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Accepting multiple simultaneous liver offers does not negatively impact transplant outcomes

Firas Zahr Eldeen, Moustafa Mabrouk Mourad, Mayank Bhandari, Garrett Roll, Bridget Gunson, Hynek Mergental, Simon Bramhall, John Isaac, Paolo Muiesan, Darius F. Mirza and M. Thamara P. R. Perera

The Liver Unit, Queen Elizabeth Hospital Birmingham, Birmingham, UK

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Correspondence
Mr. Thamara Perera FRCS, Consultant Surgeon, The Liver Unit, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham B15 2TH, UK.
Tel.: 0044 12137 14637;
Fax: 0044 12141 41833;
e-mail: Thamara.Perera@uhb.nhs.uk

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Summary

Impact of performing multiple liver transplants (LT) in a short period of time is unknown. Consecutively performed LT potentially increase complication rates through team fatigue and overutilization of resources and increase ischemia time. We analyzed the impact of undertaking consecutive LT (Consecutive liver transplant, CLT; LT preceded by another transplant performed not more than 12 h before, both transplants grouped together) on outcomes. Of 1702 LT performed, 314 (18.4%) were CLT. Outcome data was compared with solitary LT (SLT; not more than one LT in 12-h period). Recipient, donor, and graft characteristics were evenly matched between SLT and CLT; second LT of CLT group utilized younger donors grafts with longer cold ischemic times ($P = 0.015$). Implantation and operative time were significantly lower in CLT recipients on intergroup analysis ($P = 0.0001$ and 0.002, respectively). Early hepatic artery thrombosis (E-HAT) was higher in CLT versus SLT ($P = 0.038$), despite absolute number of E-HAT being low in all groups. Intragroup analysis demonstrated a trend toward more frequent E-HAT in first LT, compared to subsequent transplants; however, difference did not reach statistical significance ($P = 0.135$). In era of organ scarcity, CLT performed at high-volume center is safe and allows pragmatic utilization of organs, potentially reducing number of discarded grafts and reducing waiting list mortality.

Introduction

Liver transplant outcomes are influenced heavily by selection of both donors and recipients, and graft–recipient matching. The latter is constrained by the availability of suitable donor offers. In the United Kingdom, each transplant center manages its own transplant wait list by receiving offers for grafts available from a designated geographical area [1]. Transplant surgeons are unable to direct the time of the organ donation procedure [2]. It is therefore common that surgeons are confronted with multiple liver organ offers simultaneously. This problem is compounded at high-volume transplant centers with long waiting lists. To accommodate multiple organ offers within a short time period, careful planning, and appropriate recipient selection for each graft are paramount.

A specific guideline for which organ offers to accept or decline does not exist. Declining organ offers due to concerns of team fatigue potentially results in underutilization of liver grafts [1]. In the era of critical organ scarcity, where liver transplant wait list mortality reaches 15–20% [3], maximum utilisation of available organ offers translates to greater patient benefit [4,5]. Accommodating multiple grafts serially at one transplant center likely reduces waiting list mortality, provided the act of performing consecutive transplants in a short period of time does not result in suboptimal outcomes. There are reports that fatigue influences outcomes [6,7]. It has also been suggested that prolonged wakefulness impairs speed, accuracy, hand–eye coordination, decision-making, and memory [8,9]. We aimed to study the impact of performing consecutive liver transplants, as a proxy for heavy workload, increased

resource utilization, and increased time constraints on the operative team on recipient outcomes.

Patients and methods

We performed a retrospective analysis of a prospectively collected database at a high-volume liver transplant center in the United Kingdom. The database included patient demographics, indication for transplantation, operative details and perioperative outcomes for all adult 1702 patients undergoing liver transplantation between January 2000 and December 2012 at Queen Elizabeth Hospital Birmingham.

Definition of "Consecutive liver transplant":

The knife to skin time (KTS) was used as the start time for the purpose of this study. Consecutive liver transplants (CLT) occurred when a second (or third) transplant started within 12 h of the preceding transplant. Based on the above definition, all transplants performed within the study period were categorized into the following.

Solitary liver transplant
Solitary or single liver transplant procedure that was not followed by another transplant in 12-h period.

Consecutive liver transplants
Grouped together, this consisted LT that were preceded by another transplant performed not more than 12 h before. The CLT recipients therefore consisted of first recipients, second recipients, and occasionally third recipients.

Comparison of outcomes

The donor [age, BMI, type of donor (brain death donor versus donation after circulatory death)], recipient [age, sex, BMI, MELD score, indication for transplant, and transplant waiting time], and outcomes [operative time, length of intensive care unit (ITU) stay, length of hospital stay, and postoperative complications] were compared among groups. Intergroup analysis compared outcomes between solitary liver transplant (SLT) and CLT recipients. Subsequently, an intragroup analysis was performed within the CLT recipients. As there were four occurrences of three LT were initiated consecutively in the same 12-h period, the third LT were grouped together with the second LT to compare data within this group. Furthermore, to investigate the impact of fatigue on the operating surgeon, we compared recipients in the CLT group who were transplanted by the same or a different surgeon. Finally, 1-, 3-, and 5-year graft and patient survival were compared. IBM SPSS Statistics for Windows (V 21.0. Armonk, NY: IBM Corp, USA) was used. The analysis was performed for categorical variables with the use of Fisher's exact test. Continuous variables were analyzed using Mann–Whitney *U*-test. Survival curves were estimated with the Kaplan–Meier method and were compared using log-rank tests. Median follow-up time was estimated by Kaplan–Meier analysis with reverse meaning of the status indicator. A value of $P < 0.05$ was considered to be significant.

Results

A total of 1702 patients underwent LT during the study period, of these 314 (18.4%) LT operations fulfilled the criteria as CLT. Of the CLT recipients, there were 155 first transplants, 155 second transplants, and 4 third transplants initiated within 12hour time period as per definition. Ninety transplants of 159 (56%) second/third transplants were performed by the same surgeon, while the rest ($n = 69$) were performed by a surgeon other than the surgeon who performed the first transplant within that CLT. The remaining 1388 cases were SLT recipients.

Donor and graft characteristics

Donor and graft characteristics such as age, BMI, median cold ischemia time (CIT), percentage of deceased donors after circulatory death (DCD) grafts (10%) and split grafts (11.5%) were evenly matched on intergroup analysis (Table 1); second LT CLT recipients were more likely to receive grafts from younger donors ($P = 0.015$), and the cold ischemia time of the second transplant graft was longer ($P = 0.001$) (Table 2).

Recipient characteristics

Characteristics of the recipient cohort such as age, sex, BMI, MELD score, surgery waiting time, hospital stay, and intensive care stay were evenly matched on both intergroup (SLT versus CLT) and intragroup (within CLT) analyses (Tables 1 and 2). The most common indication for transplantation was alcoholic cirrhosis followed by hepatitis C cirrhosis.

Operative characteristics

The operative time and recipient warm ischemia time were significantly lower in CLT group ($P = 0.0001$ and 0.002, respectively) on intergroup analysis (Table 1), but not on intragroup analysis (Table 2). Difference in total blood loss, and blood product transfusion did not reach statistical significance.

Postoperative complications

Biliary complications were the most frequently observed complications with overall incidence of 16.4% vs. 18.8%

Table 1. Difference between solitary and consecutive transplants recipients.

Characteristics	Solitary SLT (*N* = 1388)	Consecutive CLT (*N* = 314)	*P*-value
Recipient			
Age*	53 (44, 60)	54 (45, 61)	0.265
Sex (*n*; % male)	796 (57%)	169 (54%)	0.257
BMI	26 (21, 30)	26 (23, 29)	0.572
Etiology (*n*; %)			
Polycystic liver disease	26 (1.9%)	3 (1%)	0.682
Alcoholic cirrhosis	226 (16.3%)	61 (19.4%)	
Hepatitis B cirrhosis	49 (3.5%)	15 (4.8%)	
Hepatitis C cirrhosis	219 (15.8%)	48 (15.3%)	
Primary biliary cirrhosis	194 (14%)	44 (14%)	
Primary sclerosing cholangitis	128 (9.2%)	26 (8.3%)	
Cryptogenic cirrhosis	64 (4.6%)	15 (4.8%)	
NASH (nonalcoholic steatohepatitis)	45 (3.2%)	8 (2.5%)	
Acute failure	173 (12.5%)	31 (9.9%)	
Other	151 (10.9%)	41 (13.1%)	
Retransplantation as indication	113 (8.1%)	22 (7%)	
MELD	13 (11, 18)	14.7 (11, 19)	0.432
Median waiting time: months	1.5 (0.3, 4)	1.7 (0.3, 4)	0.089
Hospital stay: days	11 (8, 19)	12 (8, 20)	0.413
ICU Stay: days	3 (2, 6)	3 (1, 98)	0.161
Median follow-up after LT: months	77 (21, 102)	74 (0.1, 175)	**0.0001**
Donor			
Age: years	47 (34, 57)	46 (34, 56)	0.460
DCD (*n*; %)	137 (9.9%)	33 (10.5%)	0.755
Split grafts (*n*; %)	139 (10%)	43 (13.7%)	0.068
BMI	25 (23, 28)	25 (23, 28)	0.819
Operative characteristics			
Operative time: minutes	325 (285, 377)	298 (144, 600)	**0.0001**
Cold ischemia time: minutes	542 (441, 657)	540 (166, 970)	0.316
Recipient warm ischemia time: minutes	41 (36, 47)	39 (22, 84)	**0.002**
RBC transfusion: units	3 (0, 5)	3 (1, 5)	0.115
Platelet transfusion: units	10 (0, 15)	10 (0, 15)	0.115
FFP transfusion: units	9 (4, 12)	9 (4, 12)	0.225
Total blood product transfusion: units	23 (10, 30)	21 (6, 31)	0.057
Blood loss: ml	684 (241, 1262)	532 (250, 1314)	0.977
Complications (*n*; %)			
Vascular (overall)	84 (6.1%)	23 (7.3%)	0.439
E-HAT	22 (1.6%)	11 (3.5%)	**0.038**
L-HAT	62 (4.5%)	12 (3.8%)	0.651
Time to E-HAT: days	11 (5, 17)	7 (5, 11)	0.396
Time to L-HAT: days	136 (44, 652)	381 (102, 1092)	0.259
Biliary (overall)	228 (16.4%)	59 (18.8%)	0.430
Anastomotic stricture	117 (8.4%)	27 (8.6%)	
Nonanastomotic stricture	12 (0.9%)	2 (0.6%)	
Biliary leak	31 (2.2%)	6 (1.9%)	
Retransplantation	74 (5.3%)	19 (6.1%)	0.584

DCD, donor after cardiac death; CIT, cold ischemia time; E-HAT*, early hepatic artery thrombosis diagnosed during first 21 days; L- HAT, late hepatic artery thrombosis diagnosed later than day 21.

Statistically significant p values are represented in bold.

*Continuous data has been showed in median (25th percentile, 75th percentile).

for SLT and CLT recipients, respectively. Differences in postoperative biliary complications ($P = 0.43$), and the need for retransplantation ($P = 0.58$), were not significant on intergroup analysis; however, incidence of E-HAT (diagnosed during the first 21 days after transplant) in SLT recipients was 22 vs. 11 in the CLT recipients (1.6% vs. 3.5%, respectively) ($P = 0.038$) (Table 1). The absolute number of E-HAT events in each group was low, and

Table 2. Difference between 1st and 2nd transplants in consecutive group.

Characteristics	1st transplant consecutive LT (*N* = 155)	2nd transplant consecutive LT (*N* = 159)	*P*-value
Recipient			
Age*	56 (45, 62)	53 (44, 59)	0.151
Sex (*n*; % male)	78 (50.3%)	91 (57.2%)	0.258
BMI	26 (23, 29)	26 (23, 30)	0.830
Etiology (*n*; %)			
Polycystic liver disease	1 (0.6%)	2 (1.3%)	0.191
Alcoholic cirrhosis	24 (15.5%)	37 (23.3%)	
Hepatitis B cirrhosis	6 (3.9%)	9 (5.7%)	
Hepatitis C cirrhosis	21 (13.5%)	27 (17%)	
Primary biliary cirrhosis	26 (16.8%)	18 (11.3%)	
Primary sclerosing cholangitis	14 (9%)	12 (7.5%)	
Cryptogenic cirrhosis	10 (6.5%)	5 (3.1%)	
NASH (nonalcoholic steatohepatitis)	2 (1.3%)	6 (3.8%)	
Acute failure	20 (12.9%)	11 (6.9%)	
Other	18 (11.6%)	23 (14.5%)	
Retransplantation as indication	13 (8.4%)	9 (5.7%)	
MELD	13 (11, 19)	13 (10, 18)	1
Median waiting time: months	1.7 (0.3, 4)	2 (0.4, 4)	0.638
Hospital stay: days	12 (8, 22)	11 (9, 17)	0.441
ICU stay: days	4 (2, 7)	3 (2, 6)	0.434
Median follow-up after LT: months	54 (14, 72)	54 (16, 77)	0.646
Donor			
Age	49 (36, 57)	44 (31, 53)	**0.015**
DCD (*n*; %)	21 (13.5%)	12 (7.5%)	0.098
Split grafts (*n*; %)	20 (12.9%)	23 (14.5%)	0.744
BMI	25 (22, 28)	25 (23, 28)	0.342
Operative characteristics			
Operative time: minutes	300 (248, 358)	295 (246, 348)	0.256
Cold ischemia time: minutes	517 (406, 600)	573 (455, 700)	**0.001**
Warm ischemia time: minutes	40 (36, 46)	39 (34, 44)	0.151
RBC transfusion: units	3 (0, 4)	3 (1, 6)	0.394
Platelet transfusion: units	10 (0, 11)	10 (0, 20)	0.281
FFP transfusion: units	9 (4, 12)	10 (4, 12)	0.918
Total blood product transfusion: units	20 (6, 28)	22 (6, 33)	0.364
Blood loss: CC	509 (245, 1071)	735 (250, 1477)	0.321
Complications (*n*; %)			
Vascular (overall)	16 (10.3%)	7 (4.4%)	0.052
E-HAT	8 (5.2%)	3 (1.9%)	0.135
L-HAT	8 (5.2%)	4 (2.5%)	0.252
Time to E-HAT: days	8,9 (2, 11)	6 (6, 12)	0.838
Time to L-HAT: days	689 (145, 1348)	216 (51, 483)	0.494
Biliary (overall)	29 (18.7%)	30 (18.9%)	0.303
Anastomotic stricture	16 (10.3%)	11 (6.9%)	
Nonanastomotic stricture	2 (1.3%)	0	
Biliary leak	9 (5.8%)	15 (9.4%)	
Retransplantation	11 (7.1%)	8 (5%)	0.485

DCD, donor after cardiac death; CIT, cold ischemia time; E-HAT, early hepatic artery thrombosis diagnosed during first 21 days; L-HAT, late hepatic artery thrombosis diagnosed later than day 21.

Statistically significant p values are represented in bold.

*Continuous data has been showed in median (25th percentile, 75th percentile).

within the expected international reported data for this complication. On intragroup analysis, the incidence of E-HAT was higher in the first transplants compared with subsequent transplants in the CLT group; however, difference did not reach statistical significance ($P = 0.135$) (Table 2). On further subgroup analysis of CLT recipients,

Table 3. Complications in relation to the operating surgeon in the consecutive group, whether performed by same surgeon or different surgeon.

Complications (*n*; %)*	Consecutive LT by same surgeon (*N* = 90)	Consecutive LT by different surgeon (*N* = 69)	*P*-value
Vascular (overall)	5 (5.6%)	2 (2.9%)	0.472
E-HAT	2 (2.2%)	1 (1.4%)	1
L-HAT	3 (3.3%)	1 (1.4%)	0.634
Biliary (overall)	14 (15.6%)	16 (23.2%)	0.111
Anastomotic stricture	7 (7.8%)	4 (5.8%)	
Nonanastomotic stricture	0	0	
Stricture (nonsignificant)	0	4 (5.8%)	
Biliary leak	7 (7.8%)	8 (11.6%)	
Retransplantation	4 (4.4%)	4 (5.8%)	0.728

*Other complications: Data not shown.

Table 4. Difference in overall patient and graft survival between consecutive and solitary transplants.

	Overall patient survival			Graft survival		
	1 year	3 year	5 year	1 year	3 year	5 year
Consecutive, %	85	82	78	82	78	72
Solitary, %	86	81	77	83	78	74
P-value		0.708			0.740	

Table 5. Difference in overall patient and graft survival between 1st and 2nd transplants in consecutive group.

	Overall patient survival			Graft survival		
	1 year	3 year	5 year	1 year	3 year	5 year
1st transplant, %	84	82	75	81	79	68
2nd transplant, %	87	84	80	84	80	76
P-value		0.192			0.168	

no significant outcome differences were found when operating surgeon fatigue was analyzed, that is, when the first LT and the subsequent transplant/s were performed by the same surgeon or by different surgeons (Table 3).

Graft and patient survival

There were no significant differences in overall patient or graft survival at 1, 3, and 5 years after liver transplant on intergroup analysis ($P = 0.708$ and 0.740, respectively) or on intragroup analysis ($P = 0.192$ and 0.168, respectively) (Tables 4 and 5), suggesting that recipients are not disadvantaged when multiple simultaneous organ offers are accepted.

Discussion

The field of transplantation is unique among the surgical subspecialties in that the timing of transplant is largely driven by the time of donor death [10], over which the transplant surgeon has no control. The adverse impact of prolonging CIT is well established, and delaying recipient operations could render some grafts unusable. [11]. Transplanting patients with the first acceptable organ that becomes available reduces waiting list mortality, but frequently transplant surgeons are confronted with offers for multiple recipients simultaneously. Therefore, it is important for transplant surgeons to know whether the decision to accept multiple organ offers consecutively impacts recipient outcomes.

From our analysis, it seems there was an attempt to minimize cold ischemia and warm ischemia time when a CLT was planned. This suggests that surgeons made an effort to match donor and recipients differently when multiple simultaneous offers occurred, such as selecting recipients who have not undergone previous abdominal surgery or experienced multiple episodes of spontaneous bacterial peritonitis. This type of highly specific donor and recipient matching is critical to the success of CLT, and it is possible under the current centre based allocation system in the United Kingdom.

Liver allografts from deceased donors are either accepted by a liver transplant center on the first instance, or declined at least once before being accepted for transplantation elsewhere [3,12]. Data from the United States demonstrated that, among all livers refused at least once, 92% were transplanted into recipients with an equal or a lower MELD score compared to the index candidate. Therefore, waitlist mortality is not simply a result of not having opportunity for transplantation, but also results from opportunities for transplantation that were declined [4]. If the act of performing consecutive transplantation does not increase recipient morbidity or mortality, transplant surgeons could be more likely to accept multiple simultaneous offers.

Fatigue is a concern when considering organ offers. The performance of the operating room staff, anesthesiologists, and surgeons are potentially suboptimal if multiple simultaneous offers are accepted. Fatigue could therefore have a profound effect on the rate of complications [13,14]. It has been suggested that an interval of >2 days between successive liver transplants performed by the same surgeon improved patient and graft survival at 1 year [7]. This would limit centers to accepting three liver offers a week, a

limitation that does not seem realistic at high-volume centers. The evidence addressing the impact of fatigue on surgical performance is conflicting. A single systematic review on this topic failed to meta-analyze data across studies to draw conclusions because factors such as cognitive skills, anatomical recognition, decision-making, judgment, leadership, and communication are crucial to surgeon's performance but cannot be controlled [15]. Randomized controlled trials to determine the effect of fatigue on performance in surgery would be unethical. Here, in our series there have been efforts to spread the transplant workload in case of consecutive transplants. Although this did not occur in all occasions in our series, ideal transplant set-up in high-volume centers would be to have separate operating theatre, anesthetic, and surgical teams to facilitate consecutive or even simultaneous LT in order provide maximum utility of offered liver allografts serving the patients in transplant wait lists.

The overall incidence of E-HAT in CLT recipient group is 3.5% compared with median incidence of 2.9% reported in the literature [16]. The rate of E-HAT was higher in the first recipient of a CLT compared to the second recipient. It may be argued that apparent rushed anastomosis of the hepatic artery could have led to the increased E-HAT rates in the second transplant in the CLT; this argument may be supported by slight but statistically significant difference in warm ischemia time (implantation time). The warm ischemia time is usually calculated as the time between the grafts come out of ice until the portal reperfusion is commenced; hence, the arterial anastomosis time is not included and above criticism may not be valid. It may be also possible to argue that increased rate of E-HAT in the entire CLT group was due to fatigue, and then, the rate of E-HAT in the second recipient would be expected to be greater than the rate in the first recipient. Our study used CLT performed by a single surgeon as a proxy for surgical team workload and suggests that either fatigue can be avoided by delegating the second transplant to a colleague when available, or the increased surgical workload did not have significant effects on complication rates, graft survival, or patient survival. Our data emphasize that recipients of CLT are not disadvantaged by their surgeon's decision to accept multiple simultaneous organ offers.

Our study has shortcomings, as it is retrospective. Secondly, there are inherent shifts in clinical decision-making that occur in studies as long as this one. As a result of changing clinical practices, more CLT were performed in recent years, leading to shorter median follow-up in CLT recipients. The results of this study may not be directly transferable to centers operating under different allocation systems, but the concepts driving the decision-making are clearly universal. Additionally, the conclusions drawn from this data may not be transferable to centers with fewer resources. Lastly, we used the surgeon as the proxy for team workload to study fatigue, but the issues affecting operating room staff and anesthesia providers are well not captured by this data.

In conclusion, performing multiple liver transplants within a 12-h period is safe at a high-volume liver transplant center where the required resources are available. The surgeon must take care to prevent E-HAT if avoidable but being multifactorial for its occurrence, this complication may not be completely prevented. In the era of critical organ scarcity, CLT allows pragmatic utilization of organs in busy transplant centres which permits transplant surgeons to accept multiple liver offers simultaneously, furthering the efforts to reduce waiting list. We would like to conclude by stating that this should not a long-term solution to the growing demand for transplant activity and perhaps better infrastructural and organizational arrangements would be an alternative approach.

Authorship

FZ: wrote the manuscript, contributed in study design, data collection and analysis. MMM and MB: collected and analyzed data. GR: contributed to writing of the manuscript and critical revision of the manuscript. BG: collected data. HM, SB, JI, PM and DF: critically revised intellectual content of the manuscript. MTPRP: conceptualized and designed the study and critically revised the manuscript. All authors approved the final version of the manuscript.

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