ORIGINAL ARTICLE

Assessing living donor liver transplantation outcomes through international collaboration: The Dow University experience with "the transplantation society and international liver transplantation society (TTS-ILTS) paired transplant centres programme" activity.

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Abstract

Objective: To compare the survival status and postoperative complications in liver transplant recipients in a tertiary care setting before and after the introduction of a collaborative programme.

Method: The retrospective study was conducted at the Liver Transplant and Hepatopancreatobiliary Surgery Unit of the Dow University of Health Sciences, Karachi, and comprised data of patients who underwent liver transplantation between May 2015 and December 2024. The Transplantation Society and International Liver Transplantation Society (TTS-ILTS) paired transplant centers programme was introduced in September 2023, and, as such, patients who underwent the operation till August 2023 were placed in group A, and the rest were placed in group B. Patient characteristics, including demographics, operative details and postoperative complications, were compared between the groups. Data was analysed using SPSS 22.

Results: Of the 177 patients, 124(70.1%) were in group A; 101(81.5%) males and 23(18.5%) females with median age 45 years (interquartile range: 35-52 years). There were 53(29.9%) patients in group B; 41(77.4%) males and 12(22.6%) females with median age 44 years (interquartile range: 38-52 years) ($p>0.05$). Postoperative complications, like pleural effusion and postoperative pneumonia, were significantly lower in group B compared to group A ($p<0.05$). The estimated survival rates at 1, 3 and 12 months were higher in group B, but the difference was not significant ($p>0.05$).

Conclusion: The introduction of the collaborative programme had a positive impact on the outcomes of liver transplant cases.

Key Words: Living donor liver transplantation, LDLT, Survival outcomes, Postoperative complications, Mentoring, Learning curve.

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Introduction

Living donor liver transplantation (LDLT) has emerged as a crucial treatment modality to address the shortage of deceased donation.[1] It has demonstrated excellent post-transplant and long-term survival outcomes.[2] The LDLT programmes in Pakistan have exemplified a significant advancement in healthcare, resulting in the establishment of an increasing number of liver transplant facilities across the country over a period of decades.[3] The Liver Transplant and Hepatopancreatobiliary (LT&HPB) Unit of the Dow University of Health Sciences (DUHS) in Karachi has become a significant contributor to the expansion of liver transplant services in Pakistan.

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Regardless of the successes of LDLT in Pakistan, it is imperative to acknowledge the significant challenges and risks involved in establishing such a programme. While initial experiences emphasised the necessity of technical improvements and learning curves, characterised by refining and modifying surgical techniques to enhance outcomes,[4,5] errors and challenges are unavoidable, especially in the early phases of programme implementation.[6-8] The primary challenges include the tasks of educating a competent workforce, creating appropriate infrastructure, identifying low-risk patients; and establishing standardised clinical protocols.[9-11]

Addressing these issues is vital for enhancing patient care and outcomes. As programmes progress, experiential learning provides practical insights and critical reflection to overcome these obstacles. Additionally, ongoing guidance from expert professionals is essential in improving liver transplant outcomes by enhancing human resource capabilities and assisting in the selection

of low-risk transplant candidates. This approach promotes the development of a sustainable and effective transplantation programme.[8,12,13]

The LT&HPB was established in 2014. Faculty members attained initial experience at various renowned centres worldwide, and the first three successful LDLTs were performed in 2016 with assistance from an international team.[14] Although, this mentorship continued for a limited number of transplants, a formal hands-on training of transplant faculty was accomplished at a high-volume centre within the country. After the completion of this comprehensive training, the LDLT programme was reinstated and it has been entirely managed by an indigenous team since 2020.

The re-initiation of the programme marked the commencement of experiential learning. Similar to other LDLT programmes that show improved results through a steep learning curve by enhancing surgical skills, better decision-making and transitioning from foreign support to independent performances,[4,5,8] the DUHS programme has undergone a comparable evolution. It has progressed from initially relying on external teams to establishing its own surgical unit. However, the early stages faced significant challenges, including the development of specialised support services for liver transplant procedures and high complication rates among the recipients. These problems highlighted the necessity for improved training, guidance, and implementation of standardised best practices to enhance outcomes and ensure the programme's long-term growth and sustainability.

The collaboration with the University of Chicago through The Transplantation Society and the International Liver Transplantation Society (TTS-ILTS) paired transplant centers programme[15] offered a chance to address these issues by enabling expert guidance, information sharing, and the implementation of internationally recognised protocols.

The current study was planned to compare the survival status and postoperative complications in liver transplant recipients before and after the introduction of the TTS-ILTS programme.

Materials and Methods

The retrospective study was conducted at the LT&HPB Surgery Unit of DUHS, Karachi, and comprised data of patients who underwent liver transplantation between May 2015 and December 2024. Patients with incomplete data were excluded from the study. The TTS-ILTS paired transplant centre programme was introduced in September 2023, and, as such, patients who underwent the operation till August 2023 were placed in group A, and the rest were placed in group B. The data was retrieved from medical records and institutional database after obtaining exempted from the institutional ethics review board. In the post-collaboration phase, the teams from DUHS and the University of Chicago were linked through multidisciplinary team (MDT) meetings held twice a month, quarterly mortality and morbidity discussions, a thorough audit by the University of Chicago's transplant team, and the exchange and implementation of management protocols as recommended by the University of Chicago team.[16]

The patients in both groups were evaluated for comorbidities, physical status and relevant fitness before finalisation in the transplant listing meeting. All LDLT surgeries were performed after obtaining approval from the Human Organ Transplant Authority (HOTA) of Pakistan.[17] The same team of surgeons performed recipient surgeries during this timeframe. Postoperatively, all patients were managed in the critical care unit (CCU) for five days and were stepped down to the LT&HPB unit once clinically stable. All the patients received dual immunosuppressive therapy, including steroids and tacrolimus, along with antifungal prophylaxis. After discharge, the patients were followed up in outpatient clinics weekly for one month and twice a month for the next three months. This was followed by three monthly reviews for the next six months, twice a year for one year, and then yearly thereafter.

Patients' characteristics were noted, including age, gender, body mass index (BMI), indication for liver transplant, aetiology, Child-Pugh Turcotte (CTP) grade, and Model for End-stage Liver Disease and Sodium (MELD-Na) score. Operative details included operative time duration (hours), amount of blood loss (mL), cold ischaemia time (CIT) (minutes), warm ischaemia time (WIT) (minutes), graft-to-recipient weight ratio (GRWR) (%), number of arterial anastomoses, types of portal venous anastomoses, and types of biliary anastomoses. The 1-month, 3-month and 12-month estimated survival rates between the groups were compared, and so were postoperative complications.

Data was analysed using SPSS 22. Numerical variables were expressed as median and interquartile range (IQR), whereas categorical variables were expressed as frequencies and percentages. Mann-Whitney U test and chi-square test were used to compare numerical and categorical variables, respectively. Survival analysis was conducted using the Kaplan-Meier curve, with the log-rank test was employed to compare survival between the

groups. P<0.05 was considered statistically significant.

Results

Of the 177 patients, 124 (70.1%) were in group A; 101 (81.5%) males and 23 (18.5%) females with median age 45 years (interquartile range: 35-52 years). There were 53 (29.9%) patients in group B; 41 (77.4%) males and 12 (22.6%) females with median age 44 years (interquartile range: 38-52 years) (p>0.05). BMI, indications for transplant and aetiology were not significantly between the groups (p>0.05), while MELD-Na score was significantly lower in group B than in group A (p=0.002) (Table-1). Overall, 4 (2.3%) patients developed graft failure and required re-transplantation, but intergroup difference was not significant (p=0.233).

In terms of operative variables, median CIT was 40 minutes (IQR: 22-44 minutes) in group A compared to 35 minutes (IQR: 26-46 minutes) in group B (p=0.026), median WIT was 43 minutes (IQR: 36-50 minutes_ in group A and 35 minutes (IQR: 31-47 minutes) in group B (p=0.004), median operative time duration was 9.1 hours (IQR: 7.8-11 hours) in group A compared to 8.1 hours (IQR: 7.3-9 hours) in group B (p=0.002), and the median amount of blood loss was 1,050mL (IQR: 600-1,800mL) in group A compared to 500mL (IQR: 400-900mL) in group B (p<0.001). The number of packed red blood cell (PRBC) transfusions was 330 units in the group A compared to 105 in group B (p=0.036), and the number of platelet transfusions was 237 units in group A compared to 52 in group B (p=0.044) (Table-2).

Overall, the number of postoperative complications was 16 (15.4%) in group B and 88 (84.6%) in group A (p<0.001). The incidence of pleural effusion (PE) and postoperative pneumonia was significantly lower in group B compared to group A (Table-3).

The overall estimated survival rates at 1-month, 3-months, and 1 year were 144 (81.4%), 143 (80.8%), and 141 (79.7%), respectively. Group B showed an improvement at both 1-month [97 (78.2%) in group A vs. 47 (88.7%) in group B; p=0.155)] and 3-month [96 (77.4%) in group A vs. 47 (88.7%) in group B; p=0.081] follow-up. The 12-month survival rate was also higher in group B compared to group A (Figure-1).

Table-1: Patient characteristics.

Total [n(%)]	Pre-collaboration group 124 (70.1)	Post-collaboration group 53 (29.9)	p-value
Types of graft [n (%)]			
• Right lobe graft	116 (93.5)	50 (94.3)	0.571
• Left lobe graft	08 (6.5)	03 (5.7)	
aGRWR (in %) [Median (IQR)]	0.91 (0.87-1.10)	0.93 (0.82-1.09)	0.311
Cut surface veins (segment 5 and 8 veins) [n (%)]	86 (69.4)	41 (75.5)	0.541
Inferior veins [n (%)]	24 (80.6)	16 (69.8)	0.121
Portal venous construction [n (%)]			0.181
• Conventional anastomosis	108 (87.1)	49 (92.5)	
• Portal venoplasty	09 (7.3)	01 (1.9)	
• Native portal vein	04 (3.2)	0 (0)	
• Interposition graft	03 (2.4)	03 (5.7)	
Arterial anastomoses [n (%)]			0.582
• One anastomosis	120 (96.8)	51 (96.2)	
• Two anastomoses	04 (3.2)	02 (3.8)	
Biliary anastomoses [n(%)]			0.539
• Duct-to-duct	118 (95.2)	50 (94.3)	
• Hepatojejunostomy	06 (4.8)	03 (5.7)	
Cold ischaemia time (in minutes) [Median (IQR)]	40 (22-44)	35 (26-46)	0.026
Warm ischaemia time (in minutes) [Median (IQR)]	43 (36-50)	35 (31-47)	0.004
Surgery duration (in hours) [Median (IQR)]	9.1 (7.8-11)	8.1 (7.3-9)	0.002
Blood loss (in ml) [Median (IQR)]	1050 (600-1800)	500 (400-900)	<0.001
Total bPRBCs unit transfusion (n)	330	105	0.036
Total cFFPs unit transfusion (n)	404	91	0.294
Total platelets unit transfusion (n)	237	52	0.044

a=Body mass index; b=Model for end stage liver disease with sodium; c=Out of 117 patients in pre-collaboration vs. 47 patients in post-collaboration group (excluding ALF cases)
FFP= Fresh Frozen Plasma

Table-2: Operative Details

Total [n(%)]	Pre-collaboration group 124 (70.1)	Post-collaboration group 53 (29.9)	p-value
Age (years) [Median (IQR)]	45 (35-52)	44 (38-52)	0.967
Sex [n(%)]			0.541
• Male	101 (81.5)	41 (77.4)	
• Female	23 (18.5)	12 (22.6)	
aBMI (in kg/m2) [Median (IQR)]	24.7 (21.6-29.4)	24.3 (21.3-25.8)	0.119
Indications of transplant [n (%)]			0.360
• Acute liver failure (ALF)	07 (5.6)	06 (11.3)	
• Acute on chronic liver failure (ACLF)	21 (16.9)	08 (15.1)	
• Decompensated chronic liver disease (DCLD)	78 (62.9)	35 (66)	
• Compensated liver disease (CLD)	18 (14.5)	04 (7.5)	
Etiology [n (%)]			0.233
• HBV	12 (9.7)	09 (17)	
• HCV	47 (37.9)	16 (30.2)	
• HBV/HDV	28 (22.6)	12 (22.6)	
• HBV/HCV	03 (2.4)	0 (0)	
• HAV	02 (1.9)	01 (1.9)	
• HEV	01 (0.8)	04 (7.5)	
• Cryptogenic	11 (8.9)	03 (5.7)	
• Budd Chiari Syndrome	04 (3.2)	0 (0)	
• Non-alcoholic steatohepatitis (NASH)	04 (3.2)	02 (3.8)	
• Graft failure	03 (2.4)	01 (1.9)	
• Others	09 (7.2)	05 (4.1)	
bMELD-Na [Median (IQR)]	18 (14-26)	15 (11-19)	0.004
cChild-Pugh Turcotte (CTP) [n (%)]			0.215
• Grade A (5-6)	16 (13.2)	04 (8.3)	
• Grade B (7-9)	51 (43)	19 (41.7)	
• Grade C (>10)	51 (43.8)	24 (50)	
Hepatocellular carcinoma (HCC) [n (%)]	42 (33.9)	13 (24.5)	0.219

a=Graft-to-recipient weight ratio; PRBCs=Packed red blood cells; FFP=Fresh frozen plasma

Table-3: Postoperative Complications.

Total [n(%)]	Pre-collaboration group 124 (70.1)	Post-collaboration Group 53 (29.9)	p-value
Reactionary haemorrhage	09 (7.3)	02 (3.8)	0.509
Pleural effusion	42 (33.9)	07 (13.2)	0.006
Pneumonia	34 (27.4)	02 (3.8)	<0.001
Intra-abdominal collection	25 (20.2)	07 (13.2)	0.394
Hepatic artery thrombosis	05 (4)	02 (3.8)	0.650
Portal vein thrombosis	02 (1.6)	0 (0)	0.490
Bile leak	08 (6.5)	02 (3.8)	0.725
Bile stricture	19 (15.3)	06 (11.3)	0.639
Re-exploration	11 (8.9)	02 (3.8)	0.349
Acute rejection	06 (4.8)	01 (1.9)	0.676
Chronic rejection	03 (2.4)	0 (0)	0.555
Thromobotic thrombocytopenic purpura	05 (4)	02 (3.8)	0.650

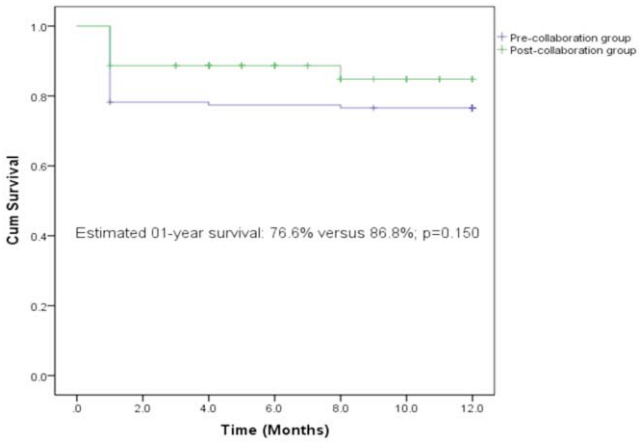

Figure-1: Estimated 01-year survival comparison between pre-collaboration and post-collaboration group.

Discussion

The current findings demonstrated that the patient characteristics between the two groups were comparable. Decompensated liver disease (DCLD) remained the predominant indication for LDLT, which was consistent with global trends.[5,18,19] Interestingly, a reduced number of acute-on-chronic ;liver failure (ACLF) cases were observed in the post-collaboration group,

although the difference was not statistically significant. This could reflect a more discerning strategy for patient management following collaboration, potentially enhanced by refined clinical decision-making processes.

The MELD-Na score is an established prognostic tool used to prioritise patients for liver transplantation.[20] In a consecutive 100 adult LDLTs, Lo et al.[5] observed a high mean MELD score in the early 50 liver transplants compared to the later 50 recipients (25.3 vs. 21.2; p=0.101), highlighting the impact of experiential learning on patient selection. Similarly, Li et al.[21] reported a trend of selecting lower MELD-Na score cases with progression of liver transplant experience. In the current study, the median MELD-Na score was significantly lower in the post-collaboration era than in the pre-collaboration phase (18 vs.15, p=0.004), indicating the selection and prioritisation of patients with less severe liver dysfunction in the post-collaboration group, reflecting improved pre-transplant management and more robust patient stratification.

In addition to a significant reduction in CIT (p=0.026) and WIT (p=0.004), the operative time was notably decreased (p=0.002) in the post-collaboration cohort along with blood loss (p<0.001). These distinguished improvements in operative details emphasised the value of the progressive transplant surgical team's skill and procedural efficiency achieved through ongoing periodic experience and mentoring. In 85 liver transplant recipients, Pomposelli et al[22,] observed a 6.4 hours surgical time in the early 25 cases compared to 5.8 hours in the later 60 cases (p=0.152). Correspondingly, Li et al.[21] showed a reduced duration of surgery and blood loss as their experience with LDLT procedures increased.

Furthermore, a marked reduction in the number of transfusions was observed in the current post-collaboration group. Lo et al.[5] retrospectively compared the first 50 and last 50 LDLTs, and noticed a significant reduction in blood loss, CIT, WIT, duration of surgery, and the number of transfusion products in the later 50 LDLT recipients (p<0.001). The improvements of these operative details in the current study might have been related to lower preoperative MELD-Na scores in the post-collaboration group.

Postoperative complications following LDLT vary across studies and are indicative of a transplant centre's ability to effectively manage and address these challenges.[5,7,21-26] In the study by Dar et al.,[23] intra-abdominal collections and PE were the most common complications, while biliary complications were more prevalent in the study by Lo et al.[5] In the current study, postoperative complications were significantly reduced in the post-collaboration group (p<0.001), further highlighting the benefits of the partnership. The frequencies of PE and pneumonia decreased substantially as well, suggesting that the enhanced expertise and guidance from an established transplant centre contributed to better perioperative management and patient care. This reduction in complications is a clear indicator of improved postoperative care protocols, which were likely influenced by the implementation of internationally recognised practices. However, certain complications such as reactionary haemorrhage and intra-abdominal collection, did not show significant differences between the two groups, suggesting that these issues may still require further refinement in clinical protocols.

Survival rates following LDLT are influenced by factors such as patient selection, the experience of the transplant centre, and its ability to manage postoperative complications effectively. The literature demonstrates that experience[5,21-23] and mentorship within liver transplant programmes significantly enhance patient survival outcomes.[7,12] In the current study, both the 1-month and 3-months survival rates improved after collaboration, and the estimated 1-year survival rate also improved post-collaboration. This improvement in survival outcomes is likely the result of the combined effect of better surgical techniques, more efficient perioperative care, and enhanced postoperative management, all fostered by the collaboration with an established transplant centre.

While the current study illustrated the beneficial effects of TTS-ILTS collaboration on survival rates and postoperative complications, it is important to acknowledge its limitations. The retrospective nature of the study precluded the assessment of the natural learning curve's impact on the observed improvements. Consequently, it remains challenging to ascertain whether the enhanced outcomes were attributable to the collaboration between the current surgical team and an established institute, or to the team's learning curve. Moreover, although there were observed enhancements in both survival and complication rates, the relatively small sample size of the post-collaboration group (n=53) restricted the statistical power, especially concerning survival outcomes.

Future studies with larger sample sizes are needed to validate the current findings, and provided a more robust analysis of the long-term impact of international collaboration on LDLT outcomes. Additionally, further research into specific elements of the collaboration, such as training programmes or standardised clinical

protocols, would provide deeper insights into how such partnerships can be optimised to improve transplant outcomes.

Conclusion

The TTS-ILTS paired transplant centre collaboration had a substantial positive effect on the outcomes of LDLT at DUHS, leading to improved surgical outcomes, reduced postoperative complications, and better survival rates, demonstrating the value of international partnerships in enhancing technical skills, clinical practices and patient outcomes, ultimately contributing to the sustainability and success of liver transplant programmes in emerging healthcare settings, like Pakistan.

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