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Impact of early reoperation on graft survival after liver transplantation: Univariate and multivariate analysis

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Abstract

Background: Data on rate, risk factors, and consequences of early reoperation after liver transplantation are still limited.

Study design: Single-center retrospective analysis of data of 428 patients, who underwent liver transplantation in period between January 2009 and December 2014. Univariate and multivariate analysis were used to study the risk factors of early reoperation and its impact on graft survival.

Results: Of 428 patients, 74 (17.3%) underwent early reoperation. Of them, 46 (62.2%) underwent reoperation within the first week and 28 (37.8%) underwent reoperation later than 1 week after transplantation. With multivariate analysis, significant risk factors of early reoperation included pretransplant ICU admission, previous abdominal surgery and diabetes. Early reoperation itself was not found to be an independent predictor of graft loss. However, early reoperation later than 7 days from transplant was found to be independent predictor of graft loss (odds ratio [OR] = 5.125; 95% CI, 1.358–19.552; $P = .016$). In our series, other independent predictors of graft loss were MELD score ($P = .010$) and operative time ($P = .048$).

Conclusions: This analysis demonstrates that early reoperations later than a week appear to negatively impact the graft survival. The timing of early reoperation should be a focus of additional studies.

Keywords

liver transplantation; graft survival; early reoperation

1 | INTRODUCTION

Liver transplantation (LT) is an established treatment for patients with acute or chronic liver failure. There have been continuous advances in surgical techniques, postoperative management, and immunosuppression protocols since the early era, resulting in significant improvement in survival rates.^{1,2} However, due to operative complexity and a substantially debilitated patient population, complications after LT remain common.³ Such complications range from minor events that require no intervention to severe complications that require operative intervention. Among them, the most common are hemorrhage, vascular thrombosis, biliary leakage, and intra-abdominal infections. Untreated, those complications can lead to graft failure and death.^{1,4} Reoperation is frequently required post- LT (9.2% to 34%) to treat these severe complications.^{5–9}

Studies from the general surgical literature have documented an increase in mortality after reoperation for postoperative complications.^{10–12} In LT, the impact of early reoperations on graft survival is still not well defined. Data on risk factors and consequences of early reoperation after liver transplantation are still limited.

The aim of this study was to investigate the incidence, indications of early reoperation, factors associated with early reoperation, and the impact on graft and recipient survival. We hypothesized that different complications and the timing of reoperation have different impact on patients' outcome.

2 | PATIENTS AND METHODS

We retrospectively studied all adult patients who underwent orthotopic liver transplantation at our single center in period between January 2009 and December 2014. To obtain a homogeneous group for analysis, we excluded those who received simultaneous liver/kidney or partial graft either living donor or split liver. All patient data were approved for use by the Institutional Review Board of Georgetown University Hospital. We defined 2 groups: group A included adult recipients who underwent early reoperation, and group B included those who did not undergo early reoperation. Early reoperation was defined as relaparotomy within 30 days of transplantation or within the same admission of transplant. Minor operations, such as tracheostomy and central venous access procedures, were excluded, as were operations not specifically related to the transplantation, such as inguinal hernia repairs.

2.1 | Post-transplant management

All patients were transferred intubated to ICU after transplant and extubated in postoperative day 1. Hourly arterial blood gases and full laboratory panel were drawn every 4 hours in first day then daily till discharge from the ICU. Duplex ultrasound was routinely performed in postoperative day 2 and day 4. Patients with history of hypercoagulability, small artery, or with donor arterial anomaly requiring reconstruction were anticoagulated with heparin intravenously (goal PTT 50– 60 seconds) and transitioned to oral anticoagulation for the subsequent 3 months.

2.2 | Post-transplant protocol for reoperation for bleeding

At our program, any recipient with post- transplant bleeding causing hemodynamic instability and/or requiring transfusion of 6 or more PRBC within the first 48 hours is taken back for surgical exploration.

2.3 | Immunosuppression

Immunosuppression consisted of tacrolimus, mycophenolate, and prednisone. Most patients were tapered to a single drug by 1 year. Basiliximab induction was used in subjects with renal insufficiency at LT or early acute kidney injury.

2.4 | Data management

We retrospectively reviewed our prospectively maintained transplant database of all patients. Recipient and donor demographics, operative notes, pathologic reports, patient and graft survival data, and operative complications were reviewed. Donor data were supplied by the United Network for Organ Sharing (UNOS). We also compared these data among the 2 identified groups.

2.5 | Definitions

Previous abdominal operation was defined as any abdominal surgery except laparoscopic cholecystectomy and appendectomy. Graft loss was defined as re transplant or patient death with a functioning graft. Cold ischemia time (CIT) was defined as the time from donor cross- clamping to the removal of the liver from the cold preservative solution preceding implantation. Warm ischemia time (WIT) was defined as the time from the removal of the liver from the cold preservative solution until portal reperfusion.

2.6 | Statistical analysis

Continuous variables were expressed as mean (standard deviation, SD) and compared by using the *t* test or expressed as median (range) and compared by using Mann-Whitney U-test depending on whether they were normally distributed or not. Categorical variables were expressed as percentages and compared using the chi-square test. The groups' patient and graft survival times were calculated by using the Kaplan-Meier method and compared using a log-rank test. Univariate and multivariate analysis were performed using the Cox regression models to identify predictors. Factors with $P = .010$ in a Cox proportional hazard model as a univariable analysis were considered potential predictors and were further analyzed in a multivariable Cox model. Hazard ratios (HR) and 95% confidential intervals (CI) were calculated for each factor. A P -value $< .05$ was considered significant. All statistical calculations were carried out by the computer program SPSS (Statistical Package for the Social Science) version 20 for Microsoft windows.

3 | RESULTS

Four hundred and seventy- five liver transplantations were performed in our center between January 2009 and December 2014. We studied 428 cases after excluding 34 simultaneous

liver/kidney, 10 split liver, and 3 living donor liver transplantations. Median follow-up time was 52.76 (18– 89.92) months.

3.1 | Recipient characteristics

The median age of our patients was 56 (range: 18–73) years, and 33.9% of recipients were female. Group A patients had higher history of DM, previous abdominal surgeries, MELD score, and pretransplant ICU admission. All recipient characteristics are shown in Table 1.

3.2 | Donor characteristics

Median age was 50 (12–88) years, and 40 % of donors were female. No significant differences were found in donor characteristics between the 2 groups apart from age, which was lower in group A, 46 (16–79) years compared to group B, 52 (12–88) years ($P = .0001$). All donor characteristics are shown in Table 2.

3.3 | Operative characteristics

Table 3 summarizes cold ischemia time (CIT), warm ischemia time (WIT), and intra-operative data in both groups. Group A had longer cold ischemia time and operative duration. Piggyback techniques and arterial reconstructions were used significantly more in group A compared to group B.

3.4 | Incidence and indications of early reoperation (Table 4)

Of the 428 patients, 74 (17.3%) underwent early reoperation. Forty-six (62.2%) underwent reoperation within the first week and 28 (37.8%) underwent reoperation later than 1 week after transplantation. Of these 28 cases, 8 cases started to have signs indicating intervention in the first week. Three cases of bleeding (early reoperation in postoperative days [POD] 8, 10, and 10) had multiple drops of their hematocrit that required blood transfusions in the first week. A case of hepatic artery stenosis (early reoperation in POD 20) underwent multiple attempts of interventional treatment. A case of hepatic artery thrombosis (early reoperation in POD 15) underwent 2 attempts of interventional treatment. A case of hepatic artery thrombosis (early reoperation in POD 9) started to have an increase in liver enzymes in POD 6. A case of hepatic artery pseudoaneurysm (early reoperation in POD 14) started to have fever and hematoma at porta hepatis in POD 6). A case of bile leak (early reoperation in POD 15) underwent multiple trials of interventional treatment. All of these 8 cases suffered from graft loss.

3.5 | Predictors of early reoperation

In multivariate analysis, significant risk factors of early reoperation included pre- transplant ICU admission (odds ratio [OR] = 5.324; 95% CI, 1.282–11.099; $P = .021$), history of previous abdominal surgery (odds ratio [OR] = 2.145; 95% CI, 1.047–4.393; $P = .037$), and history of diabetes (odds ratio [OR] = 2.548; 95% CI, 1.255–5.171; $P = .010$).

3.6 | Long term outcome

One-, 3-, and 5-year overall patient survival was 86%, 80%, and 78%, respectively, while overall graft survival was 84%, 77%, and 75%, respectively. One-, 3-, and 5- year patient

survival for group A was 81%, 74%, and 74% vs 87%, 81%, and 79% for group B ($P = .317$). One-, 3-, and 5-year graft survival for group A was 70%, 62%, and 55% vs 87%, 80%, and 79% for group B ($P = .039$). Early reoperation itself was not found to be an independent predictor of graft loss. However, early reoperation later than 7 days from transplant was found to be independent predictor of graft loss (odds ratio [OR] = 5.125; 95% CI, 1.358–19.552; $P = .016$) (Figure 1). In our series, other independent predictors of graft loss were MELD score (odds ratio [OR] = 1.035; 95% CI, 1.008–1.063; $P = .010$) and operative time (odds ratio [OR] = 1.004; 95% CI, 1.000–1.008; $P = .048$) (Table 5).

4 | DISCUSSION

The operative complexity and debilitated patient population of liver transplantation increase the incidence of reoperation. Several studies about the postliver transplantation complication rates, including early reoperation, have been reported; however, there are few reports of the factors associated with early reoperation and the impact of early reoperation on liver transplantation outcomes.

The nearly 17% early reoperation rate in our series is favorably comparable with other pre-MELD (34% to 44%)^{13,14} and post-MELD (17% to 26%) era series.^{5–7,15} Yoshiya et al reported 9.2% early relaparotomy rate after living donor liver transplantation.⁹ Previous reports indicated significantly inferior graft and patient survival rates of recipients with early reoperation^{5,9,13}; however, no multivariate analysis was performed to determine whether early reoperation is an independent predictor of patient and graft survival.⁵

In our series, the most common indication of early reoperation was postoperative hemorrhage followed by vascular flow complications. The rate of early reoperation due to bleeding (9.6%) is comparable with previous reported series in which the rate varied from 8% to 27%.^{5,8,13,16} Hemostatic balance is a concern for patients with liver failure and LT recipients.¹⁷ While routine laboratory tests of these patients show bleeding diathesis, they are actually in hemostatic balance, because both pro- and anti-hemostatic factors are affected and this is not well reflected in routine coagulation testing.¹⁸ However, this balance can easily be tipped toward a hypo- or hypercoagulable state.¹⁹ The high incidence of postoperative hemorrhage and vessel thrombosis as the cause of early reoperation is representing this situation. Further studies to investigate the ideal balance of coagulability are needed to decrease the incidence of early reoperation after LT.

Highlighting their critical illness, recipients requiring early reoperation had significantly greater MELD scores, need for pretransplant ICU, mechanical ventilation and vasopressors, and previous abdominal surgery. Not surprisingly, adhesions from earlier surgery in the setting of portal hypertension and coagulopathy increase the difficulty of dissection, the risk of bleeding, and operative time. Similar findings were reported by DiNorcia et al.⁵

We analyzed perioperative factors that might predict early reoperation as a step toward improving outcomes. In contrast to earlier reports,^{5,13,20} intra-operative blood loss was not a predictor of early reoperation after LT. Similar to a UCLA report,⁵ we found that pretransplant ICU admission and previous abdominal surgeries were predictors of early

reoperation. Another significant predictor of early reoperation in our series was history of diabetes.

Similar to an earlier report from UCLA,⁵ unadjusted Kaplan-Meier analysis demonstrated inferior graft survival in early reoperation group. However, when we used multivariate analysis in our study, we found that early reoperation was not an independent predictor of graft survival. Indeed, timing of the early reoperative intervention proved to be significantly related to graft survival. Early reoperation later than first week was found to be an independent predictor of graft loss. In assessing indications of procedures performed, there were no significant differences except that patients who underwent early reoperation within 7 days had higher rate of bleeding complications while those who underwent early reoperation later than 1 week had higher rate of SSI.

Ertel et al examined 10 295 adult liver transplant patients, using a linkage of the University Health System Consortium and Scientific Registry of Transplant Recipients databases, tracking relaparotomy rates within the first 90 days after LT. They found that early reoperations within first week or later were independent predictors of adjusted 1-year mortality. They examined the effect of operative timing on patients' outcomes. They found that patients undergoing delayed reoperation later than 30 days had 96% increased risk of 1-year mortality when compared to those undergoing reoperation within first 7 days. They were only able to capture those reoperations that occurred at the index transplantation center. They were not able to evaluate indications for early reoperations due to the lack of granularity within the dataset. They had a problem that many procedure codes were often included for a single reoperative intervention without awareness of the primary reason for reoperation. All operative procedure codes were treated equally.⁶

In the present study, we tried to evaluate the primary indication and the decision making surrounding each reoperation. We tried to answer the question, whether the increased graft loss seen with early reoperation later than 1 week could have been avoided by a timely intervention during the critical phase within the first week post-transplantation. Our data suggested that if those patients who started to have signs indicating intervention in the first week were managed correctly within the first 7 days, they might have had an opportunity for improved graft survival.

Indeed, there remains a group of patients who will require delayed reoperation due to late complications and, as a result, will continue to experience poor graft survival. Therefore, we should focus on those patients who may be potentially mismanaged in the immediate postoperative week, favoring a more conservative approach to avoid early take back. Surgeons must be more alert within the first week after liver transplant and prepared to intervene when patients show any signs necessitating a reoperation.

In the present study, we found that high MELD score was an independent risk factor for graft loss, while several other publications documented that MELD score cannot predict survival after liver transplantation.^{6,21-24} In contrast to previous reports,^{9,22,25} we found that HCV positive recipients and intra-operative blood loss were not associated with poorer graft survival after adjusting for other confounders.

The main limitation of this study is its retrospective, single-center design with small sample size. Although variation in patient management over time is a potential bias in any retrospective study, we minimized this effect by limiting the analysis to post-MELD era recipients. Another limitation is that the early reoperation group was a small inhomogenous cohort with various causes for reoperation, which may make the data inadequate to support the findings with a multivariate analysis of potential predictors of early reoperation. Further analyses with a large number of patients in a well- designed multicenter study are needed to clarify the impact of early reoperation on outcome.

5 | CONCLUSION

This analysis demonstrates that early reoperations performed later than a week after liver transplant appear to negatively impact the graft survival. This could support early intervention, rather than waiting, in the treatment of surgical complications after liver transplantation. Our study demonstrates that the timing of early reoperation should be a focus of additional studies, as those patients undergoing delayed reoperation had a significant increase in graft loss.

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FIGURE 1.
Graft survival

TABLE 1

Recipient characteristics

Recipient characteristics	Total (428)	Early reoperation Group A (74)	Nonearly reoperation Group B (354)	P value
Age	56 (18–73)	54 (18–72)	57 (18–73)	.010
Sex (Male: Female)	283 (66.1%): 145 (33.9%)	47 (63.5%): 27 (36.5%)	236 (66.7%): 118 (33.3%)	.602
Body mass index (kg/m ²)	26.8 (15.4–57.3)	27.6 (19.1–57.3)	26.5 (15.4–52.2)	.212
Previous abdominal surgery	109 (25.5%)	29 (39.2%)	80 (22.6%)	.003
Comorbidities				
Diabetes	116 (27.1%)	27 (36.5%)	89 (25.1%)	.046
Hypertension	196 (45.8%)	33 (44.6%)	163 (46%)	.820
Coronary artery disease	34 (7.9%)	5 (6.8%)	29 (8.2%)	.678
MELD	19 (6–40)	26 (6–40)	18 (6–40)	.0001
Pretransplant ICU	35 (8.2%)	12 (16.2%)	23 (6.5%)	.006
Pretransplant mechanical ventilator	18 (4.2%)	7 (9.5%)	11 (3.1%)	.013
Pretransplant vasopressors	8 (1.9%)	4 (5.4%)	4 (1.1%)	.014
Pretransplant dialysis	19 (4.4%)	4 (5.4%)	15 (4.2%)	.657
HCC	178 (41.6%)	22 (29.7%)	156 (44.1%)	.023
Liver disease				
Chronic liver disease	407 (95.1%)	64 (86.5%)	343 (96.9%)	.0001
Acute liver failure	16 (3.7%)	6 (8.1%)	10 (2.8%)	.029
Retransplant	5 (1.2%)	4 (5.4%)	1 (0.3%)	.0001

Bold indicates $P < .05$.

TABLE 2

Donor characteristics

Donor characteristics	Total (428)	Early reoperation Group A (74)	Nonearly reoperation Group B (354)	P value
Age	50 (12–88)	46 (16–79)	52 (12–88)	.0001
Sex	257 (60%); 171 (40%)	40 (54.1%); 43 (45.9%)	217 (61.3%); 137 (38.7%)	.247
Race				
White	222 (51.9%)	38 (51.4%)	184 (52%)	.184
African American	154 (36%)	24 (32.4%)	130 (36.7%)	
Hispanic	33 (7.7%)	10 (13.5%)	23 (6.5%)	
Asian	19 (4.4%)	2 (2.7%)	17 (4.8%)	
Height (cm)	170 (109–198)	170 (142–196)	170 (109–198)	.349
Cause of death				
Head trauma	115 (26.9%)	13 (17.6%)	102 (28.8%)	.155
CVA	207 (48.4%)	37 (50%)	170 (48%)	
Anoxia	95 (22.2%)	21 (28.4 %)	74 (20.9%)	
Others	11 (2.6%)	3 (4.1%)	8 (2.3%)	
Donation after cardiac death (DCD)	43 (10%)	7 (9.5%)	36 (10.2%)	.853
BMI	27.47 (16.22–63.78)	27 (18.59–49.96)	27.64 (16.22–63.78)	.171
Peak Na	154 (134–271)	155 (137–177)	154 (134–271)	.860
Peak ALT	44 (10–7469)	46 (12–3379)	43 (10–7469)	.405
Donor DM	76 (17.8%)	9 (12.2%)	67 (18.9%)	.303
Donor HTN	182 (42.5%)	27 (36.5%)	155 (43.8%)	.451
Donor CMV	276 (64.5%)	47 (63.5%)	229 (64.7%)	.848

Bold indicates $P < .05$.

TABLE 3

Operative characteristics

Operative characteristics	Total	Early reoperation Group A (74)	Nonearly reoperation Group B (354)	P value
Technique				
Conventional	412 (96.3%)	68 (91.9%)	344 (97.2%)	.029
Piggyback	16 (3.7%)	6 (8.1%)	10 (2.8%)	
CIT (hours)	5.8 (0.8–11.9)	6.2 (2.9–11.5)	5.7 (0.8–11.9)	.039
WIT (minutes)	36 (16–55)	36 (23–54)	36 (16–55)	.814
Arterial ischemia time (min)	36 (18–140)	32 (18–134)	37 (18–140)	.124
Operative duration (hours)	6.1 (3.5–11.7)	6.9 (3.5–11.7)	6 (3.6–9.8)	.012
EBL (estimated blood loss in cc)	2500 (50–45 000)	3000 (100–20 000)	2500 (50–45 000)	.177
Biliary anastomosis				
Duct to duct	384 (89.7%)	64 (86.5%)	320 (90.4%)	.314
Hepaticojejunostomy	44 (10.3%)	10 (13.5%)	34 (9.6%)	
Arterial reconstruction	22 (5.1%)	8 (10.8%)	14 (4%)	.015

Bold indicates $P < .05$.

TABLE 4

Indications of early reoperation

Indications of early re operation	Total (74 cases)	Early reoperation after 7 d (28 cases)	Early reoperation within first 7 d (46 cases)	P value
Bleeding	41 (55.3%)	7 (25%)	34 (73.9%)	.001
Vascular flow complications	15 (20.3%)	7 (25%)	8 (17.4%)	.430
Hepatic artery thrombosis	8	3	5	
Hepatic artery stenosis	2	1	1	
Hepatic artery pseudoaneurysm	2	2	0	
Portal vein thrombosis	2	1	1	
False hepatic artery thrombosis	1	0	1	
Bowel related	6 (8.1%)	4 (14.3%)	2 (4.3%)	.129
Bowel obstruction	4	3	1	
Bowel perforation	2	1	1	
Surgical site infection (SSI)	3 (4.1%)	3 (10.7%)	0	.023
Biliary complications	2 (2.7%)	1 (3.6%)	1 (2.2%)	.719
Feeding	2 (2.7%)	2 (7.1%)	0	.066
Dehiscence	2 (2.7%)	2 (7.1%)	0	.066
Others	3 (4.1)	2 (7.1%)	1 (2.2%)	.293

Bold indicates $P < .05$.

TABLE 5

Univariate and multivariate analysis of predictors of graft survival

Variables	Univariate analysis			Multivariate analysis		
	Number	P value	HR (95%CI)	P value	HR (95%CI)	
Early reoperation						
Yes	74	.0001	2.345 (1.497–3.673)	.317	1.855 (0.552–6.250)	
No	354					
Early reoperation later than 7 d						
Yes	28	.0001	2.948 (1.639–5.303)	.016	5.125 (1.358–19.552)	
No	400					
Early reoperation for bleeding						
Yes	41	.102	1.712 (0.952–3.080)			
No	387					
Early reoperation for vascular flow complications						
Yes	15	.0001	3.986 (2.002–7.934)	.564	1.521 (0.366–6.318)	
No	413					
Recipient variables						
Age						
>60	123	.122	1.407 (0.913–2.170)			
60	305					
MELD		.001	1.034 (1.014–1.054)	.010	1.035 (1.008–1.063)	
Pretransplant ICU						
Yes	35	.985	0.993 (0.459–2.145)			
No	393					
Pretransplant dialysis						
Yes	19	.151	1.839 (0.801–4.218)			
No	409					
Pretransplant ventilators						
Yes	18	.307	1.601 (0.650–3.945)			
No	310					
Pretransplant vasopressors						

Variables	Number	Univariate analysis		Multivariate analysis	
		P value	HR (95%CI)	P value	HR (95%CI)
Yes	8	.138	2.395 (0.756–7.585)		
No	320				
HCC					
No	250	.871			
Yes	178		1.035 (0.685–1.563)		
Previous abdominal surgery					
Yes	109	.230	1.312 (0.842–2.046)		
No	319				
DM					
Yes	116	.782	0.936 (0.588–1.491)		
No	312				
Acute liver failure					
Yes	16	.753	0.831 (0.263–2.627)		
No	412				
HCV					
Yes	197	.025	1.602 (1.061–2.419)	.123	1.529 (0.892–2.623)
No	231				
Donor variables					
Age					
>50	212	.192	1.315 (0.872–1.985)		
<50	216				
Race					
White	222	.648	1.156 (0.620–2.157)		
African American	154	.229	0.653 (0.327–1.306)		
Others	52				
Height					
Cause of death		.510	0.997 (0.989–1.006)		
Head trauma	115	.111	1.439 (0.934–2.218)		
Others	333				
DCD					

Variables	Number	Univariate analysis		Multivariate analysis	
		P value	HR (95%CI)	P value	HR (95%CI)
Yes	43	.305	1.374 (0.749–2.521)		
No	385				
Hepatic artery anatomy					
Abnormal	305	.157	1.363 (0.887–2.093)		
Normal	123				
Operative variables					
CIT					
>8 h	48	.130	1.610 (0.869–2.982)		
8 h	380				
WIT					
>50 min	23	.057	2.136 (0.978–4.665)	.220	1.845 (0.693–4.915)
50 min	405				
Arterial reperfusion time					
Technique		.927	1.001 (0.990–1.011)		
Piggyback	16	.312	1.593 (0.646–3.924)		
Conventional	412				
Arterial conduit or reconstruction					
Yes	22	.449	0.641 (0.203–2.027)		
No	406				
Estimated blood loss (EBL)		.082	1.000 (1.000–1.000)	.406	1.000 (1.000–1.000)
Operative duration		.047	1.003 (1.000–1.006)	.048	1.004 (1.000–1.008)

Bold indicates $P < .05$.