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Graft Related Factors Affecting the Recipient Outcome in Living Donor Liver Transplantation

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Abstract

Background: Multiple risk factors have been incriminated in poor outcome and survival after Living Donor Liver Transplantation (LDLT). We conducted this study to identify graft-related factors that affects recipient outcome and survival after LDLT.

Patients and Methods: This is a combined retrospective and prospective study that was conducted at Mansoura University Gastrointestinal Surgical Center GISC. We included 460 transplant recipients in the period between June 2004 and July 2016. Moreover, the prospective arm included 50 patients who underwent living donor liver transplantation as a sample size from starting the study in July 2016. After careful preoperative preparation for both donor and recipient, cases were scheduled for living donor liver transplantation. All cases were performed by the same transplant surgical team using the standard surgical procedure. After procedure, patients were transferred to the liver transplant ICU for 1 week, then to the liver high care unit. In addition to clinical evaluation, follow-up of the recipients was performed by laboratory and radiological investigations. Evaluation of the liver by abdominal CT was routinely performed 2 to 3 times over the first year after LT, and then once or twice per year.

Results: It was evident that acute rejection was associated with shorter cold ischemia time (31.84 vs. 42.58 minutes-p=0.016). Moreover, larger biliary stoma size was also associated with acute rejection (4.24 vs. 3.73mm -p=0.045). Regarding bile leakage, it was found to be associated with smaller hepatic venous reconstruction diameter (26.11 vs. 27.38mm-p=0.036). Additionally, it was found that incidence of biliary strictures was associated with longer warm ischemia time (51.85 vs. 45.32 minutes-p=0.019), smaller vs venous reconstruction diameter (7.41 vs. 8.52-p=0.024), and smaller biliary reconstruction diameter (3.51 vs. 3.84mm -p=0.033). Cases who developed primary graft dysfunction were having significantly prolonged warm ischemia time (66.92 vs. 46.52 minutes -p 0.011). Chronic graft rejection was associated with larger Makuuchi vein reconstruction diameter (13.40 vs. 9.62mm -p=0.020). However, other graft related factors did not seem to be different between cases who developed and who did not develop chronic rejection.

Portal vein thrombosis was associated with larger Makuuchi vein reconstruction diameter (20 vs. 9.6mm -p=0.001). Cases who developed hepatic artery thrombosis postoperatively were having larger Makuuchi vein reconstruction diameter (20 vs. 9.71mm -p=0.003), and lower numbers of single arterial reconstruction (p=0.003).

In addition, cases who developed disease recurrence after transplantation were having larger arterial reconstruction diameter (2.63 vs. 2.45-p=0.020), and more ratio of multiple biliary ductal anastomoses (p=0.018). HCC recurrence after transplant was associated with larger portal vein reconstruction diameter (12.66 vs. 11.43mm -p=0.004), larger arterial reconstruction diameter (2.78 vs. 2.47mm -p=0.029), and smaller biliary reconstruction diameter (3.24 vs. 3.83- p=0.008). On assessment of graft related factors on survivals, all factors were found to be non-significant apart from number of venous anastomoses that was significantly affecting survival (p= 0.042).

Conclusion: Multiple graft related factors were studied as risk factors for outcome, survival, and recurrence after LDLT. The rate of early graft failure is low. This was due to optimum donor selection as regards age, sex, Body Mass Index (BMI) and ABO-compatibility; computer-assisted planning and decision making in calculating optimum GRWR; short cold ischemic time; high level of expertise in our center; and timely detection of vascular, biliary and immunological complications responsible for early graft failure together with early and efficient management. Nevertheless, most of the underlying risk factors affecting either outcome, recurrence, or survival were different from each other according to the complication type as previously shown in the results. This necessitates the need for multiple studies to be conducted at this perspective. However, these studies should be specific targeting only one or a small group of complications to get more specific results.

Key Words: *Living Donor Liver Transplantation (LDLT) – Hepatocellular Carcinoma (HCC).*

Introduction

LIVER Transplantation (LT) is currently the treatment of choice to save the lives of patients with end-stage liver diseases or fulminant hepatic failure **[1]**.

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Living Donor Liver Transplantation (LDLT) has emerged as an effective alternative to Deceased Donor Liver Transplantation (DDLT). LDLT offers many advantages like decreasing waiting time and choosing more optimal timing of surgery. Nevertheless, owing to differences in graft size, quality, and preservation time, it is associated with higher risk of post-operative complications [2].

Proper selection of donors for LDLT is crucial for the success of this surgical procedure. As surgical experience increases, donor selection criteria are evolving. In LDLT, donor safety is the most important clinical issue [3].

Graft related factors that affect the outcome of LDLT include: Type of graft (right or left graft), size of graft (Graft Weight/Recipient Weight ratio (GW/RW)), graft steatosis, venous outflow (middle hepatic vein involvement), portal inflow, vascular and biliary anatomical variations and their reconstruction and time of graft ischemia [4].

More recent data show a decrease in surgical complications of recipient associated with increased experience. These complications include: Bleeding, infection, biliary complications, hepatic artery or portal vein thrombosis. Long term complications include graft dysfunction, recurrence and mortality [2].

This study was conducted to assess the graft related factors as type of graft (right or left graft), size of graft, graft steatosis, venous outflow (middle hepatic vein involvement) and others that may influence patient outcome as regard early complications, graft dysfunction, recurrence and survival after LDLT.

Patients and Methods

Study design:

This a combined prospective and retrospective study including patients who underwent living donor liver transplantation at Mansoura University Gastrointestinal Surgical center GISC. The retrospective limb of this study included 460 cases who underwent their operations in the period between June 2004 to July 2016. On the other hand, the prospective limb included another 50 cases who underwent LDLT after July 2016. The study was approved by the Local Ethical Committee.

Patient sample:

Five hundred and ten cases (n=510) who underwent LDLT were enrolled in that study.

Consent:

A written formal consent was obtained from both donors and recipients after the explanation of the details, advantages and complications of the surgical procedure.

Donor preparation:

All donors were evaluated by the same team consisting of surgeons, hepatologists, anesthesiologists, and radiologists. In addition, pathologists and psychiatrists shared in donor evaluation as well. Donor candidates were limited to blood relatives up to the 4th degree, and the spouse or equivalent of the recipient, if they manifested a strong desire to donate part of their liver of their own free will.

We accepted donors between ages of 18-45 years who were medically, psychologically fit, ABO blood group is either identical or compatible, no substantial medical disease, conventional vascular and biliary anatomy, sufficient liver volume to meet their metabolic demands (RLV/donor body weight ratio <0.8%), macro or micosteatosis <20% by liver biopsy, and normal biochemical tests. All donors were evaluated clinically, radiologically, and biochemically. Moreover, liver biopsy was ordered for all donors.

Absolute exclusion criteria included pregnancy, ABO incompatibility, mental instability, any medical condition which may increase the risk of complications, positive HBV or HCV serology, underlying liver disease, steatosis >20%, and abnormal anatomy considered by surgeons to increase the risk of hepatectomy or affect the remaining liver.

Recipient preparation:

The recipients were routinely evaluated by same team evaluating the donor. Clinical, laboratory and radiological evaluation were performed thoroughly.

Surgical procedure:

Hockey stick or J shaped incision was the one preferred by our surgical team to explore both donor and recipient. After donor exploration, complete mobilization of the right lobe was carried out. After that pedicle dissection was performed till identification of the right pedicle. Parenchymatous transection was performed either by harmonic scalpel or spray diathermy technique. After complete division of right lobe, the graft was transferred to the back table, and stumps of the right pedicle were closed using different suture types according to the structure being closed (prolene 6/0 for PV

stump, prolene 5/0 for HV stump, and PDS or Maxon 6/0 for the biliary stump).

The hepatic graft was weighed using a digital scale that was properly covered with a sterile material and previously set to zero and then infused with 3 liters of cold Custodiol HTK solution (Bensheim, Germany), through PV while immersed in sterile iced saline. Venoplasty was done when there was a vein >5mm adjacent to RHV to do one anastomosis with recipient IVC, GoreTex or autologous grafts were used in veins >5mm, two nearby bile ducts ere approximated in one stoma, and all these were done on back table.

On the recipient side, complete mobilization of the liver was performed. After that, dissection of the pedicle was carried out till end hepatectomy was reached. To avoid excess homologous blood transfusion, a cell saver is used for auto-transfusion except in HCC cases. Hepatic venous reconstruction is done by end-to-end reconstruction between graft RHV and recipient RHV stump and the IVC using running 4/0 prolene sutures, leaving a loose stitch for venting of blood. Portal vein reconstruction is done using prolene 6-0.

Hepatic arterial reconstruction is then performed using interrupted 8-0 prolene sutures under surgical loupe magnification using posterior wall first technique. Reconstruction of MHV tributaries was done in case of tributaries >5mm in diameter with significant blood flow during implantation. Reconstruction of MHV tributaries is done using natural or synthetic grafts to IVC venotomy on the recipient's side. Neither porto-caval shunt nor veno-venous bypass is used in recipient surgery.

The technique employed for biliary reconstruction was variable according to the graft biliary features. Whenever possible, biliary reconstruction by single anastomosis Duct-to Duct Anastomosis (DDA) was done between graft RHD to recipient CHD, RHD, or LHD.

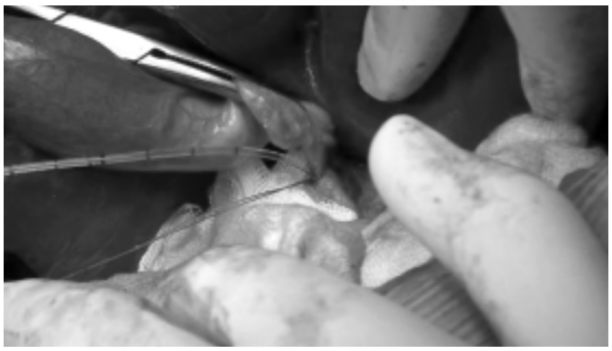

Fig. (1): Transcystic cholangiogram in donor.

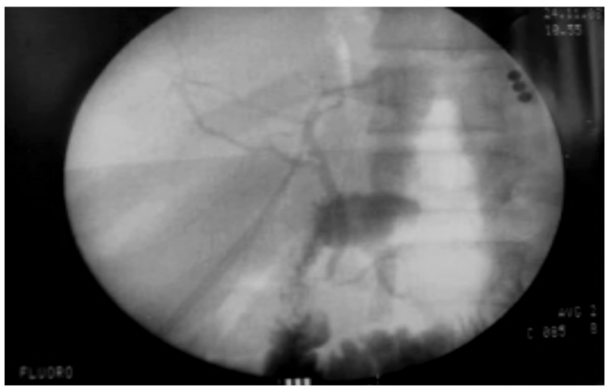

Fig. (2): Donor cholangiography showing 2 ducts to be anastomosed.

Fig. (3): Weighing of RL before transplantation.

Follow-up:

Recipients are admitted to liver ICU for 1 week. Daily LFTs, coagulation profile, renal function tests and abdominal U/S are done in the first week. The patient is transferred to a Liver High Care Unit. Evaluation of the liver by abdominal CT is routinely performed 2 to 3 times over the first year after LT, and then once or twice per year.

Results

Donor characteristics:

Starting with donor characteristics, the mean age of the included donors was 31.33 years (range, 18-47). We included 374 male donors (73.3%) while the remaining donors were females (136 cases-26.7%). The mean graft volume in this study was 950.2 grams (range, 600-1600), while GRWR had a mean of 1.13 (range, 0.7-2.12). The remaining liver residual had a mean of 38.8% (range, 30-52.78). These data are illustrated at (Table 1).

Recipient characteristics:

Regarding recipient characteristics, the mean age of the included patients was 52.33 years. We included 448 (87.2%) male recipients in our study, while the remaining ratio occupied by females (62 cases-12.8%). The mean MELD score for the in-

cluded cases was 16.31. These data are illustrated in (Table 2).

Operative data:

The mean value of both cold and warm ischemia durations was 42.6 and 46.5 minutes respectively. Single hepatic vein reconstruction was carried out in 282 cases (55.2%) while 157 cases (30.7%) had two hepatic veins reconstruction. Moreover, single Makuuchi vein reconstruction was performed in 87 cases (17.05%) whereas double reconstruction was done in 7 cases (1.3%).

When it comes to the biliary anastomosis, 271 cases (53.1%) had a single ductal anastomosis. Other 221 cases (43.3%) had double anastomoses while only 18 cases (3.6%) had three biliary anastomoses. These data are illustrated in (Table 3).

Post-operative complications:

According to Clavien-Dindo classification, 15 cases (2.9%) had grade I complication, 58 cases (11.3%) had grade II complications, 26 (5.1%) cases had grade IIIa complications, 62 cases (12.1%) had grade IIIb complications, and 22 cases (4.3%) had grade IV complications. Table (4) explains the details of post-operative complications encountered in the recipients.

Acute rejection:

As shown in (Table 5), it was evident that acute rejection was associated with shorter cold ischemia time (31.84 vs. 42.58 minutes-p=0.016). Moreover, larger biliary stoma size was also associated with acute rejection (4.24 vs. 3.73mm -p=0.045).

Bile leakage:

Regarding bile leakage, it was found to be associated with smaller hepatic venous reconstruction diameter (26.11 vs. 27.38mm -p=0.036). These data are shown in (Table 6).

Biliary strictures:

It was found that incidence of biliary strictures was associated with longer warm ischemia time (51.85 vs. 45.32 minutes-p=0.019), smaller vs venous reconstruction diameter (7.41 vs. 8.52-p= 0.024), and smaller biliary reconstruction diameter (3.51 vs. 3.84mm -p=0.033). These data are illustrated in (Table 7).

Primary graft dysfunction:

Cases who developed primary graft dysfunction were having significantly prolonged warm ischemia time (66.92 vs. 46.52 minutes -p 0.011) and (Table 8) illustrates these data.

Chronic graft rejection:

Chronic graft rejection was associated with larger Makuuchi vein reconstruction diameter (13.40 vs. 9.62mm -p=0.020). These data are illustrated in (Table 9).

Portal vein thrombosis:

As shown in (Table 10), portal vein thrombosis was associated with larger Makuuchi vein reconstruction diameter (20 vs. 9.6mm -p=0.001).

Hepatic artery thrombosis:

Cases who developed hepatic artery thrombosis post-operatively were having larger Makuuchi vein reconstruction diameter (20 vs. 9.71mm -p=0.003), and lower numbers of single arterial reconstruction (p=0.003). These data are shown in (Table 11).

Disease recurrence:

Cases who developed disease recurrence after transplantation were having larger arterial reconstruction diameter (2.63 vs. 2.45-p=0.020), and more ratio of multiple biliary ductal anastomoses (p=0.018). These data are illustrated at (Table 12).

HCC recurrence:

HCC recurrence after transplant was associated with larger portal vein reconstruction diameter (12.66 vs. 11.43mm -p=0.004), larger arterial reconstruction diameter (2.78 vs. 2.47mm -p=0.029), and smaller biliary reconstruction diameter (3.24 vs. 3.83-p=0.008). Data are shown in (Table 13).

Survival:

Kaplan-Meier patient survival analysis is shown in Fig. (4). The 1-, 3- ad 5-year survival in this series was 83.14%, 81.6% and 77.7% respectively. The median survival time 60 month. Causes of mortality are illustrated at (Table 14).

On assessment of graft related factors on survivals, all factors were found to be non-significant apart from number of venous anastomoses that was significantly affecting survival (p=0.042). Survival related factors are illustrated at (Table 15).

Table (1): Donor characteristics.

Variable	Data
Age (years)	31.33 (18-47)
Sex:	
Male	374 (73.3%)
Female	136 (26.7%)
BMI (kg/m^2)	26.32 (17.84-36.79)
Graft volume (gram)	950 (600-1600)
GRWR	1.13 (0.7-2.12)
Remaining liver volume (%)	38.8 (30-52.78)

Table (2): Recipient characteristics.

Variable	Data
Age (years)	52.33 (32-59)
Sex:	
Male	448 (87.2%)
Female	62 (12.8%)
BMI (kg/m^2)	28.7 (25-31)
MELD	16.31 (11-21)

Table (3): Operative data.

Variable	Data
Cold ischemia time (min)	42.6 (10-175)
Warm ischemia time (min)	46.5 (21-137)
Hepatic vein reconstruction:	
Single	282 (55.2%)
Two	157 (30.7%)
Three	56 (10.9%)
Four	15 (2.9%)
Hepatic vein stoma size (mm)	27.7 (16-30)
Makuuchi vein reconstruction:	
Single	87 (17.05%)
Double	7 (1.3%)
Makuuchi stoma size (mm)	9 (6-12)
V5 reconstruction:	
Number of cases	163 (31.9%)
Stoma size (mm)	8 (5-11)
V6 reconstruction:	
Number of cases	121 (23.7%)
Stoma size	8 (5-11)
Portal vein reconstruction:	
Single	481 (94.7%)
Double	29 (5.3%)
Arterial reconstruction:	
Single	505 (99.1%)
Double	5 (0.9%)
Biliary duct reconstruction:	
One duct	271 (53.1%)
Two ducts	221 (43.3%)
Three ducts	18 (3.6%)

Table (4): Post-operative recipient complications.

Complication	Number (%)
Bile leakage	40 (9.5%)
Biliary stricture	94 (17%)
Internal hemorrhage	20 (3.9%)
Collection	29 (5.6%)
Intrahepatic abscess	4 (0.7%)
Portal vein thrombosis	14 (2.7%)
Portal vein stenosis	13 (2.4%)
Hepatic artery thrombosis	8 (1.4%)
Hepatic artery stenosis	3 (0.5%)
Rejection:	
Chronic	26 (5.1%)
Acute	45 (8.1%)
Intractable ascites	24 (4.8%)
Wound infection	26 (4.7%)
Primary graft dysfunction	7 (1.4%)

Table (5): Impact of graft related factors on acute rejection.

Variable	Yes	No	*p*-value
Age	31.96	31.91	0.97
Sex	31:15	342:122	0.484
GRWR	1.202	1.1736	0.5
Steatosis	38:4:3	384:70:10	0.113
Cold ischemia time	31.84	42.58	0.016
Warm ischemia time	42.93	46.91	0.221
Venous reconstruction:			
A- No of anastomosis	21:13:9:2:0	262:145:44:13:1	0.232
B- Stoma size	27.51	27.56	0.850
Makuuchi vein reconstruction:			
A- No of anastomosis	8:1	79:6	0.668
B- Stoma size	10.40	9.75	0.589
V5 reconstruction:			
A- No of cases	13	150	0.913
B- Stoma size	8.20	8.33	0.838
V8 reconstruction:			
A- No of cases	19	102	0.060
B- Stoma size	7.43	8.20	0.410
Portal vein reconstruction:			
A- No of anastomosis	43:2	438:27	0.704
B- Stoma size	11.64	11.53	0.783
Arterial reconstruction:			
A- No of anastomosis	45:0	460:5	0.443
B- Stoma size	2.44	2.55	0.601
Biliary reconstruction:			
A- No of anastomosed duct orifice	21:23:1	250:197:18	0.449
B- Stoma size	4.24	3.74	0.045

Table (6): Impact of graft related factors on bile leak.

Variable	Yes	No	*p*-value
Age	31.46	31.97	0.683
Sex	45:9	329:127	0.079
GRWR	1.206	1.171	0.359
Steatosis	40:11:3	383:63:10	0.126
Cold ischemia time	47.91	40.81	0.144
Warm ischemia time	46.72	46.50	0.944
Venous reconstruction:			
A- No of anastomosis	27:17:9:1:0	255:142:44:14:1	0.565
B- Stoma size	26.11	27.38	0.036
Makuuchi vein reconstruction:			
A- No of anastomosis	12:1	75:6	0.981
B- Stoma size	9.93	9.80	0.903
V5 reconstruction:			
A- No of cases	15	148	0.922
B- Stoma size	7.65	8.40	0.221
V8 reconstruction:			
A- No of cases	9	112	0.289
B- Stoma size	8.63	8.00	0.602
Portal vein reconstruction:			
A- No of anastomosis	50:4	431:25	0.564
B- Stoma size	11.43	11.54	0.753
Arterial reconstruction:			
A- No of anastomosis	54:0	450:6	0.396
B- Stoma size	2.33	2.52	0.073
Biliary reconstruction:			
A- No of anastomosed duct orifice	26:26:2	245:194:17	0.728
B- Stoma size	3.61	3.80	0.389

Table (7): Impact of graft related factors on biliary stricture.

Variable	Yes	No	*p*-value
Age	31.16	32.09	0.332
Sex	66:28	308:108	0.449
GRWR	1.1898	1.1742	0.554
Steatosis	75:18:1	348:56:12	0.241
Cold ischemia time	44.67	40.86	0.255
Warm ischemia time	51.85	45.32	0.019
Venous reconstruction:			
A- No of anastomosis	48:31:13:2:0	243:128:40:13:1	0.683
B- Stoma size	27.67	27.64	0.972
Makuuchi vein reconstruction:			
A- No of anastomosis	18:1	68:6	0.975
B- Stoma size	9.16	9.99	0.381
V5 reconstruction:			
A- No of cases	30	133	0.850
B- Stoma size	7.41	8.52	0.024
V8 reconstruction:			
A- No of cases	25	96	0.786
B- Stoma size	7.00	8.30	0.123
Portal vein reconstruction:			
A- No of anastomosis	90:4	391:25	0.507
B- Stoma size	11.33	11.58	0.407
Arterial reconstruction:			
A- No of anastomosis	93:1	411:5	0.911
B- Stoma size	2.57	2.48	0.233
Biliary reconstruction:			
A- No of anastomosed duct orifice	46:42:6	225:178:13	0.268
B- Stoma size	3.51	3.84	0.033

Table (8): Impact of graft related factors on primary graft dysfunction.

Variable	Yes	No	*p*-value
Age	31.14	31.93	0.806
Sex	4:3	370:133	0.329
GRWR	1.1545	1.1758	0.826
Steatosis	6:0:1	417:74:12	0.088
Cold ischemia time	42.71	41.55	0.915
Warm ischemia time	66.92	46.52	0.011
Venous reconstruction:			
A- No of anastomosis	2:2:3:0:0	280:157:50:15:1	0.079
B- Stoma size	30.29	27.61	0.328
Makuuchi vein reconstruction:			
A- No of anastomosis	2:0	85:7	0.683
B- Stoma size	8.50	9.85	0.598
V5 reconstruction:			
A- No of cases	4	159	0.166
B- Stoma size	10.00	8.28	0.154
V8 reconstruction:			
A- No of cases	3	118	0.691
B- Stoma size	10.00	8.01	0.390
Portal vein reconstruction:			
A- No of anastomosis	7:0	474:29	0.513
B- Stoma size	11.00	11.54	0.587
Arterial reconstruction:			
A- No of anastomosis	7:0	497:6	0.771
B- Stoma size	2.57	2.50	0.843
Biliary reconstruction:			
A- No of anastomosed duct orifice	2:5:0	269:215:19	0.303
B- Stoma size	4.00	3.78	0.836

Table (9): Impact of graft related factors on chronic rejection.

Variable	Yes	No	*p*-value
Age	35.19	31.81	0.132
Sex	12:4	362:132	0.878
GRWR	1.2587	1.1728	0.296
Steatosis	13:3:0	410:71:13	0.792
Cold ischemia time	33.94	41.81	0.278
Warm ischemia time	44.69	46.59	0.720
Venous reconstruction:			
A- No of anastomosis	6:7:3:0:0	276:152:50:15:1	0.491
B- Stoma size	27.38	27.66	0.894
Makuuchi vein reconstruction:			
A- No of anastomosis	5:0	82:7	0.512
B- Stoma size	13.40	9.62	0.020
V5 reconstruction:			
A- No of cases	7	156	0.340
B- Stoma size	8.43	8.31	0.931
V8 reconstruction:			
A- No of cases	3	118	0.336
B- Stoma size	11.50	7.98	0.497
Portal vein reconstruction:			
A- No of anastomosis	16:0	456:29	0.318
B- Stoma size	10.81	11.55	0.263
Arterial reconstruction:			
A- No of anastomosis	16:0	488:6	0.657
B- Stoma size	2.63	2.49	0.476
Biliary reconstruction:			
A- No of anastomosed duct orifice	10:5:1	261:215:18	0.578
B- Stoma size	3.56	3.79	0.616

Table (10): Impact of graft related factors on portal vein thrombosis.

Variable	Yes	No	*p*-value
Age	31.93	31.90	0.988
Sex	12:3	363:132	0.558
GRWR	1.1165	1.1779	0.390
Steatosis	12:2:1	411:72:12	0.591
Cold ischemia time	48.43	41.38	0.363
Warm ischemia time	44.73	46.63	0.728
Venous reconstruction:			
A- No of anastomosis	9:4:2:0:0	274:154:51:15:1	0.942
B- Stoma size	29.67	27.60	0.123
Makuuchi vein reconstruction:			
A- No of anastomosis	2:0	85:7	0.683
B- Stoma size	20.00	9.60	0.001
V5 reconstruction:			
A- No of cases	3	160	0.281
B- Stoma size	8.67	8.31	0.816
V8 reconstruction:			
A- No of cases	3	118	0.832
B- Stoma size	6.50	8.07	0.500
Portal vein reconstruction:			
A- No of anastomosis	12:3	478:26	0.015
B- Stoma size	11.47	11.54	0.939
Arterial reconstruction:			
A- No of anastomosis	14:1	490:5	0.159
B- Stoma size	2.33	2.50	0.371
Biliary reconstruction:			
A- No of anastomosed duct orifice	12:1:2	259:219:17	0.005
B- Stoma size	4.40	3.76	0.075

Table (11): Impact of graft related factors on hepatic artery thrombosis.

Variable	Yes	No	*p*-value
Age	34.38	31.87	0.517
Sex	7:1	367:135	0.360
GRWR	1.1487	1.1766	0.760
Steatosis	6:1:1	417:73:12	0.199
Cold ischemia time	60.88	41.32	0.054
Warm ischemia time	41.00	46.65	0.447
Venous reconstruction:			
A- No of anastomosis	4:4:0:0:0	279:154:53:15:1	0.720
B- Stoma size	27.50	27.65	0.939
Makuuchi vein reconstruction:			
A- No of anastomosis	1:0	86:7	0.774
B- Stoma size	20.00	9.71	0.003
V5 reconstruction:			
A- No of cases	1	162	0.221
B- Stoma size	6.00	8.34	0.333
V8 reconstruction:			
A- No of cases	5	116	0.006
B- Stoma size	9.60	8.00	0.387
Portal vein reconstruction:			
A- No of anastomosis	8:0	473:29	0.483
B- Stoma size	12.25	11.53	0.478
Arterial reconstruction:			
A- No of anastomosis	7:1	497:5	0.003
B- Stoma size	2.25	2.50	0.319
Biliary reconstruction:			
A- No of anastomosed duct orifice	4:3:1	267:217:18	0.417
B- Stoma size	3.81	3.78	0.951

Table (12): Impact of graft related factors on disease recurrence.

Variable	Yes	No	*p*-value
Age	31.24	32.13	0.301
Sex	92:31	282:105	0.674
GRWR	1.1650	1.1798	0.599
Steatosis	105:14:4	318:60:9	0.467
Cold ischemia time	45.69	40.26	0.068
Warm ischemia time	48.04	46.05	0.365
Venous reconstruction:			
A- No of anastomosis	69:37:11:5:1	213:122:42:10:0	0.373
B- Stoma size	27.61	27.66	0.924
Makuuchi vein reconstruction:			
A- No of anastomosis	19:3	68:4	0.214
B- Stoma size	9.57	9.89	0.735
V5 reconstruction:			
A- No of cases	41	122	0.703
B- Stoma size	8.74	8.19	0.223
V8 reconstruction:			
A- No of cases	30	91	0.902
B- Stoma size	7.81	8.12	0.696
Portal vein reconstruction:			
A- No of anastomosis	114:9	367:20	0.370
B- Stoma size	11.68	11.48	0.486
Arterial reconstruction:			
A- No of anastomosis	121:2	383:4	0.596
B- Stoma size	2.63	2.45	0.020
Biliary reconstruction:			
A- No of anastomosed duct orifice	56:58:9	215:162:10	0.018
B- Stoma size	3.62	3.83	0.124

Table (13): Impact of graft related factors on HCC recurrence.

Variable	Yes	No	*p*-value
Age	30.20	32.07	0.169
Sex	28:13	346:123	0.447
GRWR	1.1265	1.1799	0.199
Steatosis	37:3:1	386:71:12	0.391
Cold ischemia time	46.05	41.17	0.294
Warm ischemia time	49.95	46.23	0.354
Venous reconstruction:			
A- No of anastomosis	18:15:4:4:0	264:144:49:11:1	0.072
B- Stoma size	27.59	27.65	0.948
Makuuchi vein reconstruction:			
A- No of anastomosis	6:1	81:6	0.481
B- Stoma size	10.43	9.77	0.616
V5 reconstruction:			
A- No of cases	13	150	0.751
B- Stoma size	9.17	8.25	0.202
V8 reconstruction:			
A- No of cases	11	110	0.744
B- Stoma size	7.38	8.12	0.536
Portal vein reconstruction:			
A- No of anastomosis	38:3	434:26	0.638
B- Stoma size	12.66	11.43	0.004
Arterial reconstruction:			
A- No of anastomosis	41:0	463:6	0.466
B- Stoma size	2.78	2.47	0.029
Biliary reconstruction:			
A- No of anastomosed duct orifice	18:19:4	253:201:15	0.075
B- Stoma size	3.24	3.83	0.008

Table (14): Recipient mortality after living donor liver transplant.

Variable	Number (%)
Medical comorbidities:	71 (11.9%)
Pneumonia	31 (5.7%)
Cerebrovascular events	21 (2.9%)
Cardiac events	10 (1.7%)
Recurrent tuberculosis	3 (0.5%)
Renal failure	4 (0.7%)
Multi-organ failure	1 (0.2%)
Transfusion-associated acute lung injury	1 (0.2%)
Graft related:	29 (5%)
Primary graft dysfunction	7 (1.4%)
Recurrent hepatocellular carcinoma	9 (1.7%)
Chronic rejection	6 (1%)
Fibrosing cholestatic hepatitis	2 (0.5%)
Small-for-size syndrome	4 (0.2%)
Liver failure (unknown cause)	1 (0.2%)
Procedure related:	20 (4.1%)
Biliary complications	9 (1.7%)
Outflow obstruction	3 (0.7%)
Hepatic artery thrombosis	4 (1%)
Lymphorea	1 (0.2%)
Hemorrhage	3 (0.5%)
Others:	2 (0.5%)
Auto accident	1 (0.2%)
Withdrawal after drug addiction	1 (0.2%)
Total number	121 (21.9%)

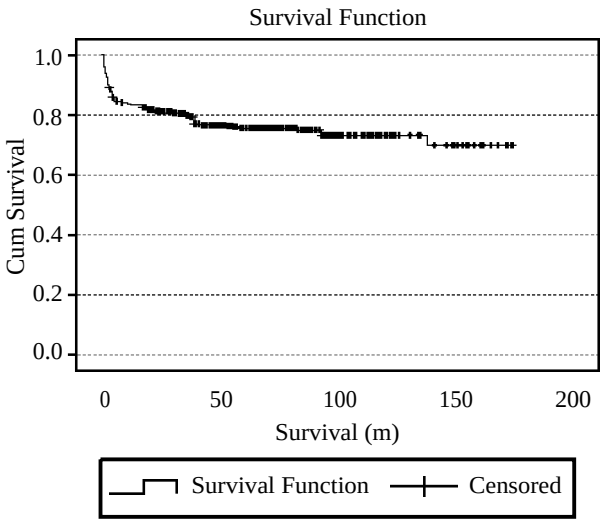

Fig. (4): Kaplan-Meier patient survival analysis.

Table (15): Impact of graft related factors on survival.

Variable	*p*-value
Donor age	0.882
Sex	0.487
GRWR	0.769
Steatosis	0.367
Cold ischemia time	0.860
Warm ischemia time	0.324
Venous reconstruction:	
A- No of anastomosis	0.042
B- Stoma size	0.054
Makuuchi vein reconstruction:	
A- No of anastomosis	0.052
B- Stoma size	0.531
V5 reconstruction:	
A- No of cases	0.239
B- Stoma size	0.848
V8 reconstruction:	
A- No of cases	0.937
B- Stoma size	0.106
Portal vein reconstruction:	
A- NO of anastomosis	0.926
B- Stoma size	0.398
Arterial reconstruction:	
A- No of anastomosis	0.640
B- Stoma size	0.450
Biliary reconstruction:	
A- No of anastomosed duct orifice	0.424
B- Stoma size	0.257

Discussion

Improved surgical outcomes have been reported due to the tremendous improvements in preoperative donor assessment, imaging modalities, surgical experience, and perioperative patient care. Nowadays, there are some reports stating that LDLT recipients have equal or increased survival when compared to deceased donors recipients [5].

This study included 510 patients underwent LDLT in the duration between May 2004 and June 2017 at Gastrointestinal Surgical Center, Mansoura University, and it was conducted to and assess the graft related factors as type of graft (right or left graft), size of graft, graft steatosis, venous outflow (middle hepatic vein involvement) and others that may influence patient outcome as regard to early complications, graft dysfunction, recurrence and survival after LDLT.

Acute rejection:

In our study, acute rejection occurred in 45 cases (8.1%) of recipients after LDLT. Short cold ischemia time (31.84 minutes) was noticed in the acute rejection group while longer duration was observed in the non-acute rejection (42.58 minutes-p=0.016). Moreover, wider biliary anastomotic reconstruction diameter (4.24 vs. 3.74mm -p=0.045) was noticed in the acute rejection patients. On the other hand, the remaining graft related factors were not significantly different between acute rejection and non-rejection group (p>0.05).

AR is a common complication after LDLT that may result in serious complications despite its immunologic advantage over deceased donor transplantation [6]. The incidence of such complication has decreased steadily over the past years due to advances in immunosuppression regimens and the introduction of new effective agents like tacrolimus and mycophenolate mofetil [7,8], but the incidence rate of AR after LT is reported to range between 20 and 80% [9,10].

Increased risk of AR has been linked to young patient age, prolonged cold ischemic time, prolonged operative time, sex match and graft-to-patient weight ratio [11,12]. Shindoh et al., found that preexisting immune liver disease as the only risk factor for such complication [13].

Bile leakage:

Bile leak has an incidence rate of 2-25% following liver transplantation [14]. Gondolesi and his associates reported that bile leakage is associated with an increased risk of graft failure and death [15].

In this study, bile leakage post LDLT was found to be associated with smaller hepatic venous reconstruction diameter (26.11 vs. 27.38mm -p= 0.036). Nevertheless, other studied graft related factors were not significant risk factors for postoperative bile leakage. Bile leakage was estimated to affect 9.5% (40 cases) of our study cases.

Gondolesi and colleagues reported that multiple biliary anastomotic reconstructions were associated with bile leakage after LDLT [15].

Another study confirmed that multiple anastomoses are considered a significant risk factor for bile leakage. Moreover, hepatitis C induced cirrhosis as an indication, and surgical experience were protective against this complication [2]. Nevertheless, number of biliary anastomoses were not significant for bile leakage in our study.

Conversely, another Korean retrospective study that included 74 LDLT recipients found that hepaticojejunostomy was associated with better long-term survival as well as less incidence of biliary complications. The reported complication in that group was 11.1% and it was significantly lower than duct-to-duct anastomosis group (complication rate 33.33%) [16].

Biliary strictures:

Multiple risk factors have been reported to be associated with increased risk of biliary strictures like ischemia to the biliary tree, cold ischemia, anastomotic type, age, gender, blood type, degree of liver steatosis, and number of biliary anastomoses. In DDLT, anastomotic biliary strictures are also influenced by transplantation in the post MELD era and the use of DCD organs [17,18].

The reported incidence of biliary strictures ranges between 8%-31% following LDLT [30,38], with a cumulative incidence of 6.6%, 10.6% and 12.3% after 1, 5 and 10 years respectively after DDLT [19].

In our study, biliary strictures were encountered in 94 cases (17%). Additionally, it was found that incidence of biliary strictures was associated with longer warm ischemia time (51.85 vs. 45.32 minutes -p=0.019), smaller V5 venous reconstruction diameter (7.41 vs. 8.52 -p=0.024), and smaller biliary reconstruction diameter (3.51 vs. 3.84mm-p=0.033).

Primary graft dysfunction:

It was reported that graft function after LT is affected by donor, procurement, transplantation procedure and recipient status [20,21]. Allograft function can be affected by donor-related factors, including age, nutritional status, degree of liver steatosis, hemodynamic stability during harvesting, liver allograft injury, and ischemia time during the procedure, as well as recipient-related factors, including recipient status and transplantation type [22].

In our study, primary graft dysfunction was encountered in 7 cases (1.4%). Cases who developed primary graft dysfunction were having significantly prolonged warm ischemia time (66.92 vs. 46.52 minutes -p=0.011). However, no other graft related factors were found to be a risk factor for such complication.

Multiple studies have identified donor age as a risk factor for this complication. Nevertheless, no clear age cut-off has been established. Graft dysfunction has been associated with liver transplantation from donors aged over 49 [52], 65 [53] or 45 years [23].

Chronic graft rejection:

The incidence of chronic graft rejection in our study was estimated to be 5.1% (26 cases). Chronic graft rejection was associated with larger Makuuchi vein reconstruction diameter (13.40 vs. 9.62mm-p=0.020). However, other graft related factors did not seem to be different between cases who developed and who did not develop chronic rejection. It was found to develop in about 24-80% (49%) of recipients in various studies as reported by a published review [24]. As donor and recipient are genetically related in LDLT, it should be associated with less rejection rates when compared to DDLT. Nevertheless, this is not a universal finding [25]. Liu et al., showed 16/50 (32%) AR in LDLT patients versus 36/49 (73%) AR in DDLT patients and this difference was attributed to sibling related donors because AR rates were not different in non-sibling related living donors and deceased donors [25].

Shaked et al., analyzed the data of 380 LDLT versus 213 DDLT. He could not find less ACR in LDLT group [26]. Additionally, patients experiencing repeated attacks of acute rejection are at increased risk of CR. Other risk factors include retransplantation for CR, male donor into female recipient, old donor age, prolonged cold ischemia time and genetically unrelated donors when compared to genetically related donors in LDLT [27,28].

Portal vein thrombosis:

In this study, portal vein thrombosis was associated with larger Makuuchi vein reconstruction diameter (20 vs. 9.6mm -p=0.001). Nevertheless, no other graft related risk factors were identified regarding portal venous thrombosis. This complication was encountered in 14 cases (2.7%).

The reported incidence of portal vein complications after LT ranges between 1-3%. Higher recipient morbidity and graft loss are associated with this complication [29]. In another recent study,

pre-operative thrombosis has identified as a definite risk factor. Nevertheless, higher complications were reported also in male recipients, compatible blood groups, and multiple PV anastomoses. Conversely, in the adult subgroup, low protein S and positive factor 5 Leiden mutation were associated with significantly higher complications rate [30].

Hepatic artery thrombosis:

In this study, cases who developed hepatic artery thrombosis post-operatively were having larger Makuuchi vein reconstruction diameter (20 vs. 9.71mm -p=0.003), and lower numbers of single arterial reconstruction (p=0.003). This complication was encountered in 8 cases (1.4%).

Several reports have extensively studied the risk factors of hepatic artery thrombosis that could be divided into several categories. Early Hat are usually due to technical problems. On the other hand, little data exists about definite risk factors for late HAT [29].

Non-surgical risk factors for HAT include; old donor age more than 60 years, prolonged cold ischemia time, ABO incompatibility, smoking, hypercoagulable states, CMV positive donor in a CMV negative recipient, rejection, regrafts and transplant for primary sclerosing cholangitis [31,32].

Indeed, other authors found no association between HAT and cold ischemic time, rejection, and donor age. Therefore, accurate determination of these risk factors is still extremely difficult [29].

Disease recurrence:

HCC recurrence after liver transplant remains a clinical issue regardless of the meticulous patient selection criteria. The recurrence of HCC remains a significant problem after LT although there has been marked improvement regarding survival rates [33].

In our study, cases who developed disease recurrence after transplantation were having larger arterial reconstruction diameter (2.63 vs. 2.45 -p= 0.020), and more ratio of multiple biliary ductal anastomoses (p=0.018). On the other hand, HCC recurrence after transplant was associated with larger portal vein reconstruction diameter (12.66 vs. 11.43mm -p=0.004), larger arterial reconstruction diameter (2.78 vs. 2.47mm -p=0.029), and smaller biliary reconstruction diameter (3.24 vs. 3.83 -p=0.008).

An Egyptian study conducted at Mansoura University concluded that prolonged warm ischemia time as well as older donor age are risk factors for HCV recurrence after LDLT. This problem could be resolved via early treatment with the direct-acting sofosbuvir [34]. Few predictors are existing regarding HCC recurrence after LDLT. Increased HCC recurrence was associated with donors more than 60 years or those who received organs through regional sharing [35].

Survival:

Some early and single center studies found that age did not significantly affect survival following LT [36,37]. Conversely, conflicting results have been published in other studies. A large population-based cohort study that included 2,938 patients who had LT, cases older than 60 years showed significantly increased mortality rates when compared to younger population [38]. Another single-center retrospective study which included 417 cadaveric liver transplant patient showed that patient's age was associated with both short and long-term survival in liver transplant patients [39].

In our study, on assessment of graft related factors on survivals, all factors were found to be non-significant apart from number of venous anastomoses that was significantly affecting survival (p=0.042). On the other hand, no other graft related factors were found to be significantly affecting survival.

Most studies have shown that a GRWR (considered to be a direct reflection of small for- size syndrome) less than 0.8% increases the opportunity for early graft failure [40,41]. On the other hand, Ben-Haim et al., 2001 showed that mortality rates among Child's class B or C patients whose GRWR less than 0.85%, three-fold greater than among those with GRWR greater than 0.85% in Child's class A [42].

Conclusion:

Multiple graft related factors were studied as risk factors for outcome, survival, and recurrence after LDLT. The rate of early graft failure is low. This was due to optimum donor selection as regards age, sex, Body Mass Index (BMI) and ABO-compatibility; computer-assisted planning and decision making in calculating optimum GRWR; short cold ischemic time; high level of expertise in our center; and timely detection of vascular, biliary and immunological complications responsible for early graft failure together with early and efficient management. Nevertheless, most of the underlying risk factors affecting either outcome, recurrence, or survival were different from each other according to the complication type as previously shown in the results. This necessitates the

need for multiple studies to be conducted at this perspective. However, these studies should be specific targeting only one or a small group of complications to get more specific results.

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آثر العوامل المتعلقة بالكبد المزروع على نتائج المريض بعد زراعة الكبد من متبرع حى

تمثل زراعة الكبد فى الوقت الحالى العلاج الآمثل لإنقاذ حياة المرضى اللذين يعانون من آمراض الكبد فى المراحل المتقدمة، آو من فشل كبدهم. وقد برزت زراعة الكبد من متبرع حى كبديل لزراعة الكبد من متوفى وذلك لعدة مزايا تتمثل فى خفض مدة الإنتظار والتحكم فى توقيت إجراء العملية، ولكنها قد تكون مصحوبة بعدد من المضاعفات للمريض.

ولا تزال زراعة الكبد من متوفى آمر مرفوض فى مصر وذلك لقضايا دينية وإجتماعية، مما جعل زراعة الكبد من متبرع حى هو النوع القائم فى مصر. وتشمل دواعى زراعة الكبد آنواع عدة من آمراض الكبد مثل إلتهاب الكبد الفيروسى سى وآورام الكبد وإلتهاب الكبد الكحولى وكذلك آمراض التمثيل الغذائى وغيرها .

وتشمل عملية نجاح العملية عوامل عديدة منها ما يرتبط بالمتبرع وإختياره قبل العملية وعوامل آخرى مرتبطة بالمريض والتى تؤثر على نجاح العملية فتشمل العمر، والنوع، ومؤشر كتلة الجسم، ونوع المريض الكبدى الذى تتم من آجله العملية والدرجة التى وصل إليها المريض حسب الضوابط العالمية التى وضعت لذلك، وقياس ضغط الوريد البابى وغير ذلك من العوامل.

ومن العوامل التى تؤثر على نتائج زراعة الكبد من متبرع حى، تلك العوامل المتعلقة بالجزء المزروع للمريض والتى تشمل: نوع الفص الكبدى (آيمن آو آيسر)، حجمه، ومقارنته بوزن المريض، ومدى التنكس الدهنى، ومدى التدفق الوريدى، وكذلك الإختلاف التشريحى للقنوات المرارية وتوصيلاتها والمدى الزمنى بين فصل جزء الكبد من المتبرع وبدء توصيله بالمريض.

ومن المضاعفات التى تؤدى إلى فشل عملية زراعة الكبد هى صغر حجم الجزء المزروع مقارنة بوزن المريض فلا يستطيع القيام بالوظائف المطلوبة، وكذلك نقص كمية التدفق الوريدى من الكبد وغير ذلك من المضاعفات، وتشمل المضاعفات النزيف، والتعرض للعدوى، والتسرب آو ضيق القنوات المرارية آو فشل الجزء المزروع، آو إنسداد الشريان الكبدى، آو صغر حجم الجزء المزروع، آو إرتداد المرض آو موت المريض.

الهدف من البحث: تحديد وتقييم عوامل التنبؤ المرتبطة بجزء الكبد المزروع مثل الحجم والنوع (فص آيمن آو آيسر) وغير ذلك من العوامل التى قد تؤثر على نتائج المرضى الخاضعين لزراعة الكبد من متبرع حى، وتحديد مدى تآثيرها على النتائج فيما يتعلق بالمضاعفات الناتجة فى وقت مبكر، وفشل الجزء المزروع عن آداء وظيفته، وتكرار المرض، ومدة البقاء على قيد الحياة بعد الجراحة.

خطة البحث: خضع للدراسة ٥١٠ مريض تم إجراء زراعة كبد لهم من متبرع حى خلال الفترة من مايو ٢٠٠٤ وحتى يونيو ٢٠١٧ بمركز جراحة الجهاز جامعة المنصورة.

نتائج البحث: تبين من نتائج البحث وجود إرتباط بين العوامل المتعلقة بجزء الكبد المزروع ومدى حدوث مضاعفات للمريض. ومنها على سبيل المثال:

- حدوث رفض مناعى حاد لجزء الكبد المزروع من قبل المريض مع قصر مدة نقص الإمداد الدموى للكبد المزروع لتصل إلى ٣١.٨ دقيقة وآيضاً مع زيادة قطر التوصيلة المرارية ل ٤.٢٤ مليمتر.
- وكذلك ثبت حدوث تسريب مرارى فى الحالات التى قل فيها قطر توصيل الوريد الكبدى عن ٢٦.١٨ مليمتر.
- ومن النتائج التى آثبتتها هذه الدراسة حدوث ضيق فى التوصيلة كلما زادت مدة الإنقاص الدموى للكبد المزروع قبل إعادة توصيله عن ٥١.٨ ثانية.
- وقد آثبتت النتائج آن الحالات التى ظهر بها تجمع صديدى (خراج) بجزء الكبد المزروع كان يقل فيها قطر توصيلة الوريد البابى عن ١٠.٣٨ملل.
- وثبت آيضاً من النتائج آن الحالات التى ظهر بها فشل وظيفى مبكر بالكبد المزروع زادت فيها مدة نقص الإمداد الدموى قبل توصيل الكبد بالمريض عن ٦٦.٩٢ دقيقة.
- وكذلك وجد آن الرفض المناعى الذى يحدث على المدى البعيد يرتبط بزيادة قطر وريد ماكوشى عن ١٣.٤مم، وقد لوحظ زيادة معدل ضيق التوصيلة المرارية فى الحالات التى يكون فيها المتبرع ذكر عن حالات التبرع من إناث.
- وهكذا وجد آن تجلط الوريد البابى يظهر آكثر فى الحالات التى إزداد فيها قطر وريد ماكوشى.
- وكذلك إرتبط زيادة معدل جلطات الشريان الكبدى بزيادة عن توصيلات الشرايين عن شريان واحد.

- ومن الملاحظ أيضاً أن الحالات التى حدث بها إصابة بأورام الكبد الأولية بعد زراعة الكبد كان يزيد فيها قطر توصيل الوريد البابى عن ١٢.٦٦مليمتر.
- كما أنه تبين عدم وجود تأثير واضح من هذه العوامل على مدة البقاء على الحياة بعد العملية إلا فيما يخص عدد توصيلات الأوردة الخاصة بجزء الكبد المزروع.

الخلاصة: أشارت هذه الدراسة إلى وجود رابط بشكل ما أو بآخر بين العوامل المرتبطة بجزء الكبد المزروع وبين نتائج زراعة الكبد من متبرع حى وحدوث مضاعفات.

ولكن يعيب هذه الدراسة أنها حاولت أن تشير لكل هذه العوامل مجمعة وبيان مدى تأثيرها وهذا أمر صعب متعدد الجوانب ولهذا فإنه من الأفضل مستقبلاً دراسة كل من هذه العوامل على حده لبيان مدى تأثيره بشكل واضح.