$ ; Fig. 1).

*Short－term survival*

As seen in Figure 1, the survival curves for re-transplanted patients showed that the major adverse events tended to occur in the first 90 days after re–LT. Twenty–five (56.8%) patients died after re–LT and 18 (72%) of these patients died within 90 days. When all patients who died within 90 days after the operation were excluded, there was no significant differences in the patient survival between re–LT and single LT ($p=0.2$). The factors associated with the 90－day survival after re－LT are shown in Table 1 (univariate analysis).

Factors affecting the 90－day survival included high preoperative total bilirubin ($p=0.009$), thrombocytopenia ($p=0.006$), decreased coagulation factor ($p=0.001$), long operation time ($p=0.01$), hospitalization (ward or ICU–bound) before re–LT ($p=0.01$) , preoperative respiratory assistance ($p=0.04$), and urgent re–LT ($p=0.03$). The indications for re－LT ($p=0.06$) and ABO–mismatching ($p=0.06$) were borderline risk factors.

On the other hand, the primary diagnosis, recipient age group, sex, preoperative creatinine, interval to re–LT, cold ischemic time, immunosuppressant after re–LT, donor age, sex, length of ICU stay before procurement, type of graft, and intraoperative blood loss had no influence on the 90–day survival. Am multivariate analysis showed coagulation factor to be the sole independent predictor of

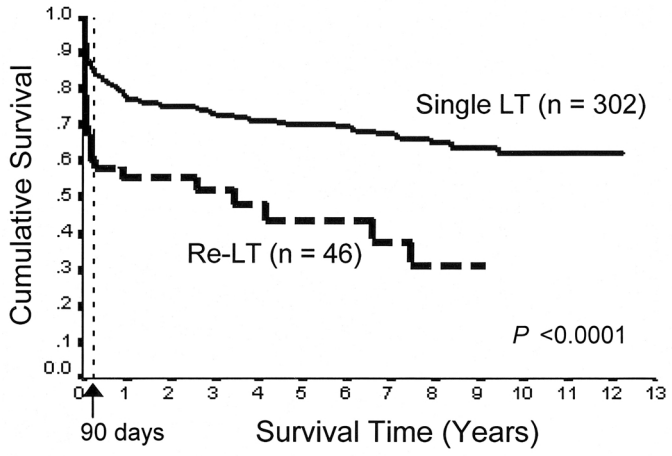


**Fig. 1.** Overall patient survival after re–LT showing the biggest drop in the first 90 days.

**Table 1.** Comparison of the recipient, donor, and surgical variables between the 90-day survivors (n=26) and nonsurvivors (n=18) after re-LT.

| Variable | Survivors (>90 days) | Nonsurvivors (<90 days) | *p* value |
|---|---|---|---|
| Recipients : | | | |
| Age group (Adult : Child) | 5.5 : 1.0 | 2.0 : 1.0 | 0.27 |
| Sex (M : F) | 1.6 : 1.0 | 1.25 : 1.0 | 0.93 |
| Primary diagnosis | | | 0.72 |
| Cirrhosis | 52.2% | 66.7% | |
| FHF | 30.4% | 16.7% | |
| Neoplasm | 8.7% | 11.1% | |
| Other | 8.7% | 5.6% | |
| Indications for re-LT | | | 0.06 |
| Rejection | 43.5% | 22.2% | |
| PNF | 4.3% | 33.3% | |
| Thrombosis | 17.4% | 11.1% | |
| Cholestasis | 26.1% | 11.1% | |
| Other | 8.7% | 22.2% | |
| Immunosuppressant | | | 0.46 |
| Cyclosporine-base | 54.5% | 72.7% | |
| Tacrolimus-base | 45.5% | 27.3% | |
| Status at re-LT | | | 0.01 |
| At home | 64.0% | 22.2% | |
| Hospitalized (Ward or ICU-bound) | 36.0% | 77.8% | |
| Urgency of re-LT | | | 0.03 |
| Urgent | 23.1% | 61.1% | |
| Elective | 76.9% | 38.9% | |
| Preoperative ventilation | 13.6% | 44.4% | 0.04 |
| Interval to re-LT (day) | 289.5 (2-2498) | 71 (2-3047) | 0.32 |
| Coagulation factor (Ⅱ, Ⅶ, Ⅹ) (U/L) | 0.9 (0.4-1.5) | 0.355 (0.1-1.5) | 0.001 |
| Total bilirubin (μm/L) | 81.5 (15-922) | 324.5 (53-893) | 0.009 |
| Creatinine (μm/L) | 109 (54-211) | 139.5 (31-438) | 0.2 |
| Thrombocyte (1,000/μl) | 203 (42-575) | 71.5 (23-393) | 0.006 |
| Donors : | | | |
| Age (yr) | 35 (4-72) | 44 (1-68) | 0.46 |
| Sex (M : F) | 1.27 : 1.0 | 3.25 : 1.0 | 0.21 |
| ICU stay (hr) | 24 (5-102) | 24 (11-192) | 0.77 |
| ABO-matching | | | 0.06 |
| Identify | 86.4% | 52.9% | |
| Compatible | 13.6% | 41.2% | |
| Incompatible | 0% | 5.9% | |
| Surgical : | | | |
| Type of graft | | | 0.15 |
| Full-size | 95.7% | 77.8% | |
| Reduced-size | 4.3% | 22.2% | |
| Operation time (min) | 350 (200-750) | 515 (285-680) | 0.01 |
| Blood loss (L) | 6 (1.5-20) | 6.5 (4-116) | 0.27 |
| Cold ischemic time (hr) | 11 (7-17) | 10 (7.1-20) | 0.98 |

Categorical variables are presented as the numbers with percentages or ratios. Continuous variables are presented as the median with range. Abbreviations : FHF, fulminant hepatic failure ; re-LT, liver retransplantation : PNF, Primary non-function ; ICU, intensive care unit.

**Table 2.** Logistic regression analysis for 90-day mortality after re-LT

| Variable | Regression Coefficient | 95% CI | *p* value |
|---|---|---|---|
| Coagulation factor (Ⅱ, Ⅶ, Ⅹ) (U/L) | −4.681 | 0.000 − 0.241 | 0.005 |

Abbreviation : CI, confidence interval.

**Table 3.** Complications and causes of death for the 90-day survivors (n=26) and nonsurvivors (n=18) after re-LT

| | Whole series | Survivors (>90 days) | Nonsurvivors (<90 days) | *p* value |
|---|---|---|---|---|
| Complications | | | | |
| Infectious complication | 12 (26.1%) | 8 (30.8%) | 4 (22.2%) | 0.50 |
| Organ failure | 11 (23.9%) | 5 (19.2%) | 6 (33.3%) | 0.49 |
| Rejection | 8 (17.4%) | 5 (19.2%) | 3 (16.7%) | >0.99 |
| Biliary complication | 8 (17.4%) | 6 (23.1%) | 2 (11.1%) | 0.43 |
| Sepsis | 8 (17.4%) | 4 (15.4%) | 4 (22.2%) | 0.71 |
| Bleeding complication | 8 (17.4%) | 5 (19.2%) | 3 (16.7%) | >0.99 |
| Vascular complication | 4 (8.7%) | 4 (15.4%) | 0 (0%) | 0.12 |
| Cause of death | | | | 0.02 |
| MOF | 7 (28%) | 4 (57.1%) | 3 (16.7%) | |
| Sepsis | 5 (20%) | 0 (0%) | 5 (27.8%) | |
| Neurologic | 5 (20%) | 0 (0%) | 5 (27.8%) | |
| Cardi ac | 4 (16%) | 0 (0%) | 4 (22.2%) | |
| Recurrence | 2 (8%) | 2 (28.6%) | 0 (0%) | |
| Other | 2 (8%) | 1 (14.3%) | 1 (5.6%) | |

Variables are presented as the number of complications or the number of patients in the case of death after re-LT. Abbreviation : MOF, multiple organ failure.

90-day mortality after re-LT (Table 2).

*Complications and causes of death*

Thirty-four (79.1%) of all retransplanted patients developed 59 complications after re-LT. Infectious complications (26.1%) and organ failure (23.9%) were the leading complications after re-LT. Rejection was more common in patients undergoing urgent re-LT ($P$=0.004). There was no significant difference in the incidences of the different complications between 90-day survivors and nonsurvivors after the re-LT (Table 3). The complication rate tended to decrease in the latter phase (phase I, 94.4% vs. phase II, 68%; $P$=0.06). Multiple organ failure (MOF) (n=7;28%) was the most common cause of death after re-LT, followed by sepsis (n=5;20%) and neurologic disorder (cerebral bleeding, n=2; brain edema, n=2; brain abscess, n=1;20%). Most deaths from sepsis and neurological and cardiac disorders occurred in the first 90 days after re-LT ($P$=0.02; Table 3).

*Long-term survival and prognostic modeling*

Comparing the patient survival rates after re-LT between phase I (1990-1996) and phase II (1997-2002), the results tended to improve in phase II, with 90-day, 1-, and 5-year survival rates of 50, 44.4, and 38.9% in phase I and 67.7, 62.8, and 39.3% in phase II (Fig. 2A). The patient survival rates following urgent re-LT were inferior to those fol-

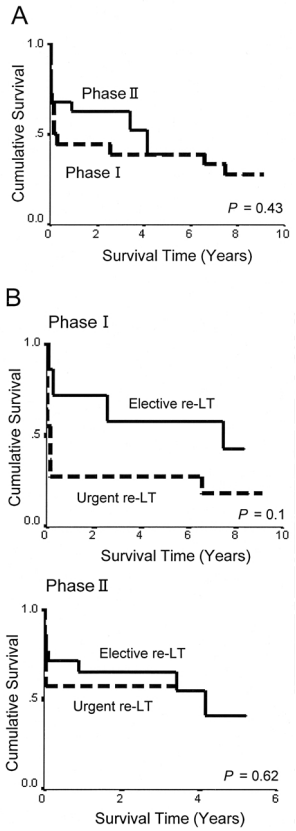


**Fig. 2.** Kaplan-Meier patient survival according to the different time periods in which re-LT was performed. (A) Patient survival after re-LT according to time period (phase I: 1990-1996, and phase II: 1997-2002). (B) Patient survival following patient stratification into urgent and elective retransplantation for each time period.

lowing elective re–LT, although these differences were not statistically significant ($p=0.09$). Furthermore, the patient survival tended to increase for urgent re－LT in the latter phase (urgent vs. elective in phase Ⅰ; $p=0.1$, in phase Ⅱ; $p=0.62$; Fig. 2B).

Seven variables were found to be significantly associated with the long–term outcome of the patient (univariate analysis ; Table 4). The only two factors independently associated with a poor outcome were a low level of coagulation factor at the time of re–LT and a long operation time (multivariate analysis ; Table 4). There was no difference in operation time according to the graft type. The Cox model allows the calculation of the mortality risk score according to the following formula：risk score ＝0.006* operation time (each increase of 1 minute) －2.919* coagulation factor (each increase of 0.01 U/L). The resulting Cox equation for estimating the 5－year survival in retransplanted patients is shown：$estimated\ survival=0.4375^{exp\ (R-0.51315)}$, where 0.4375 is the mean 5－year patient survival after re–LT and $R$ is the individual patient risk score. The mean overall risk score for the study group was 0.51315 (range, －2.4001 to 3.4962).

This survival model can be used to predict our patient survival after re–LT. In order to demonstrate the patient survival after re–LT according to risk score groups, we further stratified our patients into 3 groups based on model–predicted risk scores with an equal range for each group：low－risk group ($<-0.43467$), moderate–risk group (between $-0.43467$ and 1.53077), and high–risk group ($>1.53077$). As shown in Figure 3, the outcome of re–LT was far worse in the high–risk group in comparison to the other groups (high–risk vs. low–risk ; $P<0.0001$, and high–risk vs. moderate－risk ; $P=0.004$). All patients within the high–risk group (n＝8) died within the first 90 days after re–LT. On the other hand, the outcomes in the low–risk groups were comparable to those after single LT ($P=0.97$).

## Discussion

We focused on liver re–LT in our whole series with the aim of helping to predict survival and to improve the presently poor survival rates. The rate of liver re–LT in our program (13.4%) is similar to that reported in another registry (9–22%)[2)–5)] and the patient mortality after re–LT in this series (55.4 and 43.8% for 1– and 5–year survival, respectively) is comparable to that of other series (48－72 and 42–65% for 1– and 5–year survival, respectively).[4)10)–12)] In most series, the survival rates of retransplanted patients are still inferior to those of patients receiving an initial graft；the present study corroborated those observations. However, in our program, it is noteworthy that the results tended to improve after re–LT in the latter phase, especially when considering urgent situations. Advances in the field of perioperative management for emergency patients in extremely poor condition may have contributed to these improved results in the latter phase. In fact, the recent introduction of high–volume plasmapheresis,[13)] cerebral microdialysis,[14)] and a molecular adsorbents recirculating system[15)] to high risk patients is considered to have contributed to the better results after LT.

Although factors associated with poor outcomes in re–LT have been previously reported,[10)11)16)] very few studies have focused on all potential factors associated with the donor, the recipient, and the operation. In clinical practice, a number of prognostic factors synchronously have influence the outcome following re–LT. Therefore, we attempted to assess all factors available at re–LT. The biggest drop in survival occurred in the first 90 days after re–LT, thus suggesting that perioperative factors are strongly related to the outcome. We found that coagulation factor to be the sole independent risk factor for 90–day survival after re–LT. The adverse influence of this factor associated with the short–term survival of patient has also received attention in a previous study.[5)] The patients with severe coagulopathy in the present study had extremely poor conditions with hospitalization (ward or ICU－bound) and were hemodynamically unstable with multiorgan failure at re–LT (data not shown). Consequently, the short–term mortality was significantly higher in these patients.

The most important complication after re–LT was infection. Sepsis and neurologic disorder were the leading causes of death within 90 days af-

**Table 4.** Variables with univariate and multivariate (Cox regression) sigmificance regarding patient survival after re-LT

| Variable | Umivariate analysis | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|
| | Relative hazard | 95%CI | *P* value | Log hazard | Relative hazard | 95%CI | *p* value |
| Coagulation factor (Ⅱ, Ⅶ, Ⅹ) (U/L) | 0.125 | 0.034－0.459 | 0.002 | －2.919 | 0.054 | 0.008－0.348 | 0.002 |
| Bilirubin (μm/L) | 1.002 | 1.000－1.003 | 0.02 | | | | NS |
| Creatinine (μm/L) | 1.007 | 1.002－1.011 | 0.006 | | | | NS |
| Hospitalized or ICU-bound (y/n) | 2.510 | 1.056－5.968 | 0.04 | | | | NS |
| PNF as indication for re-LT (y/n) | 3.388 | 1.276－8.994 | 0.01 | | | | NS |
| Operation time (min) | 1.004 | 1.001－1.007 | 0.009 | 0.006 | 1.006 | 1.001－1.010 | 0.01 |
| Blood loss (L) | 1.000 | 1.000－1.000 | 0.04 | | | | NS |

Abbreviations : CI, confidence interval ; ICU, intensive care unit ; PNF, primary non-function ; re-LT, liver retransplantation ; NS, not significant.

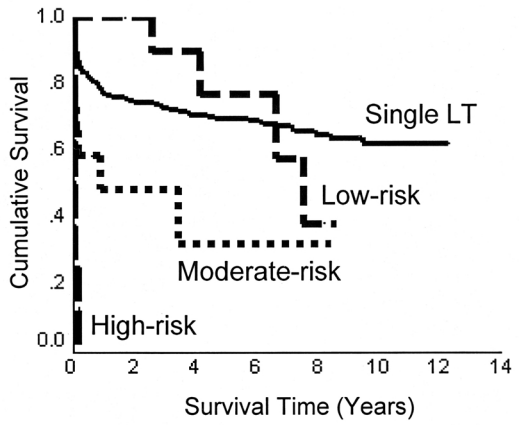


**Fig. 3.** Patient survival based on a comparison of single LT to re-LT in high-risk, moderate-risk, and low-risk groups. Each risk group is defined by a risk score : of <— 0.43467 for low-risk, between －0.43467 and 1.53077 for moderate－risk, and ＞1.53077 for high-risk, respectively.

ter re-LT, and this finding is consistent with previous reports.[10)11)] The extremely poor condition of these patients before re-LT has been attributed as the cause of death from sepsis after re-LT.

The coagulation factor, which helped to predict 90-day survival, was also found to predict the long-term survival, thus indicating that the existence of adverse events in the first 90 days after re-LT affect the long-term outcome of retransplanted patient. This was confirmed by the result that the outcome of 90-day survivors after re-LT was comparable to that after single LT. We further demonstrated that a long operation time was also an independent risk factor associated with the long-term survival of patient. Some authors have found a poorer long-term outcome in retransplanted patients who had higher bilirubin and creatinine levels before re-LT,[5)-7)] however, we found no such influence. One explanation for this discrepancy could be that variables such as coagulation factor level and operation time, which have not been examined simultaneously in some previous reports, have more explanatory power than preoperative creatinine and bilirubin levels. Interestingly, prolonged cold ischemic time, a well-known risk factor for graft and patient survival after LT,[6)17)] failed to achieve significance in our study. Presumably, this is reflective of the fact that the majority of our patients (98%) received second grafts that had been preserved for less than 18 hours. In addition, some reports have demonstrated a close relationship between the warm ischemic time and the anhepatic phase of recipient with outcome after LT.[18)-20)] Although we did not focus on these factors, the long operation time may be responsible for the prolonged warm ischemic time and anhepatic phase.

By incorporating these two factors into the final model, we defined a mathematical equation that adequately predicts survival after re-LT. In order to demonstrate the graded survival curves according to individual risk scores, we further stratified our population into 3 groups based on model-pre-

dicted risk scores. The high-risk group (risk score >1.53077) had far worse outcomes, with a 90-day survival rate of 0%. Therefore, we suggest that re-LT should at least be avoided in the subgroup of high-risk patients because of their very slight chance of survival. On the other hand, re-LT is fully justifiable when performed on patients without either risk factor (low-risk group), coagulopathy or long operation time. Unfortunately, our Cox model has one important drawback as a preoperative predictor of patient survival : namely, it is difficult to estimate the exact operation time preoperatively. When a patient has severe coagulopathy and is facing re-LT under a situation expected to increase length of operation time such as re-LT with a long interval from first LT or with a technical challenge, re-LT should therefore be considered with extreme caution, if not contraindi cated. Under the current "Model for End-Stage Liver Disease" system based on "sickest first" policy at LT,[21] the clinical condition of most recipients will be too poor to undergo re-LT. Therefore, we propose that re-LT must be indicated before deterioration of the patient's condition. Of course, our Cox model may require modification depending on improvements in patient survival that come with future advances in surgical techniques, immunosuppression, and perioperative management. In addition, although such a model as presented herein should assist the clinical decision-making for the rational selection of patients suitable for re-LT, the decision not to perform re-LT in a high-risk patient should be determined on an individual basis based on clinical experience, morals, and ethics.

The differences between the patient survival after a single LT and that after re-LT can not yet be fully explained by the present study, but could be partially explained by the number of patient deaths during first 90 days after re-LT, caused by poor clinical conditions at the time of re-LT, especially in urgent situations. Although re-LT is still considered to be an effective therapy for many patients whose primary grafts have failed, strict patient selection and timely re-LT are necessary to achieve better results after re-LT.

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