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Title: Determining the optimal timing of liver transplant for paediatric patients after Kasai portoenterostomy based on disease severity scores

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Abstract: Background
The objective of this study was to determine the most optimal timing of liver transplant (LT) for post-Kasai portoenterostomy (KPE) patients based on disease severity scores.

Methods
This was a retrospective study and the clinical data of all LT recipients aged <18 years (n=89) with a history of KPE were analyzed. They were divided into three groups according to their PELD/MELD scores at the time of LT (A: <15; B: 15-25; C: >25). The effect of LT on the clinical outcomes and hospitalization status were analyzed.

Results

There were 33, 34 and 22 patients in group A, B and C respectively. There was no significant difference in 3-year graft survival rate between the three groups but group C patients had the highest incidence of vascular or biliary complications (p=0.022). Group C patients had a significantly lower hospital admission frequency (p=0.036) and shorter hospital stay (p=0.041) after LT when compared with their pre-LT status and with non-LT patients with similar disease severity scores. On the other hand, the hospitalization frequency and duration were similar in patients with the lowest disease severity score (group A) before, after and without LT.

Conclusions

The benefit of LT was less obvious when the disease severity score is <15. A high complication rate was reported when LT was performed at a score > 25. Donor availability, the patient's general condition and parental wish should be considered during individual assessment.

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Keywords: Liver transplantation; PELD score; MELD score biliary atresia

Type of study: Clinical research paper

Level of evidence: Level III

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Introduction

Biliary atresia (BA) is a congenital fibrotic disorder of the biliary tract, which results in obstructive jaundice and liver cirrhosis in neonates and early infants. Although Kasai portoenterostomy (KPE) can restore biliary drainage in more than half of patients, the long-term outcome remains suboptimal. It is estimated that only 40–60% of patients can achieve long-term survival without liver transplant (LT) because of disease progression [(1)]. Patients with KPE may still suffer complications of liver failure, including persistent jaundice, coagulopathy, growth failure, recurrent cholangitis, portal hypertension and hepato-pulmonary syndrome. LT has been widely accepted as the ultimate treatment for these patients but there is a lack of consensus about its optimal timing. While a late referral may result in the development of life-threatening complications, the risk of morbidity and mortality may outweigh the benefit if LT is performed too early.

At most LT centres, the priority for deceased donor graft allocation is based on disease severity score systems, which are the Paediatric End-Stage Liver Disease (PELD) and the Model for End-Stage Liver Disease (MELD) scores. These two systems were developed in early 2000s to rank waitlisted patients according to their probability of survival [2, 3]. The MELD score is commonly used in patients older than 12 years, while the PELD score, which takes growth failure into account, is used in children younger than 12 years [4]. At centres where living-donor liver transplant is also performed, these scoring systems also influence the scheduling of the operation.

The objective of this study was to determine the optimal timing of LT for patients with persistent cholestasis (serum bilirubin > 20uml/L) after KPE based on clinical outcomes. Comparisons were made between i) post-LT patients with different disease severity scores, ii) LT recipients before and after transplantation, and iii) post-LT patients and native-liver survivors with similar disease severity scores.

Materials and Methods

Our centre is the only paediatric LT centre in the territory and the first operation was performed in 1993. In this retrospective study of the period from 1993 to 2017, we conducted a review of all LT recipients aged <18 years at the time of LT who had a primary diagnosis of BA and received KPE before LT. The primary KPEs were performed at our centre or other regional paediatric surgical centres which subsequently referred the patients to us. Patients with BA who had undergone primary LT were excluded from this study. The studied patients were categorized into three groups according to their PELD/MELD scores at the time of LT (A: <15; B: 15–25; C: >25). Firstly, the operative outcomes including the complication rate and graft survival rate were compared between the three groups. Secondly, admission frequency and hospital stay (per year per patient) before and after LT (excluding the hospital stay immediately after LT) were compared. These were also compared with non-LT native liver survivors with similar PELD/MELD scores.

The data were analyzed with a standard statistical package (Windows, version 21.0; SPSS Inc., Armonk, NY, USA). Categorical variables were compared by the chi-squared test. Continuous variables were expressed as medians (ranges) and compared by the Kruskal-Wallis test. The Kaplan-Meier survival method was used to analyze disease-free survival. A p-value <0.05 was considered to be statistically significant. This retrospective study had been approved by the appropriate ethics committee and was performed in accordance with the ethical standards in the

Declaration of Helsinki.

Results

A total of 89 post-KPE patients having LT (68 with living donors and 21 with deceased donors) were included in this study (Table 1). The median age at LT was 3 years (range: 4 months to 16 years). The median follow-up period was 116.7 months (range: 1 to 292 months). The median score at the time of LT was 12.6 (range: -9 to 44). Thirty-three patients (37.1%) belonged to group A, 34 patients (38.2%) belonged to group B, and 22 patients (24.7%) belonged to group C. The median ages at operation in groups A, B and C were 3.5 years (range: 10 months to 12 years) vs 2 years (range: 6 months to 16 years) vs 3 years (range: 7 months to 9 years) (p = 0.671). The overall 3-year graft survival rate was 84.3%, while the 3-year graft survival rates in the three groups were 87.9% (29/33), 88.2% (30/34) and 72.7% (16/22) in groups A, B and C respectively (p = 0.384) (Figure 1). As there were 4 patients with graft failure that were salvaged by re-transplant, the overall 3-year survival rate was 88.8%. The patient survival rates in group A, B and C were 93.9% (31/33), 91.2% (31/34) and 77.3% (17/22) respectively (p=0.245)

The median operative duration in the 89 patients was 730 minutes (range: 480 to 1120 minutes). The median operative time in A vs B vs C was 640 mins (range: 480 to 858 mins) vs 718 mins (range: 562 to 1027 mins) vs 856 mins (range: 543 to 1120 mins) ($p = 0.135$). Regarding vascular or biliary complications that might adversely affect the graft function, the overall incidence was 38.2% (34/89). The incidence of these complications was highest in group C (A vs B vs C = 27.2% (9/33) vs 32.4% (11/34) vs 63.7% (14/22), $p = 0.022$). The patients took tacrolimus or sirolimus as a long-term immunosuppressant to prevent graft rejection. Eighteen patients (20.2%) had histologically proven post-transplant lymphoproliferative disease (PTLD). There was no difference in the incidence of PTLD between the three groups (A vs B vs C = 21.2% (7/33) vs 20.6% (7/34) vs 18.2% (4/22), $p = 0.515$) (Table 2).

As to admission frequency and hospital stay, the median disease-related admission frequency/hospital stay (per year per patient) including emergency and elective admissions in groups A, B and C before LT was 0.8/5.82 days vs 1.4/10.23 days vs 3.9/29.3 days. In the post-LT period, the median disease-related admission frequency/hospital stay (excluding the hospital stay immediately after LT) in groups A, B and C was 0.6/4.23 days vs 0.5/6.65 days vs 0.7/5.59 days. The post-LT hospital admission status of these LT recipients was also compared with that of 53 BA native liver survivors with KPE performed during the same study period. Among these 53 patients, 33 had a score <15 (group A'), 16 had a score between 15–25 (group B') and 4 patients had a score >25 (group C') as recorded during their last follow-up visit. The admission frequency/hospital stay (per year per patient) in these native liver survivors was 1.1/5.10 days in group A', 1.6/8.21 days in group B', and 2.6/18.52 days in group C'. On statistical analysis, there were significant reductions in hospital admission frequency ($p = 0.036$) and duration of stay ($p = 0.041$) in post-LT patients with the highest disease severity scores (group C) (Figures 2 and 3).

Discussion

Even though the worldwide incidence of BA is not high and varies from 1/5000 in Asians to 1/18000 in Caucasians, it is the commonest indication for LT in children [(5)]. Since the introduction of KPE in 1957, it has become the first-line surgical treatment for BA (6). Although extensive research on the operative technique and peri-operative management has been conducted with an aim to improve the outcome of this operation, long-term native liver survival rate remains unsatisfactory, and more than half of these patients will eventually require LT. In general, indications for LT after KPE include persistent or recurrent jaundice, intractable cholangitis, portal hypertension, hepatopulmonary syndrome and growth failure [7, 8]. However, the timing of LT for these patients remains unclear owing to the rarity of BA, and this precludes the development of an objective referral system. At many LT centres, the priority for deceased donor graft allocation follows the PELD and MELD scoring systems. At which point a child should be offered LT is still undetermined and largely centre-based. There is a need to define the optimal timing of LT for the best outcome. Some centres advocate early LT because the risk of complication will increase if LT is performed too late when the liver cirrhosis is advanced [9]. In addition, a graft may not be available at the time of acute liver decompensation. However, there is a growing concern about the disadvantages of this approach, including the higher operative risk in small-sized recipients and the side-effect of prolonged immunosuppression [10]. A higher incidence of PTLD associated with the early use of immunosuppressants in young infants has been reported [11]. Furthermore, the 5-year mortality risk in LT is in the range of 10% to 20%, and it would be a major distress to the family and the surgeon if mortality happened on a relatively 'healthy' child [12]. Using the Markov Simulation Analysis model, Ronen et al tried to address this issue, but the study was not based on real patient data [13]. In our present study, the patients were categorized into three groups with reference to the study by Ronen et al, while the analysis was based on actual clinical outcomes of LT. In addition to the analysis of survival, we also evaluated the operative risk and the change in the status of hospitalization.

In our study, patients with the highest PELD/MELD (>25) scores had apparently the longest operative duration, although this was not statistically significant. As all of these patients had prior KPE and the LT operations were performed by the same team of transplant surgeons, the finding might suggest that in an advanced disease stage, the operation would be more difficult and require a longer time to complete. When liver failure is advanced, the presence of coagulopathy and portal hypertensive changes will increase technical difficulty. The poor nutritional reserve was likely another factor accounting for the worst outcome. The overall vascular and biliary complication rates were highest in group C patients, who had the most advanced disease. We analyzed these two types of complications as they might lead to graft failure. Indeed, a slightly lower graft survival rate was also noticed in group C patients even though graft failure might be related to problems which were not related to operation, such as medication compliance. In this study, the association between the age at operation and operative outcomes was not tested. However, we have reported in an earlier study that body weight did not affect the complication rate [14]. On the other hand, the incidence of PTLD was similar in all the patients regardless of their scores. Taking the above findings together, we believe that operation at an advanced disease stage would be associated with more technical difficulty and LT-related complications but the development of PTLD is not related to pre-LT disease severity.

The other objective of this study was to examine the changes in the overall well-being of patients after LT. Since liver function is expected to improve in all patients after LT, it could not be used as an outcome measurement. There were different quality of life measurements but they would require prospective data collection and therefore did not fit into our study design. We chose to evaluate admission frequency and hospital stay since hospital admission would inevitably affect general activities, peer relationship and school performance, which are major components of quality of life measurement in growing children. Pre-LT hospital admission was significantly less frequent and shorter in patients with milder disease (group A) but post-LT hospital admission was comparable. In intra-group comparison, the largest difference was found in group C patients, with admission frequency reduced from 3.9 episode/year/patient (before LT) to 0.7 episode/year/patient (after LT). Their hospital stay was also shortened from 29.3 days/year/patient (before LT) to 5.59 days/year/patient (after LT). On the other hand, the differences were not significant in group A patients. Patients with advanced liver failure commonly suffer from ascites and complications of portal hypertension such as bleeding varices that require prolonged in-patient care. Previous studies have reported the relationship between hospital stay and the psychological impact on growing children [15]. After LT, some of the patients may need hospital admissions for blood taking and liver biopsy for monitoring of graft function, but in general these procedures require a short stay only. In contrast, patients in group A, who had less advanced disease, might not suffer from major complications and hence had a lower hospital admission frequency. Their pre-LT and post-LT hospital admission frequencies and stay durations were comparable. Thus, performing LT on these patients had not significantly lessened or shortened their hospital admissions. A similar but less prominent advantage associated with LT was also observed in group B patients.

To further reflect the impact of LT on hospital admission, the hospitalization of the LT recipients was also compared with that of native liver survivors with similar disease severity scores. Similar to the previous comparison between the statuses of the LT recipients before and after LT, the most significant difference was found in patients with advanced disease. Although the hospital admission frequency in group C' was 2.6 episode/year/patient, patients in this group had the longest hospital stay (18.52

days/year/patient). It is postulated that during each hospital admission, there was prolonged management given for the underlying problem. When these were compared with the outcomes in the post-LT patients in group C, we concluded that LT should be carried out as it could significantly reduce hospitalization.

This study is limited by its retrospective nature but a prospective randomized study would require complicated logistics and involve ethical issues. The post-KPE patients were referred from different centres and there was a lack of standard criteria for referral. Hence, the patients had different disease severity when they were presented to us. While all the LT operations were performed by the same team of surgeons at our hospital, the previous KPEs were done in a few different hospitals, and this might have affected the technical difficulty in the subsequent LT operations that could not be measured in this study. This study attempted to determine the optimal timing of LT based on objective data of PELD and MELD scores only. While it could serve as a clinical reference, it should not be soley dependent during decision making. In clinical practice, other factors such as the willingness of the family for LT, the general condition of the patients, donor availability and the expertise of the transplant team should be considered during the assessment for LT.

Conclusion

In conclusion, based on the study’s findings, patients with a PELD/MELD score reaching 15 should be referred for LT to reduce hospitalization. When liver cirrhosis is advanced (score >25), LT will be more difficult, with an increased risk of post-operative complications and possibly a lower graft survival rate. On the other hand, the benefit of LT is less obvious if the recipient has a lower PELD/MELD score (<15). However, other factors such as donor availability, technical expertise and parental wish should also be taken into account during individual assessment.

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Figure and table legends

Figure 1) Kaplan-Meier survival analysis of the graft survival in group A, B and C ,(p = 0.384)

Figure 2) The frequency of hospital admission (per year per patient) (y-axis) among the three different groups (x-axis) with status before, after and without LT

Figure 3) The duration of hospital stay (days per year per patient) (y-axis) among the three different groups (x-axis) with status before, after and without LT

Table 1) Demographic data of the 89 post-KPE LT recipients in the current study

Table 2) Comparison of the peri-operative events among patients with different PELD/MELD scores

Figure 1

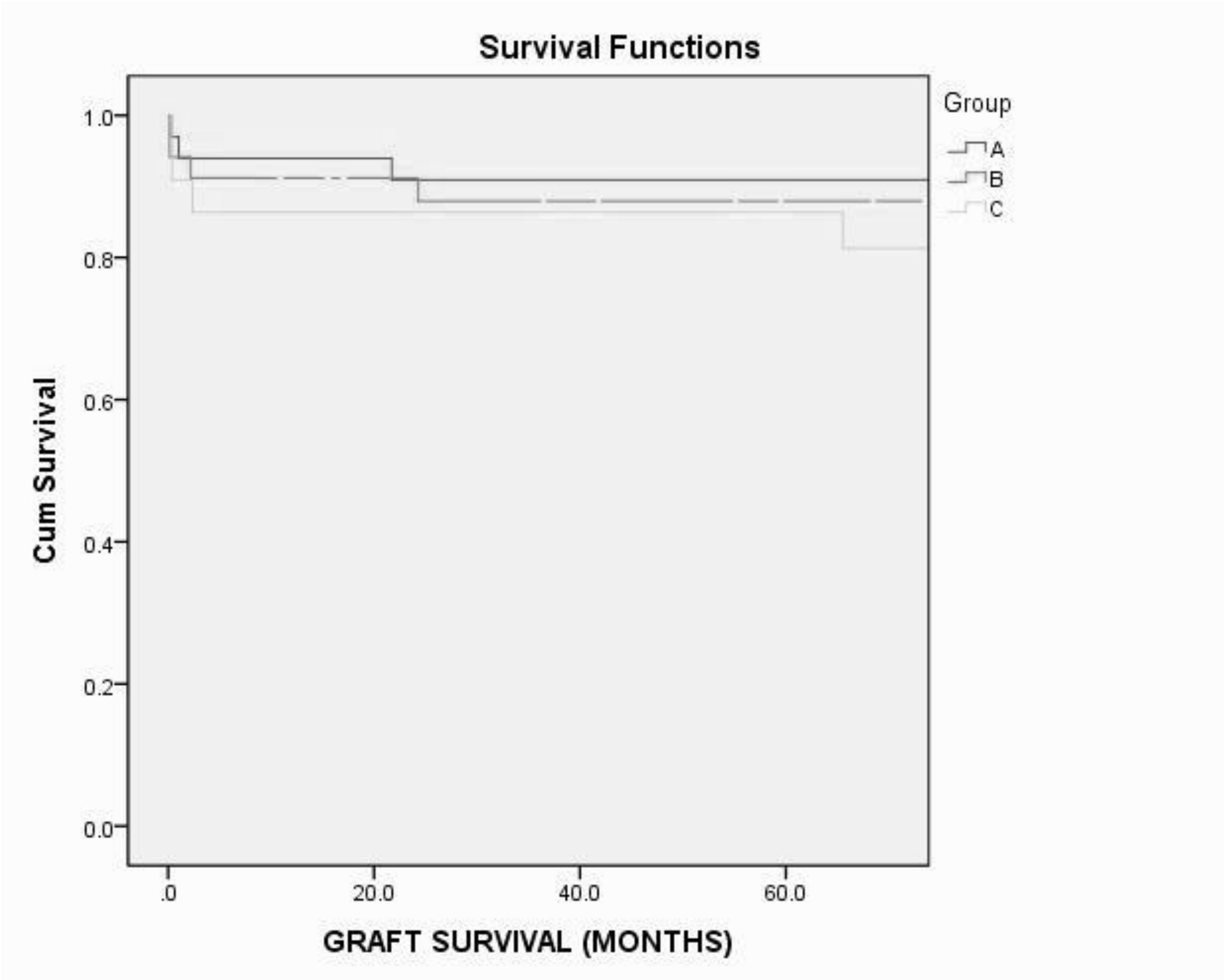

Survival Functions
Cum Survival
1.0
0.8
0.6
0.4
0.2
0.0
.0
20.0
40.0
60.0
GRAFT SURVIVAL (MONTHS)
Group
A
B
C

Figure 2

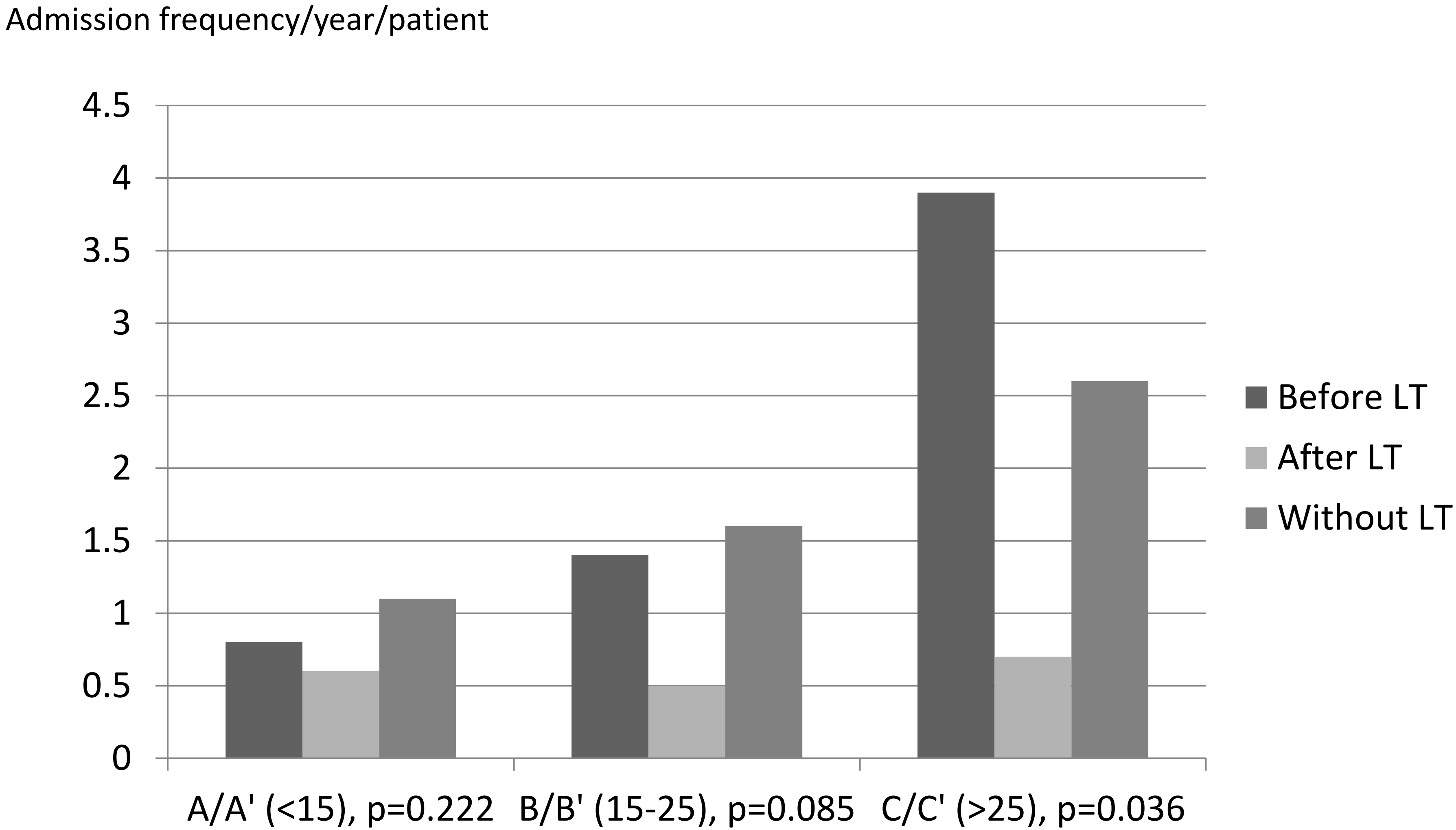
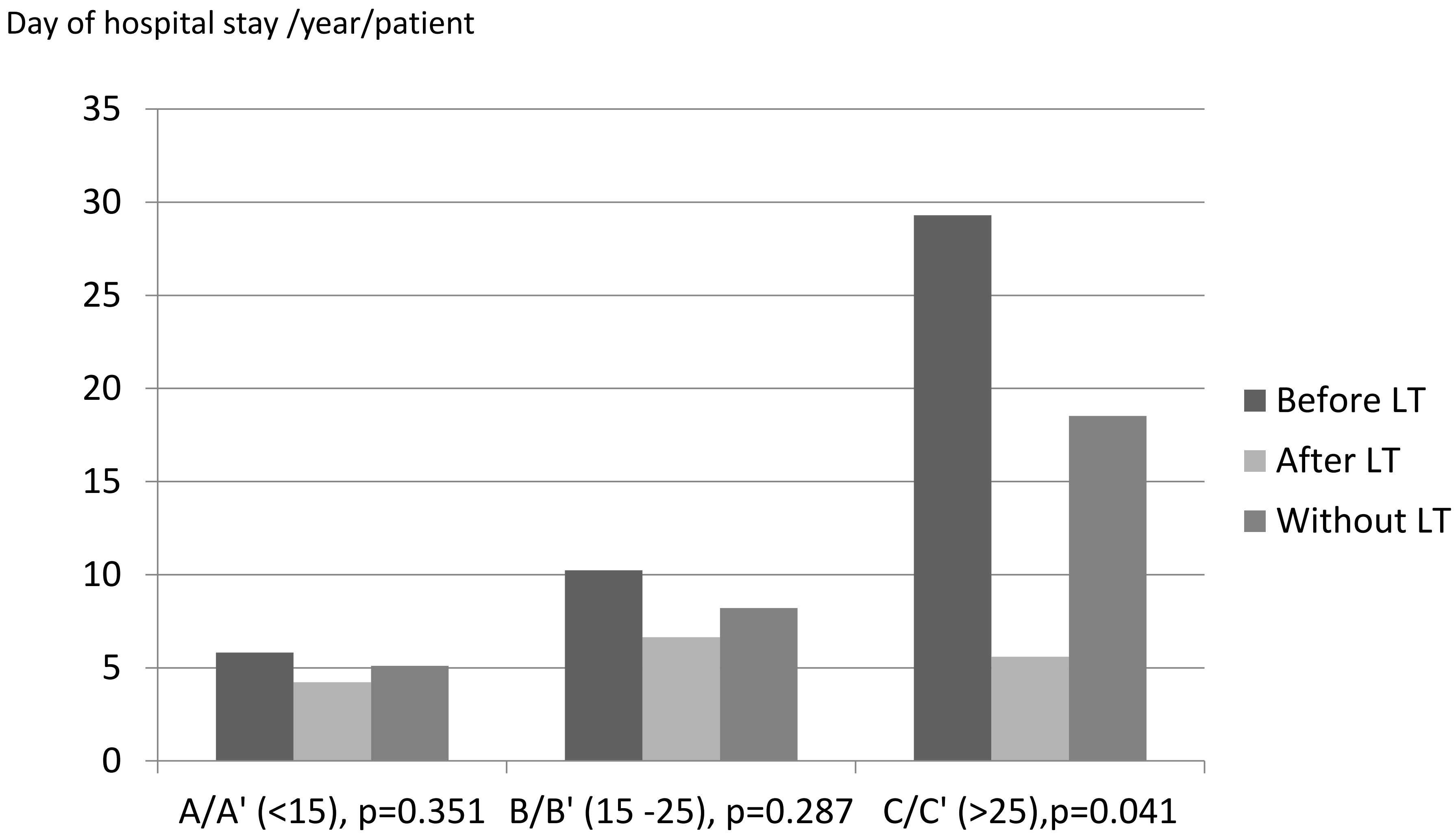

Admission frequency/year/patient
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
A/A' (<15), p=0.222
B/B' (15-25), p=0.085
C/C' (>25), p=0.036
Before LT
After LT
Without LT

Figure 3



Day of hospital stay /year/patient
35
30
25
20
15
10
5
0
A/A' (<15), p=0.351
B/B' (15 -25), p=0.287
C/C' (>25),p=0.041
Before LT
After LT
Without LT

Table 1

Table 1 Demographic data of the 89 post-KPE LT recipients in the current study

Variables	n=89 % (n) or median (range)
Sex - Male - Female	 42.7% (n=38) 57.3% (n=51)
Type of operation - DDLT - LDLT	 23.6% (n=21) 76.4% (n=68)
Age at LT	3 years (4 months – 16 years)
Follow up period	116.7 months (1 to 292 months)
3-year graft survival	87.9%
3-year patient survival	88.8%
No of patient with PELD/MELD score - <15 - 15 - 25 - >25	 37.1% (n=33) 38.2% (n=34) 34.7% (n=22)

Table 2

Table 2 Comparison of the peri-operative events among patients with different PELD/MELD scores

	A (*<15)	B (*15-25)	C (*>25)	p value
Number of patients	33	34	22	-
Age at liver transplant #	3.5 yrs (10m – 12 yrs)	2 yrs (6m – 16yrs)	3 yrs (7m – 9yrs)	0.671
Operative duration (mins) #	640 (480-858)	718 (562 – 1027)	856 (543 – 1120)	0.135
Incidence vascular or biliary complications	27.2% (n=9)	32.4% (n=11)	63.7% (n=14)	0.022
Incidence of PTLD	21.2% (n=7)	20.6% (n=7)	18.2% (n=4)	0.515
3-year graft survival	87.9% (n=29)	88.2% (n=30)	72.7% (n=16)	0.384
3-year patient survival	93.9% (n=31)	91.2% (n=31)	77.3% (n=17)	0.245

*PELD/MELD score

Values are expressed as median (range)