

# Building a liver transplant program in a resource limited country: a 15-year retrospective analysis of 648 patients operated in the Romanian National Program

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## ABSTRACT

**Background:** Liver transplantation (LT) has become an established treatment for end-stage liver disease, with more than 20.000 procedures yearly worldwide. The aim of this study was to analyze the results of Romanian National Program of LT after 15 years of activity.

**Methods:** Between April 2000 and April 2015, 648 pts received 678 LTs in Romania. Male/female ratio was 382/266, while adult/pediatric ratio was 588/60, with a mean age of 45 years (median 50 yrs; range 7 months – 68 yrs). Main LT indications were HBV-related cirrhosis (176 pts; 27.1%), hepatocellular carcinoma (128 pts; 19.7%), and HCV-related cirrhosis (118 pts; 18.2%). Waiting time and indications for LT, patient and donor demographics, graft features, surgical procedures, and short and long-term outcomes were analyzed.

**Results:** DDLT was performed in 532 pts (82.1%): whole LT in 512 pts (79%), split LT in 16 pts (2.5%), reduced LT in 2 pts (0.3%), and domino LT in 2 pts (0.3%). LDLT was performed in 116 pts (17.9%): right hemiliver in 78 pts (12%), left lateral section in 26 pts (4%), left hemiliver in 7 pts (1.1%), left hemiliver with segment 1 in 3 pts (0.4%), and dual graft LDLT in 2 pts (0.3%). Overall major morbidity rate was 43.8% (284 pts), while perioperative mortality was 7.9% (51 pts). Retransplantation rate was 4.6% (30 pts): 23 whole LTs, 3 reduced LTs, 3 split LTs, and 1 LDLT. Long-term overall 1-, 3-, and 5-year estimated survival rates for patients were 88.8%, 82.5%, and 79.2%, respectively, while for transplanted grafts were 77.9%, 71.6%, and 68.8%, respectively ( $p < 0.001$ ). Median waiting time for LT decreased significantly over time: from 107, 99, 51, and 45 months to 28, 18, 34, and 20 months in case of OI, All, BIII, and ABIV group pts, respectively. One-year overall mortality on waiting list also decreased significantly over time from 31.4% to 11.8%.

**Conclusions:** The liver transplantation program in Romania addresses all causes of acute and chronic liver failure or liver tumors in adults and children, using all surgical techniques.

The program constantly increased over time, leading to less time and lower mortality rate on the waiting list.

**Abbreviations:** LT: liver transplantation, DDLT: deceased donor liver transplantation, LDLT: living donor liver transplantation, HBV: hepatitis B virus, HCV: hepatitis C virus, HCC: hepatocellular carcinoma, ECD: extended criteria donors, MELD: model of end-stage liver disease, PELD: pediatric end-stage liver disease

**Key words:** Liver transplantation, high-volume transplantation center; national experience

## INTRODUCTION

Liver transplantation (LT) has become an established treatment for end-stage liver disease, with more than 20,000 procedures yearly worldwide (1). Survival rates after LT have significantly improved due to refinement in surgical techniques, excellent anesthetic management, aggressive nursing care, and prompt detection and treatment of complications. The request for LT continues to increase while the donor pool size remains inadequate.

### *Evolution of liver transplantation in Romania*

In Romania, after several experimental LT carried out during the second half of the 20th century, the first (unsuccessful) LT was performed in 1997 by I. Popescu et al at Fundeni Clinical Institute in Bucharest. In 2000, the first successful LT (with whole graft) was carried out by the same surgical team, followed by the first living donor liver transplantation (LDLT) (successful) later the same year (2). By the end of 2006 the transplant center surpassed 20 LTs per year, the minimum number recommended for satisfactory results (3, 4, 5, 6). Later on, in 2011, the center became a high-volume center exceeding 50 LTs per year (3, 4, 5, 6). In 2014, a second LT center was open at "Sfanta Maria" Hospital in Bucharest based on professionals and expertise from the main transplantation center (Fundeni Clinical Institute).

## MATERIAL AND METHODS

### *Recipients*

From April 2000 to April 2015, 648 pts who received 678 LTs in Romania were retrospectively analyzed. Out of these patients, 629 (97%) were operated at Fundeni Clinical Institute in Bucharest, and 19 pts (3%) at "Sfânta Maria" Clinical Hospital in Bucharest (starting with January 2014). All recipients were regularly followed-up

by a multidisciplinary team. Main medical records were collected prospectively and data were completed by retrospective review.

All candidates for LT were evaluated using standardized criteria based on general status, clinical symptoms and investigations results of liver disease, MELD/PELD score, and liver tumor features (when the case). These candidates were preoperatively evaluated by a multidisciplinary transplant team that included a surgeon, hepatologist, pediatrician, anesthesiologist, psychologist, during weekly meetings. Patients with hepatocellular carcinoma (HCC) were preferably within Milan criteria for LT in HCC (7), but those outside these criteria were also considered for LT. Patients with hepatitis B viral-related liver diseases received hepatitis B immunoglobulin and lamivudine prophylaxis after LT.

Patients were divided into 3 groups, in function of the development phase of the main transplantation center: early stage of development as low-volume center defined by up to 20 transplanted pts yearly (Group 1), intermediate stage of mid-volume center (Group 2) defined by 20 to 50 transplanted pts yearly, and advanced stage of high-volume center defined by over 50 transplanted pts yearly (3, 4, 5, 6). Consequently, the groups were as follows: Group 1 included the 96 pts transplanted from April 2000 to December 2006, Group 2 included the 148 pts transplanted from January 2007 to December 2010, and Group 3 included the 404 pts transplanted from January 2011 to April 2015.

### *Waiting list*

Patients with end-stage liver disease, acute liver failure and/or with hepatic tumors who may benefit from LT were registered on the waiting list according to ABO blood type, body mass index, degree of medical urgency, Child-Pugh score. More recently, each patient received a priority score based on MELD (model of end-stage liver disease) score in adults (8) and PELD (pediatric end-stage liver disease) in children. Patients on the waiting list were periodically evaluated and continuously treated; those with the highest scores had priority for transplantation (9). In case of HCC, patients benefited for specific treatment while on waiting list (transarterial chemoembolization, thermal ablation, and/or liver resection) with the purpose to maintain the tumor within Milan Criteria (10) or to downstage it to within these criteria.

### *Donors*

Liver grafts for transplantation were harvested from both deceased and living donors. Consequently, a total of 670 donors were recorded.

### *Deceased donors*

Potential donors were declared brain dead and investigated according to a standard protocol (11). Informed consent had to be obtained from close relatives. Consequently, 551 donors were harvested (82.2% of the total donor pool): 512 of these whole grafts were used for whole LT, 8 whole grafts and 1 partial graft (segments 4-8) for split LT, 2 whole grafts for reduced LT, 1 whole graft for domino LT, while 27 whole grafts and 1 partial graft (left lateral section) were used for 29 retransplantations (23 whole grafts, 3 reduced grafts, and 3 partial grafts). Only 1 donor was non-heart beating.

### Extended criteria liver graft donors

To increase the donor pool, extended criteria donors (ECD) were accepted since the beginning of LT program. The considered extended criteria were according to international consensus (12): donor-related features (age over 65 yrs, body mass index over 30 kg/m<sup>2</sup>), factors related to intensive care (ICU stay and ventilation support more than 7 days, hypotension and inotropic support - at least two pressors at any time, high-dose dopamine or epinephrine, resuscitated cardiac arrest), liver steatosis (macrosteatosis, more than 30% but less than 60%), biochemical imbalances (hypernatremia over 165 mEq/L), liver dysfunction (elevated AST/ALT more than 3 times, total bilirubin over 3 mg/dl), cold ischemia time more than 12 hours, viral infections (positive serology for HBV or HCV hepatitis), sepsis-related factors (positive blood culture, meningitis), malignancy risk factors (history of extra-hepatic malignancy, low-grade central nervous system tumors), and non-heart beating donors.

### Other sources for liver grafts

Other sources for liver grafts were used in 12 pts (2.1%): methanol-poisoning (4 donors), liver graft trauma (5 donors), benign tumors in liver graft (2 donors) and Takayasu's syndrome (1 donor).

### *Living donors*

The potential living donor benefited from a medical and psychiatric assessment using an extensive workup which included Doppler ultrasonography, computed tomography with volumetry, and magnetic resonance cholangiography. The criteria for living donor selection evolved with improved surgical management and accumulated experience. Controversial donors included those with small future remnant liver volume (<40% of total liver volume), complex anatomical anomalies of

liver vessels and biliary tree, advanced liver steatosis, previous extensive abdominal surgery, significant associated medical illness, hepatitis B surface antigen or hepatitis C antibody-positive; elderly donors over 60 years of age were systematically excluded. Each potential donor was assessed by a multidisciplinary team. Donor safety was the main concern in all cases.

There were 119 living donors (17.8% of total donor pool): 78 pts donated the right hemiliver, 26 pts the left lateral section, 7 pts the left hemiliver, 3 pts the left hemiliver together with segment 1, 4 pts were harvested for 2 dual graft LDLTs (right hemiliver and left lateral section, and left hemiliver and left lateral section, respectively), while 1 pt donated the left lateral section for a retransplantation after DDLT.

### *Indication for liver transplantation*

LT was indicated in adult and pediatric patients with chronic end stage liver disease (decompensated liver cirrhosis, cholestatic liver, metabolic and vascular liver disease), liver tumors (such as HCC), acute liver failure, or miscellaneous disease (such as adult polycystic liver disease, Caroli's disease).

### *Donor-recipient matching*

Each donor graft was matched to a specific recipient. The main criteria were ABO blood type compatibility, body mass index and graft weight. ECD grafts were usually allocated to recipients with decompensated liver cirrhosis with low MELD score, and/or HCC. ECD grafts were avoided when possible in case of recipients with significant associated diseases, high MELD score and/or with HCV infection. Additionally, liver grafts from cadaveric donors with age above 50 years were usually avoided in recipients with HCV-related decompensated cirrhosis, with the purpose to avoid early post-transplant HCV recurrence (13). Moreover, LDLT in HCV-infected recipients was generally considered as a life-saving procedure (14). In case of HCC, recipients with tumors within Milan Criteria with controlled disease progression benefited from the same policy as the non-HCC recipients, while recipients with HCC within Milan Criteria and aggressive disease progression while on waiting list, or those beyond Milan Criteria were usually matched with ECD grafts or grafts harvested from living donors (15).

### *Surgical technique*

The surgical techniques for graft harvesting and implantation were standard and described elsewhere (11, 16, 17, 18).

Particularly, in case of orthotopic whole LT, the

venous reconstruction of liver graft was recently performed using a modified surgical technique involving triangular cavo-cavostomy (donor's inferior vena cava with a 6-8 cm vertical slit in its posterior wall was anastomosed in a latero-lateral fashion to the recipient's inferior vena cava with bridged ostia of the hepatic veins trunks together with a 6-8 cm vertical incision along the anterior wall); this technique replaced the piggy-back technique that was used in early experience. Another particularity is that for biliary reconstruction using choledoco-choledocal anastomosis, consisting in the elimination after early experience of the protection by T-tube biliary drainage.

In case of LDLT, the preferred graft was the right hemiliver without median hepatic vein, with reconstructed venous drainage of the anterior section and/or posterior section in case of segmental veins larger than 5 mm in diameter.

**Immunosuppression**

All patients received immunosuppressive induction, currently based on basiliximab; methylprednisolone was used as protocol during early experience, but lately only in selected cases. Maintenance immunosuppression regimens are currently based mainly on tacrolimus (standard), cyclosporine (alternative to tacrolimus) or sirolimus (in pts transplanted for HCC), in association with mycophenolate mofetil.

**Statistical Analysis**

Medical records were explored based on patient demographics, waiting list parameters (indications for LT, blood type, body mass index, MELD/PELD score), graft type, intraoperative parameters (operative time, blood loss, warm and cold ischemia time), short and long-term outcome. Categorical data were analyzed using the Chi-squared test. Continuous data were described as the average and standard deviation, or

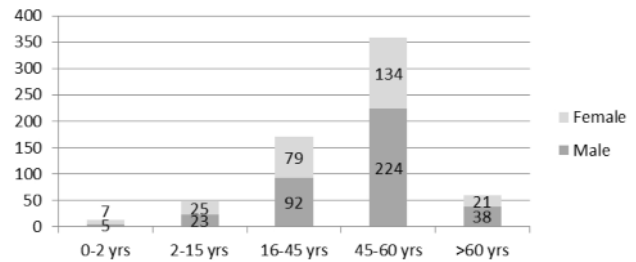


Figure 1 - Gender and age distribution of LT recipients

median and range, and analyzed using Student's t-test. Perioperative mortality included deaths occurred intra-operatively and 1 month postoperatively. Long-term survival was analyzed in patients with more than 1 month follow-up using the Kaplan-Meier method and the Log rank test. A p value of <0.05 was considered statistically significant.

**RESULTS**

**Recipients**

In the overall group (N=648), the gender ratio was 382/266, the adult/pediatric was 588/60, and the mean age of 45 yr (median 50, range 7 months – 68 yr).

Recipients with age between 45 and 60 yrs represented the majority (358 pts; 55.2%), with a male/female ratio of 224/134 (figure 1). The main increase tendency over time was recorded in the age groups of 45-60 yrs and over 60 yrs (figure 2).

**Waiting list**

Median waiting time for LT in patients with OI, AII, BIII, and ABIV blood type was 107, 99, 51, and 45 months before 2011 (Group 1 and 2), and 28, 18, 34, and 20 months after 2011 (Group 3), respectively. One-year overall mortality on the waiting list was 31.4% before 2011 (Group 1 and 2), and 11.8% after 2011 (Group 3).

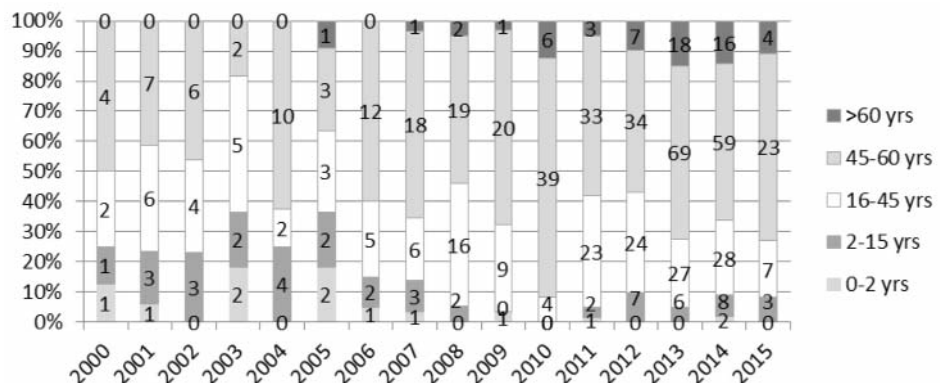


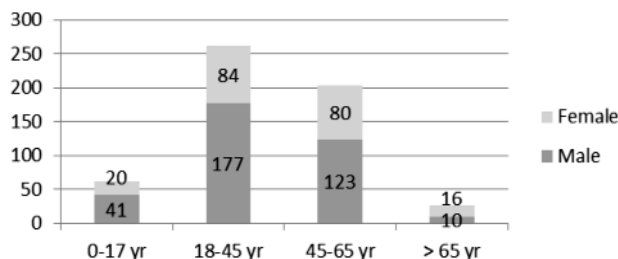
Figure 2 - Evolution of age groups in LT recipients

**Donors**

*Deceased donors*

Median donor age was 41 yrs (mean 39; range 2-78), and male/female ratio was 351/200. Donor blood types were as follows: 192 pts were OI (34.8%), 238 pts were AII (43.2%), 82 pts were BIII (14.9%), and 39 pts were ABIV (7.1%).

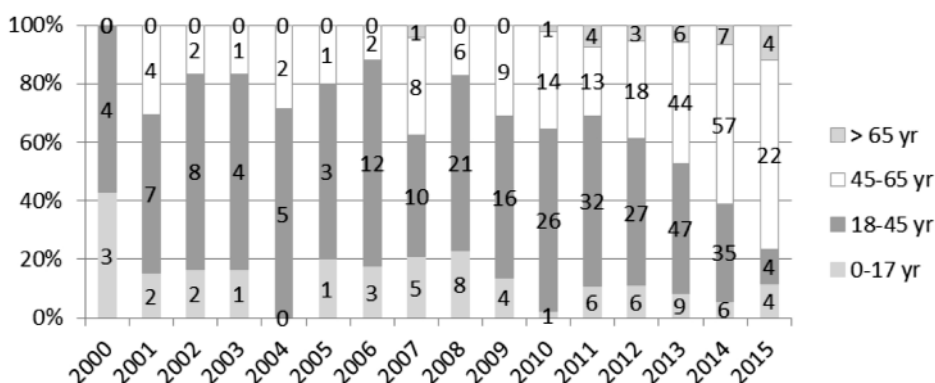
Among the 551 deceased donors, those with age between 18 and 45 yrs represented the majority (261 donors; 47.3%), with a male/female ratio of 177/84 (figure 3). The evolution over time in terms of age groups was mainly in favor of 45-60 yrs and over 60 yrs (figure 4). The main cause of death in donors was stroke (270 donors; 49%), with an incidence that increased over time, followed by trauma (246 donors; 44.6%) (figure 5); other causes (35 donors; 6.4%) were asphyxiation (13 donors), cerebral tumor (3 donors), intoxication (11 donors), resuscitated cardiac arrest (5 donors), ruptured aortic aneurysm (1 donor), and acute hydrocephalus (1 donor). The median graft weight was 1535 g (mean 1560; range 465-3150). The median cold



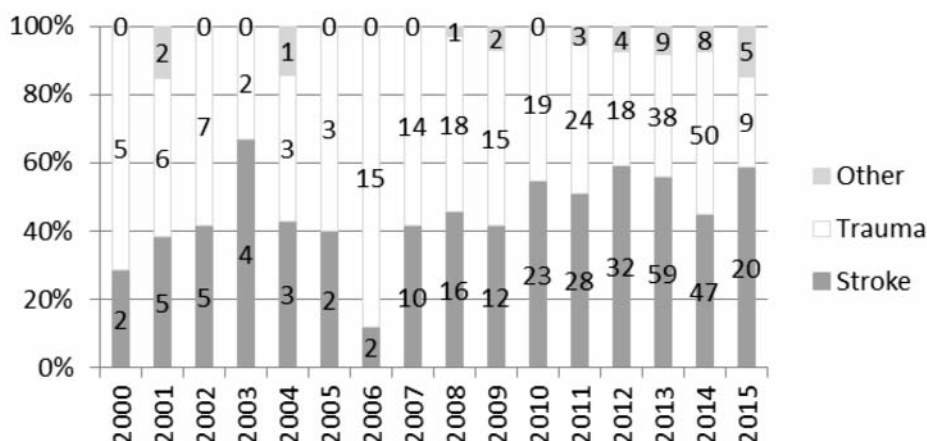
**Figure 3 - Age and gender distribution of deceased donors**

ischemia time was 5:43 h (mean 5:32; range 1:29 - 16:41), while the median warm ischemia time was 0:30 h (mean 0:35; range 0:05 - 05:38).

The ECD grafts represented 58.6% of the 551 deceased donor LTs (DDLTL) (N=323). The extended criteria found in the 323 deceased donors are presented in table 1; 126 ECDs (39%) had multiple such criteria. The main allocation of ECDs was to cirrhotic recipients (198 pts; 61.3%), and HCC recipients (72 pts; 22.3%) (figure 6).



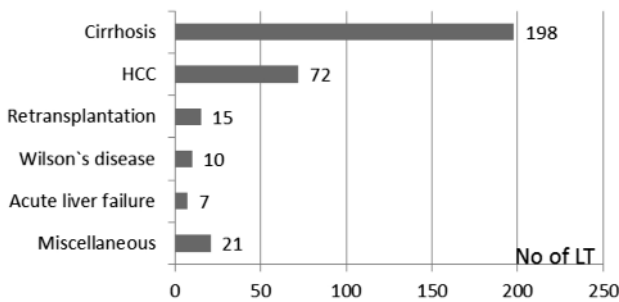
**Figure 4 - Evolution of deceased donor age groups**



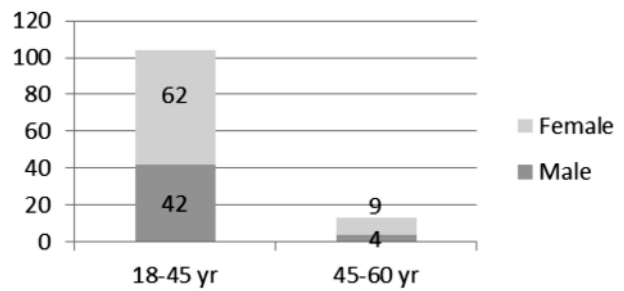
**Figure 5 - Evolution of causes of death in donors**

**Table 1 - Extended criteria for liver grafts (N=373)**

	Extended criteria for liver grafts	No of pts
Donor-related features:	Age > 65 yrs	26
	Body mass index > 30 kg/m	21
Factors related to ICU:	ICU stay and ventilation support >7 days	36
	Hypotension and inotropic support (≥ 2 pressors at any time, high-dose dopamine or epinephrine)	111
	Resuscitated cardiac arrest	83
Liver steatosis:	Macrosteatosis (>30% but ≤60%)	36
Biochemical imbalances:	Hypernatremia (peak serum Na >165 mEq/L)	24
	Liver dysfunction (AST/ALT>3X; BT>3mg/dl)	108
Cold ischemia time	> 12 hours	1
Viral infections:	Positive serology for HBV hepatitis	7
	AgHBs (+)	4
	AgHbc (+)	3
	Positive serology for HCV hepatitis	1
Sepsis-related factors:	Sepsis with positive blood culture	3
	Meningitis	-
Malignancy risk factors:	History of extrahepatic malignancy	1
Non-heart beating donors		1



**Figure 6 - Allocation of liver grafts from extended criteria donor (ECD) in function of cause for liver transplantation (LT)**



**Figure 7 - Age and gender distribution of living donors**

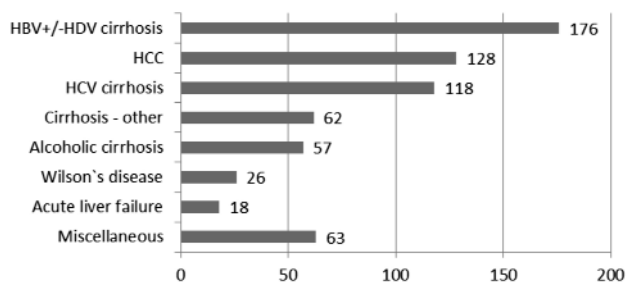
*Living donors*

The median age was 33 yrs (mean 34; range 19-53), and male/female ratio was 47/72. Donor blood types were as follows: 45 pts were OI (37.8%), 51 pts were AllI (42.9%), 16 pts were BIII (13.4%), and 7 pts were ABIV (5.9%). The majority of living donors were in the 18-45 yr age group (N=104), with a male/female ratio of 42/62 (figure 7). Major complication rate was 3.4% (4 pts), the re-intervention rate was 1.7% (2 pts), and mortality was nil.

**Liver transplantation**

*Indications*

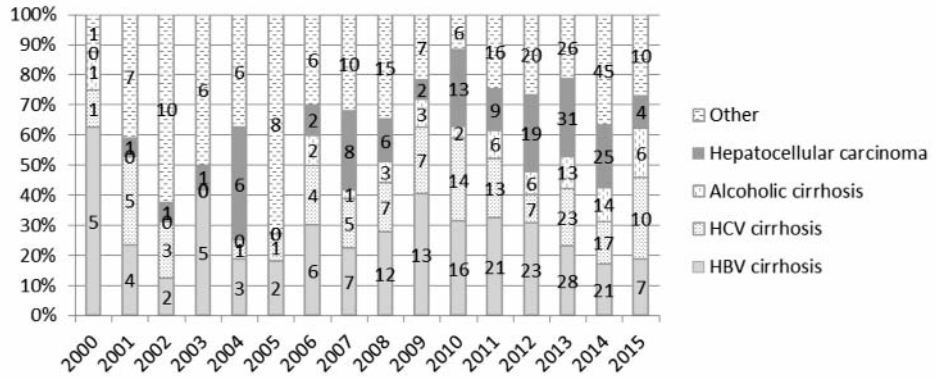
Main LT indications were HBV cirrhosis (176 pts; 27.2%), HCC (128 pts; 19.8%), and HCV cirrhosis (118 pts; 16.8%) (figure 8); the other causes of cirrhosis and miscellaneous indications are presented in detail in figures 10 and 11. Figure 9 shows the evolution of LT



**Figure 8 - Indication for LT in the overall group**

indications over times; particularly, the incidence of VHB-related cirrhosis decreased in favor of VHC-related cirrhosis. In case of HBV-related cirrhosis, HDV co-infection was present in 117 out of 176 pts (66.5%). In 31 out of the 118 pts with HCV-related cirrhosis, HBV infection was also present (26.3%). Among the 128 pts with HCC, 83 pts were within Milan Criteria (64.8%). In adult recipients (N=588), the main indications were

**Figure 9 - Evolution of main indications for LT in the overall group**



similar to the overall group: HBV-related cirrhosis (175 pts, 29.8%), HCC (127 pts, 21.6%), and HCV-related cirrhosis (117 pts, 19.9%) (figure 10). In pediatric patients (N=60), the main indication for transplantation were congenital biliary anomalies (biliary atresia, hypoplasia or ductopenia) (12 pts; 20%), Wilson’s disease (11 pts; 18.3%), glycogenosis (8 pts; 13.3%), and congenital liver fibrosis (7 pts; 11.7%) (figure 11).

*Technical aspects*

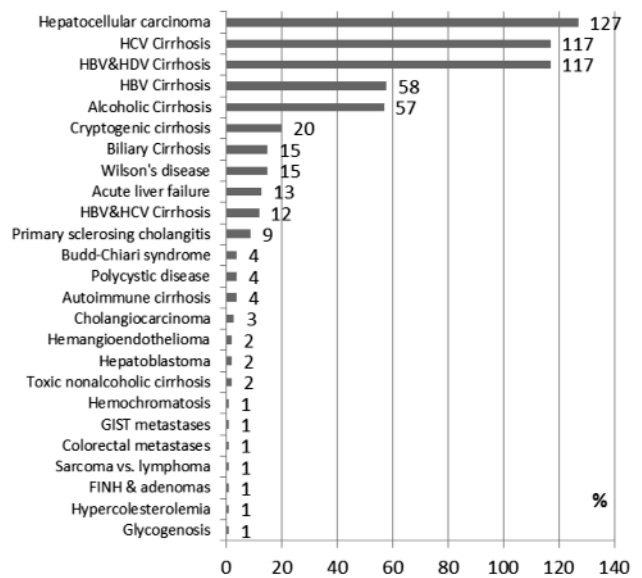
In the overall group (648 pts), the DDLT was performed in 532 pts (82.1%) and LDLT in 116 pts (17.9%). The DDLT were whole organ LT (512 pts; 78.9%), split graft LT (17 pts; 2.6%), reduced graft LT (2 pts; 0.3%), and domino LT (1 pt; 0.1%) (figure 12). Split graft LT was performed with left lateral section in 6 pts, left hemiliver in 2 pts, right hemiliver in 2 pts, and right extended hemiliver in 7 pts. In particular, domino LT was performed for HCC on cirrhosis using a whole liver harvested from a living donor with homozygous familial hypercholesterolemia, who received in turn a split LT with right extended hemiliver (18).

LDLT (116 pts) was performed with right hemiliver in 78 pts, left lateral section in 26 pts, left hemiliver in 7 pts, left hemiliver with segment 1 in 3 pts, and dual graft LDLT in 2 pts. In particular, dual graft LDLT was performed in 2 cases: one received a right hemiliver and a left lateral section (17), and one received a left hemiliver and a left lateral section.

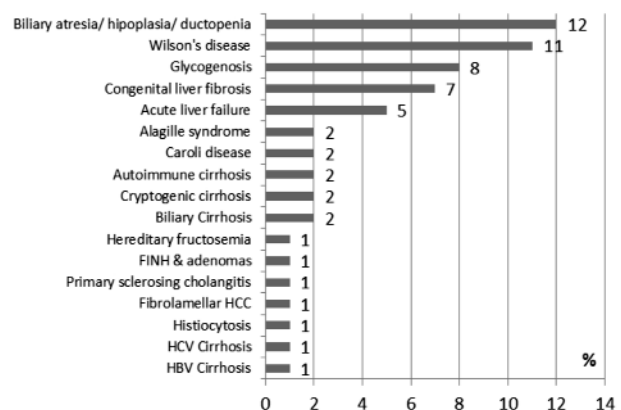
Technical aspects (operative time, cold ischemia time, warm ischemia time, and intraoperative blood loss) of DDLT and LDLT procedures are presented in table 2 and 3, respectively.

*Results*

Overall major morbidity (Dindo-Clavien class III and IV) rate was 43.8 (284 out of 648 pts); in DDLT and LDLT, major morbidity rates were 41.7% (222 pts) and 53.4%



**Figure 10 - Indication for LT in adult patients**



**Figure 11 - Indications for LT in pediatric patients**

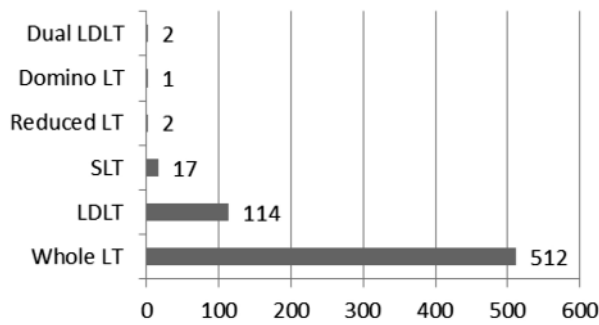


Figure 12 - Surgical techniques used for LT in the overall group

(62 pts), respectively (p=0.064). In the 3 studied groups, major morbidity rates were 57.3% (55 out of 96 pts) in Group 1, 51.4% (76 out of 148 pts) in Group 2, and 37.9% (153 out of 404 pts) in Group 3 (p = 0.045).

Overall retransplantation rate was 4.9% (30 pts); in DDLT and LDLT, retransplantation rates were 3.2% (17 pts), and 11.3% (13 pts), respectively (p=0.001). The techniques used in retransplantation were: 23 whole LTs, 3 reduced LTs, 3 split LTs (2 with left lateral section, and 1 with right hemiliver), and 1 LDLT (with left lateral section).

Overall perioperative mortality rate was 7.9% (51 out of 648 pts). In DDLT and LDLT, perioperative mortality rates were 6.4% (34 out of 532 pts) and 14.6% (17 out of 116 pts), respectively (p= 0.033).

In the 3 studied groups, perioperative mortality rates were 11.5% (11 out of 96 pts) in Group 1, 8.1% (12 out of 148 pts) in Group 2, and 6.9% (28 out of 404 pts) in Group 3 (p = 0.049).

Median follow-up was 26 months (mean 34, range 1-179). In case of HBV infection, the 1-, 3-, and 5-yr viral recurrence-free rates were 95.9%, 94.2%, and 91%, respectively, while for HCV infection were 49.3%, 35.9%, and 29.3%, respectively. The 1, 3-, and 5-yr HCC recurrence-free rates were 86.2%, 72.9%, and 68.7%, respectively.

Long-term overall 1-, 3-, and 5-year estimated survival rates for patients were 89%, 82.5%, and 79.2%, respectively, while for transplanted grafts were 77.9%, 71.6%, and 68.8%, respectively (p<0.001) (figure 13). Long-term 1-, 3-, and 5-year estimated survival rates in function of gender were 90.1%, 81.5%, and 76.6% (males), and 88.8%, 86.8%, and 86.8% (females), respectively (p=0.115). In pediatric, adult, and elderly patients, long-term 1-, 3-, and 5-year estimated survival rates were 91.9%, 88.5%, and 88.5% (0-17 yrs), 89.2%, 83.7%, and 80.8% (18-60 yrs), and 87.9%, 71.2%, and 71.2% (over 60 yrs), respectively (p=0.317).

In what LT indications are concerned, long-term 1-, 3-, and 5-year estimated survival rates in HBV-related cirrhosis were 92.2%, 87.2%, and 83.4%, in HCV-related cirrhosis were 84.7%, 73.5%, and 73.5%, in alcoholic

Table 2 - Overall and comparative operative parameters of recipients of deceased donor liver transplantation (DDLTL) in low-volume center phase (Group 1), mid-volume center phase (Group 2), and high-volume center phase (Group 3)

Parameters	Group 1 (N= 66)	Group 2 (N= 122)	Group 3 (N= 344)	p (1 vs 2)	p (2 vs 3)	p (1 vs 3)	Overall (N=532)
Age (year)	43 ± 12	48 ± 11	48 ± 14	0.029*	0.145	0.765	47 ± 13
Gender (M/F)	37/29	78/44	208/136	0.402	0.538	0.384	323/209
Operative time (min)	375 ± 92	399 ± 91	367 ± 97	0.838	0.029*	0.327	379 ± 96
Cold ischemia time (min)	358 ± 117	409 ± 123	313 ± 99	0.521	0.001*	0.034*	344 ± 116
Warm ischemia time (min)	35 ± 52	37 ± 17	34 ± 22	0.631	0.753	0.379	35 ± 25
Blood loss (l)	11.1 ± 15.4	7.6 ± 9.7	4.9 ± 7.8	0.039*	0.001*	0.001*	5,5 ± 6,5

Table 3 - Overall and comparative operative parameters of recipients of living donor liver transplantation (LDLT) in low-volume center phase (Group 1), mid-volume center phase (Group 2), and high-volume center phase (Group 3)

Parameters	Group 1 (N= 30)	Group 2 (N=26)	Group 3 (N= 60)	p (1 vs 2)	P (2 vs 3)	P (1 vs 3)	Overall (N=116)
Age (year)	20 ± 20	39 ± 20	37 ± 19	0.399	0.008*	0.225	33 ± 21
Gender (M/F)	14/16	15/11	30/33	0.306	0.279	0.552	59/57
Operative time (min)	573 ± 175	508 ± 119	446 ± 105	0.016*	0.022*	0.001*	493 ± 139
Cold ischemia time (min)	175 ± 67	172 ± 66	143 ± 46	0.659	0.046*	0.037*	158 ± 59
Warm ischemia time (min)	56 ± 28	41 ± 15	52 ± 34	0.042*	0.105	0.651	51 ± 30
Blood loss (l)	12.4 ± 25.2	5.6 ± 5.3	5.5 ± 5.3	0.042*	0.909	0.043*	6.7 ± 11.3

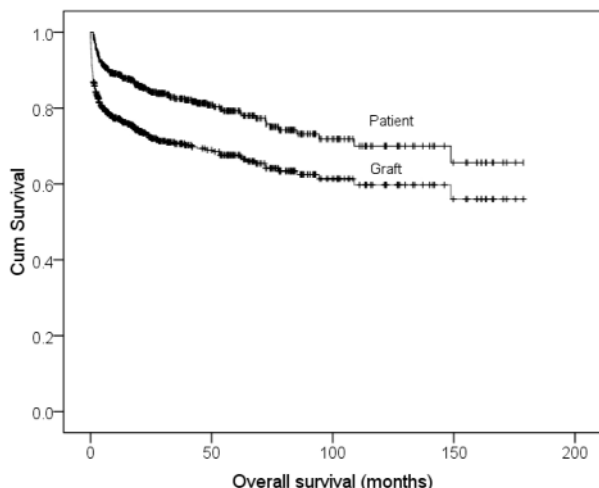


Figure 13 - Overall patient and graft survival ( $p < 0.001$ )

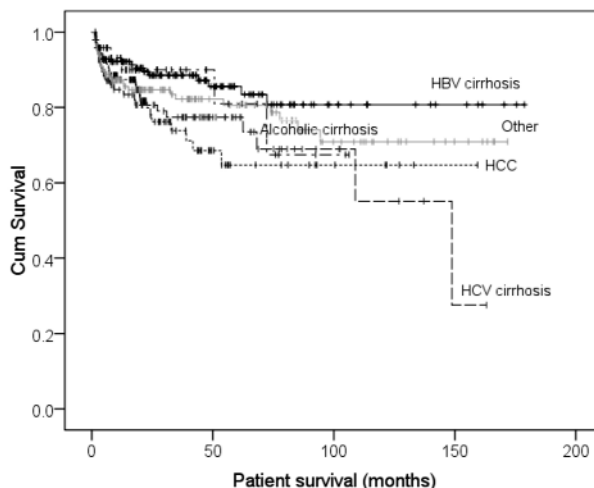


Figure 14. Survival in function of indications for liver transplantation (LT) ( $p = 0.106$ ).

cirrhosis were 93.2%, 81.1%, and 81.1%, while in HCC were 86%, 71.2%, and 64.7%, respectively ( $p = 0.106$ ) (figure 14).

In the 3 studied groups, long-term 1-, 3-, and 5-year estimated survival rates were 77.1%, 71.4%, and 69.8% (Group 1), 90.1%, 82%, and 78.3% (Group 2), and 90.1%, 84.2%, and 77.8% (Group 3), respectively ( $p = 0.042$ ) (figure 15).

**DISCUSSION**

LT is a well-established therapeutic option that has proved its effectiveness by long post-operative survival (longest survival recorded is 42.7 years) and good quality of life (19).

The number of LT procedure constantly increases worldwide (23,986 LTs reported in 2012) as well as in Europe (7,173 LTs reported in 2013) (20). In Romania, the LT program was started as a stringent necessity in 2000, while in Europe over 4,500 procedures were recorded that year and almost 45,000 overall. Among Eastern European countries (table 4), Romania is the third in what LT rate is concern (5.6 pmp), after Croatia (26.7 pmp, the highest in Europe) and Poland (8.8 pmp), being also the third as population number (21.3 million), after Ukraine (45.6 million) and Poland (38.5 million) (20).

**Waiting list**

The LT waiting list has grown continuously over the past decade in the context of a profound organ shortage, with consequent increased mortality rate on the waiting list, prolonged waiting time, and lack of

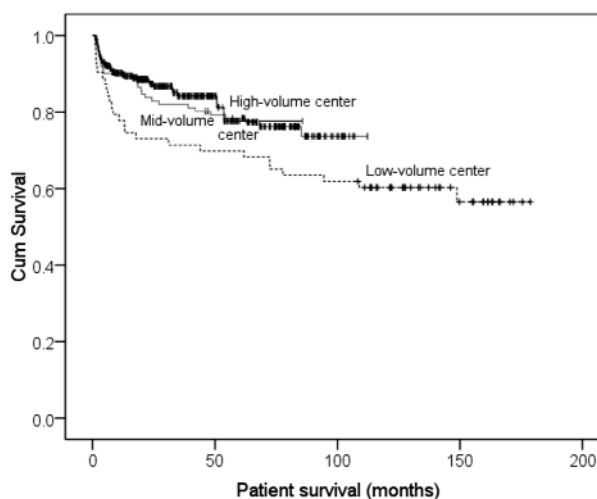


Figure 15 - Patient survival during the 3 periods of the main center development (low-, mid-, and high-volume center) ( $p = 0.042$ )

Table 4 - Liver transplantation and donation rates in Eastern European countries; pmp = procedures per million population (20)

Eastern European country	Population (millions)	LT rate (pmp) (2013)	Donation rate (2013)
Bulgaria	7.3	1.0	2.9
Hungary	9.9	4.5	15.5
Moldova	3.5	0.9	0.0
Poland	38.5	8.8	15.5
Romania	21.3	5.6	6.1
Serbia	7.2	-	-
Slovakia	5.4	4	10.9
Ukraine	45.6	0.3	0.2
Croatia	4.4	26.7	33.5

emergency LT supply (8, 9). Approximately 10,000 patients are added each year on the waiting list in US, with around 15,000 patients still on waiting list by the end of the given year. In Romania, 151 patients were enrolled on the waiting list in 2014, with around 544 still on waiting list by the end of the year (10). One-year overall mortality on waiting list decreased significantly over time from 31.4% (before 2011) to 11.8% (after 2011).

Despite the progressive increase in the number of LTs, the mortality on the waiting list remains between 5%-10% worldwide (8) and 11.8% in Romania, and patients have to deal with long waiting periods. Our main goal was to continuously reduce the drop-out rate on waiting list (due to mortality and morbidity) by shortening the waiting time for LT insured by providing the necessary grafts, including for urgent LT (acute liver failure and emergency re-transplantation).

### ***Organ donation***

Cadaveric donors account for the majority of liver grafts (over 90% in Europe and China), but this source is severely constrained due to social, cultural or legal factors. Consequently, the donation rates vary from 35.3 pmp in Spain (highest worldwide), to 25.8 pmp in US, 19.5 pmp in Europe (20), and less than 8 pmp in Asia (21). Among Eastern European countries, Romania occupies the Vth place, with a donation rate of 6.1 pmp (20). About 75-80% of donors provide a liver for LT.

During early 1990s, severe cerebral trauma due to traffic accidents was the main cause of death for donors worldwide. In contrast, in the recent years, this cause of death significantly decreased, being replaced by stroke. A similar trend was noted in Romania, with a decrease of severe cerebral trauma incidence from 61.2% in Group 1 (23 out of 67 deceased donors) to 39.3% in Group 3 (139 out of 354 deceased donors), and a concomitant increase of stroke incidence from 34.3% in Group 1 (23 out of 67 deceased donors) to 52.5% in Group 3 (186 out of 354 deceased donors).

According to international statistics, Spain and Italy are the European countries with the highest percentage of over 70 year donors, representing over 20% of total donors registered in these two countries (22). In Romania, donors over 65 yrs were avoided during early experience (Group 1), but progressively accepted over time (1.5% and 6.8% in Group 2 and 3, respectively).

Even though criteria for marginal donors vary from center to center, the use of extended criteria grafts has become a common policy worldwide due to organ scarcity. Moreover, the limits of extended criteria are constantly pushed, and organs that were previously

considered unacceptable are nowadays used. However, the association of multiple marginal features seems to have a negative impact on graft function and should therefore be avoided (23). Development and implementation of methods to avoid and/or treat the ischemia/reperfusion graft injuries represents the key to further push the limits of extended criteria while improving the LT outcome (24).

Additional sources for liver grafts, such methanol-poisoned donors (25), grafts with trauma lesions or benign tumors and other rare conditions such Takayasu's syndrome, even though relatively scarce, represents a source for grafts that should not be neglected.

Recently, there has been a steady increase of living donors worldwide, mainly due to the lack of deceased donors, a similar trend being recorded in Romania: Group 3 included 52.1% (62 pts) of all 119 living donors, while Group 1 and 2 included only 25.2% (30 pts), and 22.7% (27 pts), respectively.

### ***Liver transplantation***

Recipient's age has increased during this period of time. As a result, in the last decade, around 30% of the pool of recipients both on the waiting list and finally transplanted were over 60 years old. Elderly recipients may benefit from a senescent immune system, with consequent decreased requirements for immunosuppression, and possibly lower rate of acute allograft rejection. Despite good overall short-term survival in the elderly, long-term survival may be worse because of an increased rate of long-term complications not necessarily related to transplantation, such as malignancy and vascular disease (26). In Romania, the recipient's age increased during the analyzed period, in accordance with the literature data: the mean age in Group 3 was significantly higher than the one in Group 1 (47 yrs vs 36 yrs, respectively;  $p=0.034$ ). Overall, 19.7% of the pool of recipients (59 pts) was over 60 years old.

Since the first successful DDLT performed by Starzl TE (USA) in 1967 (27), whole organ LT still remains the main procedure in LT, but the need to increase the number of transplanted patients involves the implementation of other techniques, such as LDLT, split graft LT, and domino LT.

Even though LDLT was described in 1969 (28), it was introduced in clinical practice much later, in 1989 by Broeschl et al (USA) (29), Strong et al (Australia) (30) and Raia et al (Brasil) (31), representing one of the most remarkable steps in the field of LT. It involves an unique source of grafts because the liver is directed to only one specific candidate, with no need for an alloca-

tion system. In Europe, LDLT represents only 3.6% (20) of all LT procedures, while in US - 21.5% (32), and in Asia (except China) - over 90% (33). For pediatric patients, LDLT has become the main source of donors, while in adults represents a good indication in selected cases. Advantages of LDLT include the ability to be performed on an elective basis, with optimal timing and no waiting time for the recipient, the graft is in excellent condition (preselected graft, healthy donor), with short ischemic time, while the indications for transplantation may be extended (i.e. HCC beyond Milan criteria). As disadvantages, LDLT has donor mortality, even though as low as 0.5-1% (34, 35), high rate of vascular (5-15%) and biliary (10-30%) complications for both donor and recipient, and risk of small-for-size syndrome (36). Even though postoperative complication rate may be higher in case of LDLT, with proper treatment the long-term outcome may be similar in comparison with DDLT (37). Although complex and expertise demanding, dual graft LDLT has proven to be a safe procedure and a feasible solution to overcome the risk of small-for-size graft syndrome, when the selection of an optimal single donor fails (17, 38). Even though only 2 cases were performed in our experience, it remains part of our strategy to increase the number of LTs.

Split graft LT involves graft with normal anatomy and no risk factors for compromised liver function. Currently, split LT accounts for about 5% of total LTs, but about 20% of donors are potential candidates, hence the necessity of proper identification and harvest (39). In-situ split LT may provide comparable long-term survival results with those for whole liver LT, even though with a higher incidence of biliary and vascular complications (40). The drawbacks of ex-vivo split LT include time-consuming procedure, prolonged cold ischemia time, increased inflammatory response on reperfusion, poor function of the graft, while for in-situ split LT the disadvantages are prolonged procurement time and need for more experienced surgeons.

Domino LT, although rare, remains a viable alternative in selected cases with hereditary metabolic disease, such as familial amyloidotic polyneuropathy and homozygous familial hypercholesterolemia (18, 41, 42, 43).

In our experience, the results after LT continuously improved over time, in terms of operative parameter (cold and warm ischemia time, operative time and blood loss), major morbidity and postoperative results. The major complication rate decreased significantly over time, from 57.3% during the low-volume center period to 37.9% in the high-volume center period ( $p=0.038$ ). The perioperative mortality also decreased significantly over time, from 11.5% during

the stage of low-volume center to 6.9% in the stage of high-volume center. The long-term overall 1-, 3-, and 5-year estimated survival rates for patients in our experience (89%, 82.5%, and 79.2%, respectively) were similar to other centers (44). The long-term results also improved over time, a significant improvement being observed during mid- and high-volume center period when compared to low-volume center period, with 1-, 3-, and 5-year estimated survival rates of 90.2%, 83.8%, and 79.9% compared to 77.1%, 71.4%, and 69.8%, respectively ( $p=0.023$ ).

In order to increase the number of LTs, our main strategy was to increase the donor pool by optimizing the laws for organ donation, training the medical professionals (European funded educational program for doctors since 2007), mass education (Orthodox Church recognition in 2000, Romanian Association of transplanted patients since 2010, national TV educational campaign in 2013), and by improving the donor hospital efficiency (transplant coordinators and key donation persons implementation in 2012). Furthermore, the use of existing deceased donors was maximized by means of ECD grafts and use of other sources for liver grafts, such as poisoned donors (methanol) and grafts with particular lesions (trauma, benign tumors, etc.). Technical variant grafts, such LDLT, split LT, dual graft LT and domino LT, were also used in order to further increase the number of LTs.

## CONCLUSION

In conclusion, the liver transplantation program in Romania addresses all causes of acute and chronic liver failure or liver tumors in adults and children, using all surgical techniques, with good long-term outcome.

The use of strategies to extend the donor pool relieved the pressure on the waiting list, with good recipient survival rates. The limits of the extended criteria for deceased donors were constantly pushed over time, but there are still empirical, based on clinical practice. LDLT is nowadays a standard procedure and an established method to increase the donor pool size and its importance continuously increases as the scarcity of deceased donor remains unresolved and the need for LT continues to grow. Split LT, dual graft LDLT and domino LT, although rare, proved to be good methods to expand the donor pool. Proper donor-recipient matching is the key for the optimal use of marginal and surgical variant grafts.

The program constantly increased over time, leading to less time and lower mortality rate on the waiting list.

**Conflict of interest**

No source of support for the present work.

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