Complications and mortality after adult to adult living donor liver transplantation: A retrospective cohort study

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HIGHLIGHTS

- Mortality was higher among complicated cases.
- Vascular complication was independent predictors of poor outcome.
- Small for size syndrome was independent predictors of poor outcome.
- Proper management of the previous complications improve outcome of LDLT.

ARTICLE INFO

ABSTRACT

Background and aims: Living donor liver transplantation (LDLT) is widely performed for patients to resolve the critical shortage of organs from cadavers. Despite rapid implementation of the procedure, both complications and mortality of LDLT are annoying problems. The aim of this study was to analyze complications and mortality of patients after adult to adult LDLT (A-ALDLT) in a single center. Methods: Between April 2003 and November 2013, 167 (A-ALDLT) recipients in National Liver Institute, Egypt were included. We retrospectively analyzed complications and mortality in them.
Results: The overall incidence of complications was 86.2% (n = 144) and classified as biliary 43.7% (n = 73), vascular 21.6% (n = 36), Small for size syndrome (SFSS) 12.6% (n = 21), Gastrointestinal tract (GIT) 19.8% (n = 33), wound 12.6% (n = 21), chest 19.8% (n = 33), neurological 26.3% (n = 44), renal 21% (n = 35), intra abdominal collection 21.6% (n = 36), recurrent hepatitis C virus (HCV) 16.8% (n = 28), recurrent hepatocellular carcinoma (HCC) 2.4% (n = 4), acute rejection 19.2% (n = 32). 65 (45.1%) of 144 complicated patients died, while 10 (43.5%) of 23 non complicated died. The incidence of whole, in hospital and late mortalities were 44.9%, 28.7% and 16.2% respectively. Conclusions: Mortality was higher among complicated cases where vascular complications and SFSS had significant effect on it so prevention and treatment of them is required for improving outcome.

1. Introduction

Liver transplantation (LT) is currently the treatment of choice for patients with advanced chronic liver failure for which no other therapy is available. Despite great technological and immunological advances in the field of LT, there are still significant complications of recipients [1]. These complications include biliary, vascular, neurological, SFSS, early rejection, pneumonia, gastrointestinal hemorrhage, renal insufficiency or failure, bowel obstruction, postoperative collections, infection and malignant recurrence [2—7]. The previous complications have a significant impact on the morbidity and mortality of recipients [8]. Examples of mortality causes are infections, disease recurrence, malignancy, cardiovascular event, and renal failure [9]. So, these potential complications need to be minimized to improve immediate and long-term outcomes after LDLT [10]. The purpose of this work was to analyze

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List of abbreviations			
A-ALDLT	adult to adult living donor liver transplantation	HCV	hepatitis C virus
BMI	body mass index	HTK	hydroxy tryptophan ketoglutarate
BCS	budd chiari syndrome	HPB	HepatoPancreatoBiliary
CUSA	cavitron ultrasonic surgical aspirator	IC	intermediate care
CNIs	CalciNeurin Inhibitors	ICU	intensive care unit
CNS	central nervous system	IRB	institutional review board
CsA	CycloSporine	LDLT	living donor liver transplantation
DDLT	deceased donor liver transplantation	LT	liver transplantation
ERCP	endoscopic retrograde cholangio pancreatography	MELD	model for end stage liver disease
FK or FK-506	tacrolimus	MMF	Mycophenolate MoFetil
GDA	gastroduodenal artery	MHV	middle hepatic vein
GIT	gastrointestinal tract	MRCP	magnetic resonance cholangio pancreatography
GRWR	graft recipient weight ratio	NLI	National Liver Institute
HAT	Hepatic artery thrombosis	PBC	primary biliary cirrhosis
HBV	hepatitis B virus	PSC	primary sclerosing cholangitis
HCC	hepatocellular Carcinoma	PVT	portal vein thrombosis
HVT	hepatic vein thrombosis	SFSG	small for size graft
		SFSS	small for size syndrome
		SRL	sirolimus

complications and mortality of patients after (A-ALDLT) in a single center.

1.1. Patients and methods

After approval of institutional review board (IRB), we did this retrospective cohort study that analyzed complications and mortality in recipients in the department of hepatopancreatobiliary (HPB) surgery, national liver institute (NLI), university of Menoufiya, Menoufiya, Egypt, in the period from April 2003 to November 2013 with median follow up period of 24.7 ± 25.9 m (range, 0—120 m). The study included 167 (A—A LDLT) patients who had operations between April 2003 and February 2013. The data were collected from our records in the liver transplantation unit of our institute and written informed consents were obtained from both donors and recipients regarding operations and researches. We excluded patients with missing data and who did not complete the follow-up.

I Patients

The characteristics of recipients and donors (including operative parameters) and the indication for liver transplantation are shown in Tables 1 and 2.

A Characteristics of patients and their donors (including operative parameters)

They were classified as 147 (88%) males, and 20 (12%) females. Their mean age was 46.3 ± 8.2. Their donors were classified as 114 (68.3%) males and 53 (31.7%) females, their mean age was 26.9 ± 6.5. The patients were classified according to Child-Pugh score into 9 (5.4%) class A, 50 (29.9%) class B, and 108 (64.7%) class C, and mean model for end stage liver disease (MELD) score was 16.1 ± 4.2. Sixty one (36.5%) of them had co morbidities, in the form of Hypertension, DM, cardiac diseases and morbid obesity. Portal HTN affected 160 (95.8%) of them. The donor to recipient Bl. Group matching was classified into identical in 119 (71.3%) and Compatible in 48 (28.7%) of them. The right lobe graft was given to 159 (95.2%) and the left lobe was given to 8 (4.8%) of them. The mean actual graft weight and actual graft recipient weight ratio

(GRWR) were 819.4 ± 172.1 gm and 1.04 ± 0.20 gm respectively. While the mean cold and warm ischemia times were 74.9 ± 52.1 min and 52.1 ± 16.05 min respectively. The mean intra-operative blood transfusion was 7 ± 7.4 units Table 1.

B Indications of LT

The most frequent indications were HCV followed by HCC Table 2.

Table 1
Characteristics of patients and their donors including intra-operative parameters.

Donor age (years) (Mean ± SD)	26.9 ± 6.5
Recipient age (years) (Mean ± SD)	46.37 ± 8.2
Donor gender	
Males	114 (68.3%)
Females	53 (31.7%)
Recipient gender	
Males	147 (88%)
Females	20 (12%)
BMI of donor (Mean ± SD)	25.2 ± 3.4
Child class	
A	9 (5.4%)
B	50 (29.9%)
C	108 (64.7%)
MELD score (Mean ± SD)	16.1 ± 4.2
Co morbidity	61 (36.5%)
Portal HTN	160 (95.8%)
Bl. group	
Compatible	48 (28.7%)
Identical	119 (71.3%)
Graft type	
Right lobe	159 (95.2%)
Left lobe	8 (4.8%)
Actual graft weight (Mean ± SD)	819.4 ± 172.1
Actual GRWR	1.04 ± 0.20
Cold ischemia time (min) (Mean ± SD)	74.9 ± 52.1
Warm ischemia time (min) (Mean ± SD)	52.1 ± 16.05
intra-operative blood transfusion	7 ± 7.4
Duration of operation (hours) (Mean ± SD)	13.08 ± 3.2
Hospital stay (post-operative) (days) (Mean ± SD)	22.7 ± 16.05
Immunosuppression regimen	
Regimen including FK	144 (86.2%)
Regimen including Cyclosporine	51 (30.5%)
Regimen including **sirolimus**	19 (11.4%)

BMI: Body mass index, MELD: Model for end stage liver disease, GRWR: Graft recipient weight ratio.

Table 2
Indications of LT.

HCV	91 (54.5%)
HCC on top of HCV	55 (32.9%)
HCC on top of HBV	2 (1.2%)
Cryptogenic cirrhosis	7 (4.2%)
HBV	4 (2.4%)
BCS	2 (1.2%)
PSC	2 (1.2%)
PBC	1 (0.6%)
Wilson's disease	1 (0.6%)
Autoimmune hepatitis	1 (0.6%)
Alcoholic cirrhosis	1 (0.6%)

HCV: Hepatitis C virus, HCC: Hepatocellular carcinoma, HBV: Hepatitis B virus, BCS: Budd Chiari syndrome, PSC: Primary sclerosing cholangitis, PBC: Primary biliary cirrhosis.

II Methods

All donors were <19 years old and the donor work-up included liver function tests, liver biopsy, ultrasound examination, psychological assessment and CT angiography, along with hepatic volumetric study and vascular reconstructions [11].

A The donor and recipient operations
1 In the donor operation, the right or left lobes of the liver were mobilized and the vena cava was dissected. The CUSA device was used to divide the liver parenchyma without inflow occlusion. The falciform ligament was reconstructed, the stumps of the divided hepatic and portal veins were closed by continuous nonabsorbable sutures, after graft harvesting, it was perfused in the back-table with hydroxy tryptophan ketoglutarate (HTK) solution and weighted to determine the actual GRWR (graft weight per gram × 100/patient weight per KGx1000), if it was less than 0.8, the graft was named small for size graft (SFSG) [12].
2 In the recipient surgery, the native liver was explanted while carefully preserving the inferior vena cava. After reconstructing the hepatic and portal veins, the hepatic artery was anastomosed by the use of a surgical loupe or microscopy. The biliary tract was reconstructed by a duct-to-duct hepatico-choledochostomy or a Roux-en-Y hepatico-jejunostomy [13].
B post-operative management
1 Patients were given prophylactic therapy (Based on our institutional policy) in the form of:
a Antibiotics: This began 2 days before operation by using 3rd generation cephalosporine (cefotaxime 1 g m/12 h, then intraoperative we began with either Tazobactam (piperacillin + sulbactam) 4.5 g/8 h plus metronidazole 500 mg/8 h. Or Imepanem (Tinam) 1 g m/6 h plus metronidazole 500 mg/8 h. Then we changed antibiotics according to culture and sensitivity [14–17].
b Antifungal: Fluconazole (Diflucan)100 mg/24 h till pod 7 [18–20].
c Antiviral: Acycloviral 200 mg/8 h s began from POD 8 for 6 months for prophylaxis against CMV infection [14,21].
c Anticoagulants: Heparin infusion up to 180–200units/kg/day but when thrombocytopenia occurred, heparin was shifted to clexan 20 mg/12 h, then at POD8 dipyridamole was given 150 mg/12 h [22–24].
2 Based on our institutional policy: Immunosuppression and postoperative anti-HBV protocols: the standard was combination of 3 drugs calcineurin inhibitors (CNIs), steroids and mycophenolate mofetil (MMF). The initial methylprednisolone dose was 500 mg intra-operatively with a brief taper of prednisone from 240 to 40 mg/d over 6 days followed by 5–20 mg/d maintenance treatment, with complete withdrawal at the end of 3rd month

post LDLT. Cyclosporine (CsA) was used when neurotoxicty or nephrotoxicity developed with Tacrolimus. When CNIs were contraindicated or their side effects halted their use, sirolimus (SRL) was given at an initial dose of 3 mg/m^2 and adjusted over time to achieve blood trough levels of approximately 5–8 ng/mL. The post-operative anti-HBV protocols consisted of lamivudine combined with therapy with a low-dose of intramuscular hepatitis B immune globulin. Hepatitis B immune globulin was administered to all recipients with HBV infection during and after the transplantation [12,14–16].
3 post-operative follow-up until the end of follow-up period (The follow-up of post transplant patients was conducted by a team with transplant surgeon and transplant hepatologist) to detect:
a Complications (Biliary, vascular, small for size syndrome and etc … …..). Clavien's modified 5-tier scoring system [25] was used for grading recipient complications Table 3 in preference to his original version [26] which had only four grades [26].
b Mortality of patients: i- In hospital mortality (during the 1st hospital admission). ii- Late mortality (after discharge till the end of the follow-up period).

1.1.1. Statistical techniques
All data were tabulated and processed with SPSS software (statistical Product and Service solutions, version 21, SSPS Inc, Chicago, IL, USA) and Windows XP (Microsoft Corporation, Redmond, Washington, USA).

Qualitative data were expressed in frequency and percentage and analyzed with the chi-square or Fisher exact tests. Quantitative data were expressed as the mean and standard deviation or median and range and were compared with the t or Mann whitteny test. The previous (preoperative, intra-operative and post-operative) variables were descriptively studied. Univariate analysis and then multivariate analysis for significant predictors in univariate analysis were done to detect the relationship between complications and mortality of patients in the follow up period after A-ALDLT. The Kaplan–Meier method was applied for survival analysis and compared using log-rank tests. In all tests, a P value of <0.05 was considered significant.

2. Results

One hundred forty four (86.2%) of our patients had one or more than one complication graded from two to five regarding Clavien's modified 5-tier scoring system (26) where biliary complications were the most frequent 73/167 (43.7%) in the form of biliary leak, biliary stricture or leak with stricture, and according to Clavien grading, grades II, III, IV and V involved 8, 52, 1 and 12 of them respectively (Table 4). These biliary complications were managed as follow:1- for biliary leak the 1st treatment option was insertion of pigtail for drainage or conservative treatment but if failed; endoscopic retrograde cholangio pancreatography (ERCP) with stent or surgical repair were done. 2- for biliary stricture, the 1st treatment option was ERCP with stent but if failed surgical repair was done. Figs. 1 and 2.

The incidence of vascular complications was 36/167 (21.6%) that was classified into HA problems (HA stenosis, HAT(a case associated with HA aneurysm) or HA injury), PV problems (PV stenosis or PVT), HV problems (HV stenosis or HVT) and IVC injury. As regard Clavien grading, grades II, III, IV and V involved 6, 18, 2 and 10 of them respectively (Table 4). The management of vascular complications included: medical (anticoagulants or thrombolytic therapy), angiography (dilatation, stenting, coling of GDA or thrombolytic therapy) or surgery (thrombectomy or reanastomosis) Figs. 3 and 4.

Table 3
Clavien classification of surgical complications [25].

Grades	Definition
I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications; blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic or radiological intervention a Intervention not under general anesthesia b Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications) requiring IC/ICU management a Single organ dysfunction (including dialysis) b Multiorgan dysfunction
V	Death of a patient

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

Table 4
Complications in patients.

Type of complications	Clavien grade II	Clavien grade III	Clavien grade IV	Clavien grade V	Total No/167	(%)
Biliary					**73**	**(43.7%)**
1-Bile leak	8	14	0	9	31	(18.6%)
2-Biliary stricture	0	27	0	2	29	(17.4%
3-Stricture & bile leak	0	11	1	1	13	(7.8%)
Vascular					**36**	**(21.6%)**
1-HA problems	**4**	14	2	4	24	(14.3%)
2-PV problems	2	2	0	5	9	(5.3%)
3-HV problems	0	2	0	0	2	(1.2%)
4-IVC tear	0	0	0	1	1	(0.6%)
SFSS	11	0	0	10	**21**	**(12.6%)**
Recurrent HCV	28	0	0	0	**28**	**(16.8%)**
Recurrent HCC	1	1	0	2	**4**	**(2.4%)**
Acute rejection	32	0	0	0	**32**	**(19.2%)**
Bacterial infection	16	0	1	19	**36**	**(21.6%)**

IVC: Inferior vena cava, SFSS: Small for size syndrome, HCC: Hepatocellular carcinoma.
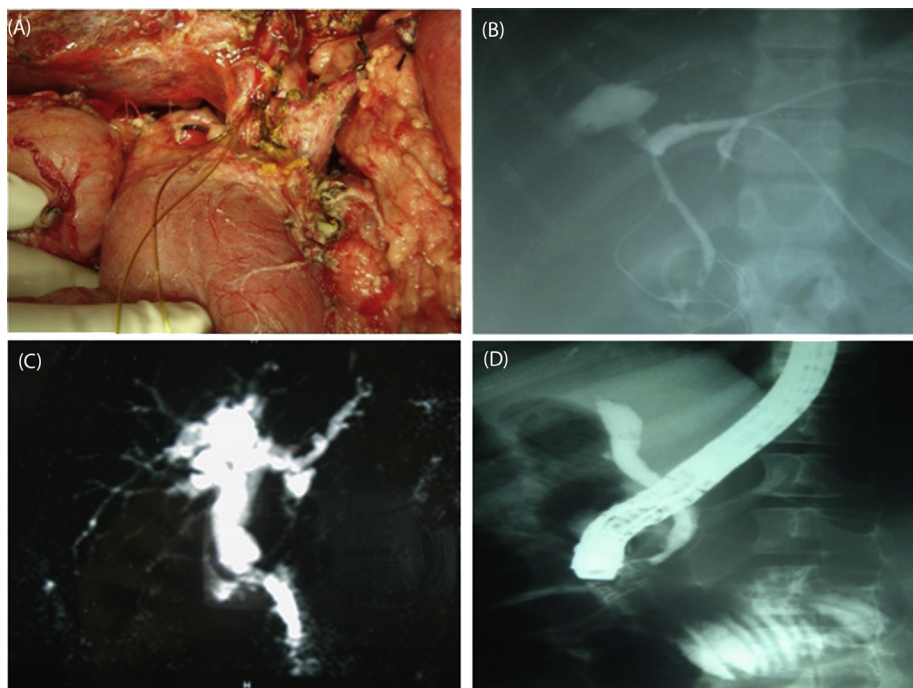
Fig. 1. A-a case with 3 "duct to duct" biliary anastamoses" B- Tube cholangiogram showing a case with anastomotic biliary leak. C- Magnetic resonance cholangio pancreatography (MRCP) shows a case with anastamotic stricture. D- ERCP shows anastomotic biliary stricture.
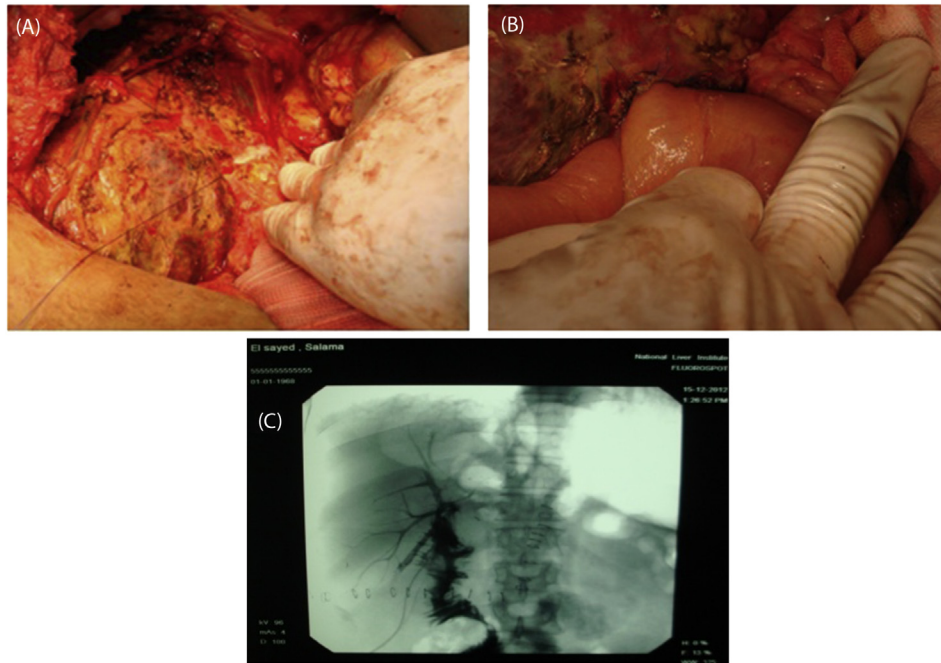
Fig. 2. A- Identification of 2 graft bile ducts in case of biliary stricture after LDLTx, B- The same patient underwent biliary enteric anastamosis on the 2 graft bile ducts. C- Tube cholangiogram after HJ with good biliary drainage.

SFSS (characterized clinically by a combination of prolonged functional cholestasis, intractable ascites, and delayed functional recovery of both prothrombin time and encephalopathy) affected 21/167 (12.6%) of our patients and for prevention of this syndrome we performed splenectomy in some cases with SFSG and performed multiple HV anastomoses (MHV, RT inferior V, segment 5 or segment 8 v) to improve venous drainage. Furthermore, Grades II and V involved 11 and 10 of them respectively. (Table 4).

Recurrent HCV affected 16.8% of our patients and treated with PEG-IFN-α-2b (PEG-Intron, Schering Plough, Kenilworth, NJ, USA) which was administered subcutaneously at a weekly dose of 1 μg/kg of body weight plus Ribavirin (Rebetol, Schering Plough, Kenilworth, NJ, USA) that was administered orally at the starting daily dose of 400–800 mg/day. Planned duration of treatment was 48 weeks. Patients who were HCV RNA-positive after 12 weeks of treatment were considered as non-responders and treatment was stopped. On the other hand 4 patients had recurrent HCC and managed with surgery followed by nexavar (3 patients) or radiotherapy for bone recurrence (1 patient). Table 4, Fig. 5.


Fig. 4. A patient with HAT and multiple hepatic abscesses managed with stenting of HAT and pigtail and antibiotics for abscesses.

Acute rejection affected 32 patients and was treated with steroid pulses (IV methylprednisolone 200–500 mg/d for 3 days), which were tapered over several days to the baseline dose Table 4.

Bacterial infection affected 21.6% of patients and was treated by antibiotics according to culture and sensitivity Table 4.
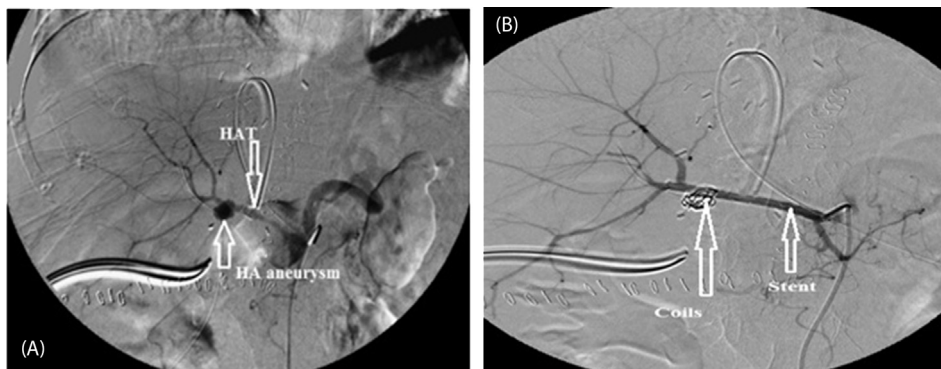
Fig. 3. A- A patient with HAT and aneurysm. B- The patient underwent coiling of aneurysm and stenting of HAT.
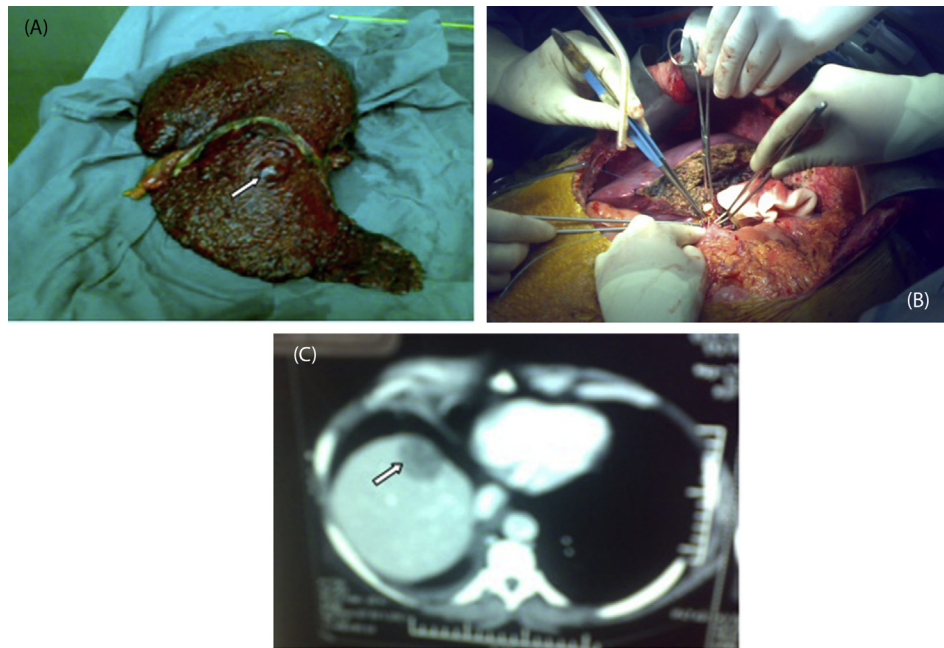
Fig. 5. (A)- Picture of a native liver of HCC patient (1 FL, 3.5 cm, within Milan), (B)- The picture of the graft after implantation to the patient. (C)- Triphasic CT abdomen of the previous patient, with HCC recurrence, in the form of hepatic recurrence, 35 months, post transplantation, he underwent surgical exploration.

In our work, biloma affected 12 patients and was managed conservatively or by pigtail drainage. However three patients suffered multiple hepatic abscesses and were managed with antibiotics, multiple pigtail drainage and treating the predisposing vascular cause (I.e. HAT). Table 5.

Lastly, neurological and renal complications were managed with neurological and renal supportive treatment respectively Table 5.

4 Outcome of patients

The overall mortality was 75 (44.9%). The incidence of in hospital mortality was 28.7% and its most frequent cause was SFSS (6%), while the incidence of late mortality was 16.2% and its most frequent cause was sepsis (7.2%). On the other hand, the overall 6-months, 1-, 3- 5- and 7-year survival of our patients were

Table 5
Complications in patients.

Type of complications	Clavien grade II	Clavien grade III	Clavien grade IV	Clavien grade V	Total No/167	(%)
GIT					**33**	**(19.8%)**
1-Biloma	2	7	0	3	12	(7.1%)
2-Gastrointeritis	5	0	0	0	5	(3%)
3-Intestinal obstruction	4	2	0	0	6	(3.6%)
4-GIT bleeding	0	7	0	0	7	(4.2%)
5-Multiple hepatic abscesses	1	0	0	2	3	(1.7%)
Wound					**21**	**(12.6%)**
1-Wound infection	11	0	0	0	11	(6.6%)
2-Incisional hernia	0	10	0	0	10	(6%)
Chest					**33**	**(19.8%)**
1-Chest infection	17	0	1	7	25	(15%)
2-Effusion	4	0	0	0	4	(2.4%)
3-Pneumothorax	0	2	0	0	2	(1.2%)
4-Pulmonary embolism	1	0	1	0	2	(1.2%)
Neurological					**44**	**(26.3%)**
1-Drop foot	3	0	0	0	3	(1.8%)
2-Peripheral neuropathy	9	0	0	0	9	(5.4%)
3-Psychosis	7	0	0	0	7	(4.2%)
4-Convulsions	4	0	0	0	4	(2.4%)
5-Tremors	3	0	0	0	3	(1.8%)
6-Neurotoxicity	10	0	0	0	10	(6%)
7-Lt hemiplegia	4	0	0	0	4	(2.4%)
8-Lt facial palsy	1	0	0	0	1	(0.6%)
9-Hallucination	3	0	0	0	3	(1.8%)
Renal impairment	33	0	0	2	**35**	**(21%)**
Intra abdominal collection					**36**	**(21.6%)**
1-Ascites	29	0	0	0	29	(17.4%)
2-Free biliary collection	0	0	0	6	6	(3.6%)
3-Blood	0	0	0	1	1	(0.6%)

Table 6
Outcome of patients.

Total number	167 (100%)
Mortality	75 (44.9%)
In hospital mortality	48 (28.7%)
Causes	
SFSS	10 (6%)
Sepsis	7 (4.2%)
intra-operative bleeding	6 (3.6%)
Post operative bleeding	7 (4.2%)
PVT	5 (3%)
MOF	4 (2.4%)
ARDS	3 (1.8%)
Early graft dysfunction	3 (1.8%)
Renal impairment	2 (1.2%)
Electrolyte imbalance	1 (0.6%)
Late mortality	27 (16.2%)
Causes	
Sepsis	12 (7.2%)
Bleeding	6 (3.6%)
Metastatic cholangiocarcinoma	2 (1.2%)
Recurrent HCC	2 (1.2%)
Early graft disfunction	1 (0.6%)
Electrolyte imbalance	1 (0.6%)
Ischemia reperfusion injury	1 (0.6%)
MOF	1 (0.6%)
Sudden death	1 (0.6%)
Over all	
6 months survival	109 (65.3%)
1-year survival	102 (61.1%)
3-year survival	95 (56.9%)
5-year survival	94 (56.3%)
7-year survival	92 (55.1%)
Survival per months ((Mean ± SD) (Range)	24.7 ± 25.5 (0–120)

PVT: Portal vein thrombosis, MOF: Multiorgan failure, ARDS: Adult respiratory distress syndrome.

109(65.3%), 102 (61.1%), 95 (56.9%), 94 (56.3%) and 92 (55.1%) respectively. Table 6.

5 Complications as predictors of outcome
A On univariate analysis, the following complications were found to be statistically significant predictors of poor outcome: Vascular, wound, intra abdominal collection and SFSS complications. On the other hand, there were trends towards significant poor outcome with the following complications: biliary, chest, neurological and acute rejection complications Table 7. Fig. 6.
B On multivariate analysis by Cox regression analysis, vascular complications and SFSS were independent predictors of poor outcome. Table 8.

3. Discussion

LDLT can now be performed with a reasonably high rate of success attributable to judicious patient selection, careful preoperative evaluation, excellent anesthetic management and aggressive care to promptly detect and treat complications [27]. A-ALDLT has a high surgical risk and complications for the recipient because of the differences in graft quality, size, and preservation time [5]. In our study, the mortality was higher among our complicated cases but without statistical significance. On the other hand, it was significantly higher in patients with complications in Ho et al., 2004 [28].

The overall post-operative complication rate in our study was 86.2%, and this high rate occurred due to including all types of complications (single, multiple, minor, major, complications treated medically, by intervention endoscopy, radiology and that treated surgically), Similarly it was 60%, 78.13%, 66%, and 58.3% in Goldstein et al., 2003 [14], Tsui et al., 2009 (29), Marsh et al., 2009 (30), and Väli et al., 2010 [31] studies respectively. In contrast, the

Table 7
Complications as risk factors of outcome.

Category	Survival No (%)	p-value
Number of patients	92/167 (55.1%)	
Complications		>0.05
Yes	79/144 (54.9%)	
No	13/23 (56.5%)	
Biliary complications		0.1
Yes	36/73 (49.3%)	
No	56/94 (59.6%)	
Vascular complications		0.010
Yes	13/36 (36.1%)	
No	79/131 (60.3%)	
Small for size syndrome		0.002
Yes	5/21 (23.8%)	
No	87/146 (59.6%)	
GIT complications		>0.05
Yes	18/33 (54.5%)	
No	74/134 (55.2%)	
Wound complications		0.033
Yes	7/21 (33.3%)	
No	85/146 (58.2%)	
Chest complications		0.214
Yes	15/33 (45.5%)	
No	77/134 (57.5%)	
Neurological complications		0.184
Yes	28/44 (63.6%)	
No	64/123 (52%)	
Renal complications		>0.05
Yes	18/35 (51.4%)	
No	74/132 (56.1%)	
Intra-abdominal collection		0.010
Yes	13/36 (36.1%)	
No	79/131 (60.3%)	
Recurrent HCV		>0.05
Yes	12/28 (42.9%)	
No	80/139 (57.6%)	
Recurrent HCC		>0.05
Yes	2/4 (50%)	
No	90/163 (55.2%)	
Acute rejection		0.299
Yes	15/32 (46.9%)	
No	77/135 (57%)	
Bacterial infection		0.068
Yes	15/36 (41.7%)	
No	77/131 (58.8%)	

complications within 3 m post Lt were 39.9% in Du et al., 2013 [5] study because they did not include the long term complications.

The overall incidence of biliary complications in LDLT patients ranges from 15 to 60% [29,30,32,33]. On the other hand, it was 43.7% in our study and 33.6%, 31% and 25% in Shin et al., 2013 [4], Goldstein et al., 2003 [14] and Väli et al., 2010 [31] studies respectively. These biliary complications remain a major cause of morbidity and mortality after LT [6,34–36]. Similarly there was a trend towards significant mortality among our biliary complicated cases.

Vascular problems such as thrombosis and stenosis of the hepatic artery, portal vein, and hepatic vein are among the most serious complications reported after LT and are more frequently seen among recipients of LDLT. The prevalence of vascular complications after LT ranges from 7% to 25% [37]. However it was 21.6% in the present study and 13.1%, 21%, 12.1%, 15%, 16.6%, 7%, and 13% of the LDLT group in Shin et al., 2013 [4], Goldstein et al., 2003 [14], Lin et al., 2004 [27], Marsh et al., 2009 [30], Väli et al., 2010 [31] Steinbrück et al., 2011 [38] and Khalaf, 2010 [39] studies respectively. On the other hand, it was higher (48.5%) In Abdelaziz et al., 2013 [7] study and lower 5.6% in Du et al., 2 0 1 3 [5] study. These vascular complications were independent predictor of mortality in our study, similarly it was associated with poor
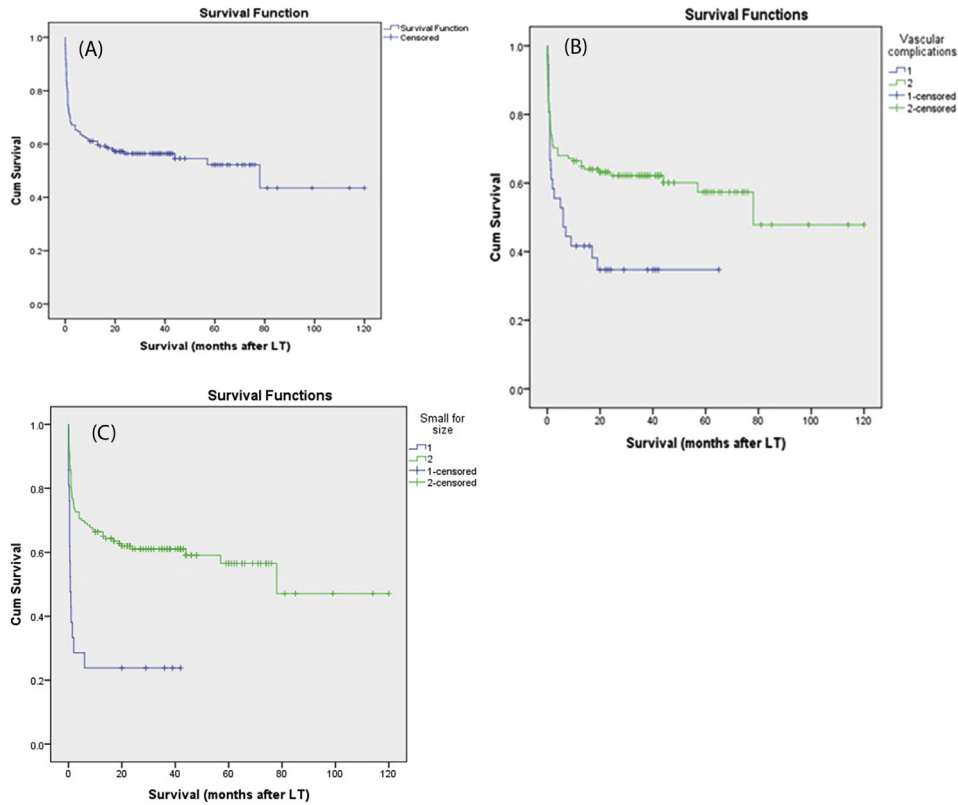
Fig. 6. Kaplan−Meier survival curves. A: KM survival curve. B: VC and survival (Log rank = 0.01). C: SFSS and survival (Log rank = 0.00).

outcome in Steinbrück et al., 2011 [38] and Khalaf, 2010 [39] studies.

The use of SFSG leads to SFSS, including poor bile production, delayed synthetic function, prolonged cholestasis and intractable ascites, with subsequent septic complications and higher mortality [40−42]. Similarly, SFSS was independent predictor of high mortality in our study, In contrast, it did not affect mortality in Kiuchi et al., 2010 [43] study. The incidence of this syndrome in our study was 12.6%, however it was 15.7% and 22% in Du et al., 2013 [5] and Goldstein et al., 2003 [14] studies respectively.

The incidence of renal impairment (RI) was 21% in our study, however it was 6.2%,19.2%, 62.7%, and 29% in Du et al., 2 0 1 3 [5], Lin et al., 2004 [27], Kuramitsu et al., 2014 [44], and Akamatsu et al., 2006 [45] studies respectively, in our study RI did not affect survival, similarly, it did not affect survival, in Akamatsu et al., 2006 [45] study. In contrast, it lead to mortality in Iwata et al., 2014 [46] study.

Acute rejection is a common cause of graft failure, clinical, laboratory and radiological findings are non-specific and the definite diagnosis is achieved only after liver biopsy [47]. In our study, the incidence of acute rejection was 19.2%, however it was 14.4%,10.6%, 6%, 13%, and 15.7% and in Shin et al., 2013 [4], Du et al., 2 0 1 3 [5],

Abdelaziz et al., 2013 [7], Goldstein et al., 2003 [14] and Lin et al., 2004 [27] and studies respectively. The higher incidence of acute rejection in our study occurred due to adjusting the immunosuppressant dose to their lower limit for fear of neurotoxicity and nephrotoxicity and to avoid the occurrence of sepsis that was the 2nd cause of early mortality in our work.

Recurrence of hepatocellular carcinoma (HCC) after LT is considered to result from undetected extrahepatic metastasis before surgery or the release of tumor cells during surgical manipulation [48]. The most common site of recurrence is the lung and the second most common site is the liver [49]. In Abdelaziz et al., 2013 [7] study, 60% developed hepatic recurrent HCC and 23% suffered from intrahepatic and extrahepatic HCC recurrence at 1- y after transplantation. In (Du et al., 2 0 1 3 [5] study. On the other hand, only 7% had recurrent HCC in our study. The reason for this low incidence was that a large number of our HCC cases had in-hospital mortality so there was no enough time to detect HCC recurrence.

The incidence of hepatitis C recurrence was 56.4%, 33.3%, and 26.3% in Shin et al., 2013 [4], Du et al., 2 0 1 3 [5], and Yosry et al., 2008 [50] studies respectively and 19.2% in our study. This low incidence was due to putting strict criteria for detecting HCV recurrence, these are the biochemical, serological and histological evidences of recurrence, so we did not mention that HCV recurrence occurred until the patient fulfill all the previous parameters.

The incidence of neurological problems after LT ranges from 10 to 47% [2,51]. On the other hand, it reached 26.3% in our study. The spectrum of the clinical presentations is extremely wide, ranging from mild to potentially life-threatening disorders, mainly affecting the central nervous system (CNS) [52,53]. There was a trend towards high mortality with neurological complications in our study, similarly, they were associated with significant mortality in Wang

Table 8
Multivariate analysis of complications as risk factors of outcome (Cox regression).

	P value	Exp(B)	95% C.I. for EXP(B)	
			Lower	Upper
Vascular complications	0.042	1.7	1.01	2.8
Wound complications	0.185	1.5	0.8	2.7
Intra-abdominal collection	0.470	1.2	0.6	2.4
SFSS	0.020	2.4	1.1	5.06
Biliary complications	0.815	0.9	0.5	1.5
Recurrent HCV	0.131	0.6	0.3	1.1

et al., 2000 [54] study, in contrast, Saner et al., 2010 [53] observed that the occurrence of NC in adult living-donor LT did not influence the clinical outcome.

The overall mortality rate until the end of follow up period was 44.9% in our study (this high rate was due to increased incidence of in-hospital mortality in our work and this was mainly in our early cases, however it improved in our late cases, furthermore, the sepsis rate that lead to in-hospital and late mortalities was high in early cases and improved after this after improving our infection control policies). However it were 24%, 39.9%, and 30% in Shin et al., 2013 [4], Xiao et al., 2009 [55] and Stey et al., 2013 [56] studies respectively. On the other hand, it was lower 18.7% and 10.1% in Kuramitsu et al., 2014 [44] and Toshima et al., 2014 [57] and studies respectively. The early (hospital, 1-month and 3-months) mortalities were 1.4%, 17%, 6%, and 15.8%, in Lin et al., 2004 [27], Stey et al., 2013 [56], Jo et al., 2014 [58], and Chung et al., 2013 [59], and studies respectively. Conversly, the early (Hospital) mortality in our study reached 28.7%, and this high rate due to frequent cases of SFSS, and sepsis. The late mortalities rates were 11.9% and 13% in Xiao et al., 2009 [55], and Stey et al., 2013 [56] studies respectively. On the other hand, it was 16.2% in the recent work.

Infection is a common cause of morbidity and mortality after liver transplantation [60,61]. Bacterial infections, especially those involving gram-negative bacteria, represent a major complication in liver transplant recipients, the frequency ranging between 13.3% and 80% of cases, and they contribute to morbidity and mortality [15,17,62]. Similarly bacterial infection affected 21.6% of our patients with a trend towards significant high mortality. On the other hand it affected 51.2%, 32.7% and 23.6% in Shin et al., 2013 [4], Seoul Kim et al., 2009 [63] and Essen Saner et al., 2008 [64] studies respectively.

Most patients died of multiorgan failure (MOF) in Xiao et al., 2009 [55] study due to sepsis caused by a preoperative pulmonary infection or spontaneous peritonitis or respiratory failure caused by adult respiratory distress syndrome (ARDS). On the other hand, Sepsis was the most frequent causes of death in Goldstein et al., 2003 [14] and Douthitt et al., 2012 [65] studies. However it was one of the most frequent causes of mortality In Toshima et al., 2014 [58] study and it was a cause of mortality in Du et al., 2 0 1 3 [5]and Kuramitsu et al., 2014 [44] studies. Similarly, it was the 2nd most frequent cause of in hospital mortality, and the most frequent cause of late mortality in our study.

SFSS was one of the most frequent causes of graft losses and death in Goldstein et al., 2003 [14] study. Similarly, it was the most frequent cause of in hospital mortality in our study.

4. Conclusions

Mortality was higher among complicated cases where vascular complications and SFSS had significant effect on it so prevention and treatment of them is required for improving outcome.

N.B: This is a retrospective cohort study limited to patients with complete data obtained from our records and patients with complete follow-up, while patients with missing data and who did not complete the follow-up were excluded.

Ethical approval

The approval by our institutional review board (IRB).

Author contribution

Emad Hamdy Gad: Study design, data collection and writing.
Ayman Alsebaey: Data collection and data analysis.
Maha Lotfy: Data collection.
Mohamed Eltabbakh: Data collection.

Conflicts of interest

No conflict of interest to declare.

Guarantor

All the authors of this paper accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

ISRCTN

This is a retrospective study (not RCT).

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