


## ORIGINAL ARTICLE

# Assessment of the global practice of living donor liver transplantation

Juliet Emamaullee<sup>1,2</sup> , Claire Conrad<sup>2</sup>, Michelle Kim<sup>1,2</sup>, Cameron Goldbeck<sup>1</sup>, Yong Kwon<sup>1,2</sup>, Pranay Singh<sup>1</sup>, Claus U. Niemann<sup>3,4</sup>, Linda Sher<sup>1,2</sup> & Yuri Genyk<sup>1,2</sup>

1 Department of Surgery, University of Southern California, Los Angeles, CA, USA

2 Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

3 Department of Anesthesiology, University of California-San Francisco, San Francisco, CA, USA

4 Department of Surgery, University of California San Francisco, San Francisco, CA, USA

## Correspondence

Juliet Emamaullee MD, PhD, FRCSC, FACS, 1510 San Pablo Street, Suite 412, Los Angeles, CA 90033, USA.  
Tel.: 323.442.5908;  
fax: 323.442.6887;  
e-mail:  
Juliet.emamaullee@med.usc.edu

## SUMMARY

Criteria that drive the selection and utilization of living liver donors are limited. Herein, the global availability of living donor liver transplantation (LDLT) and components of donor selection and utilization were assessed via an international survey. There were 124 respondents representing 41 countries, including 47 from Asia/Middle East (A/ME), 20 from Europe, and 57 from the Americas. Responses were obtained from 94.9% of countries with  $\geq 10$  LDLT cases/year. Most centers (82.3%) have defined donor age criteria (median 18–60 years), while preset recipient MELD cutoffs (median 18–30) were only reported in 54.8% of programs. Overall, 67.5% of programs have preset donor BMI (body mass index) ranges (median 18–30), and the mean acceptable macrosteatosis was highest for A/ME ( $20.2 \pm 9.2\%$ ) and lowest for Americas ( $16.5 \pm 8.4\%$ ,  $P = 0.04$ ). Americas (56.1%) and European (60.0%) programs were more likely to consider anonymous donors versus A/ME programs (27.7%,  $P = 0.01$ ). There were no differences in consideration of complex anatomical variations. Most programs (75.9%) perform donor surgery via an open approach, and A/ME programs are more likely to use microscopic arterial reconstruction. Despite variations in practice, key aspects of living donor selection were identified. These findings provide a contemporary reference point as LDLT continues to expand into areas with limited access to liver transplantation.

*Transplant International* 2021; 34: 1914–1927

## Key words

donor selection, global health, living donor liver transplantation

Received: 8 April 2021; Revision requested: 16 June 2021; Accepted: 20 June 2021; Published online: 14 September 2021

## Introduction

For patients with end-stage liver disease, the need for liver transplantation (LT) has outpaced the availability of organ donors. Due to regional and cultural variations affecting the availability of deceased organ donors, surgeons have innovated the use of partial liver allografts from living donors [1]. With increasing experience over the past two decades, many of the early technical

challenges observed in living donor liver transplantation (LDLT) have been resolved, including inflow modulation for potentially small-for-size grafts. Recent data have demonstrated that LDLT can provide superior graft and patient survival when compared to deceased donor liver transplant (DDLT), for both pediatric and adult recipients [2–6]. However, even in experienced centers, 40% of living liver donors experience postoperative complications, and thus donor safety and

informed consent remain central to the LDLT procedure [7,8].

The process of evaluation and selection of potential living liver donors varies between programs, with many contributing factors, including patient characteristics, recipient complexity, and overall willingness to accept risk by the transplant team [9–12]. As well, external pressures such as limited access to deceased donor allografts can affect the decision-making algorithm [13]. While technical aspects, such as the graft-to-recipient weight ratio (GWRW) are fairly well established, other specific parameters regarding the upper limits of donor age, impact of donor obesity, risk of heritable liver disease, and risk with known hypercoagulable states are not well defined. Performing a randomized trial to address each of these issues is not practical. As a result, based on prior experience and retrospective data, several society-authored clinical practice guidelines have been developed to address the evaluation and selection of living liver donor candidates [14–16]. Even with these guidelines, it is evident that individual centers are challenged to make assessments about donor candidacy and recipient eligibility for LDLT without discrete data to inform their decisions.

Recognizing inherent geographic variations in LDLT volume and practice patterns, the study aimed to identify key aspects of living donor screening criteria, LDLT candidacy, living donor evaluation, and surgical considerations to inform policy development. The availability of LDLT was examined for each country in the World Health Organization (WHO) Global Observatory on Donation and Transplantation, and a comprehensive international survey was conducted to understand the contemporary practice of donor and recipient selection for LDLT [17].

## Methods

This study was approved by the Institutional Review Board at the University of Southern California (HS-18-00482) and is therefore compliant with the Declaration of Helsinki (2000) and the Declaration of Istanbul (2008).

### Global prevalence of LDLT

Potential survey sites were identified through the WHO Global Observatory on Donation and Transplantation Registry in the most recent reporting year (2015–2017; [17]). The data for each country included the population and the total number of LDLT performed (Table S1). Liver transplant data for countries with no LDLT cases in the WHO Registry were cross-referenced with the

International Registry in Organ Donation and Transplantation (IRODAT) to identify additional LDLT cases [18]. A literature search was conducted to identify LDLT cases for countries not otherwise identified with LDLT activity in either registry. Sixty-eight countries with at least one LDLT case in the study period were identified, representing every United Nations Geographic Region [19]. The Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) Statement and Checklist were followed in this analysis [20].

### Development and validation of survey instrument

A unique questionnaire was designed to assess factors contributing to living liver donor evaluation, utilization, and programmatic experience. Several documents, including Vancouver Forum data, society guidelines, and prior studies were considered during survey development [12–15,21–23]. The survey evaluated four content areas: program demographics, donor assessment and selection, recipient factors that might impact utilization, and surgical techniques (full survey available in Data S1). Initial survey questions were refined through a series of reviews with relevant experts within our institution and a PhD expert in biostatistical survey design. Feedback was obtained from the American Society of Transplant Surgeons Scientific Study Committee and International Liver Transplantation Society (ILTS) leadership for survey content validity and completeness. The final set of questions was transferred to a web-based platform (Project Meridian; Akido Labs, Los Angeles, CA, USA) for electronic distribution and piloted by research staff to identify technical issues prior to broad distribution.

### Survey distribution

Potential respondents from the U.S. were identified using the Organ Procurement and Transplantation Network liver transplant program director list. International respondents were identified using transplant registry contacts, center-specific publications, and personal references. An attempt was made to establish contact with at least one physician associated with programs in each country identified to have LDLT activity. In addition, we attempted to obtain responses from multiple unique programs within high-volume countries (Table 1). Individual survey links were discretely associated with each respondent's email and were distributed electronically over 6 months in late 2018 (approximately 200 overall), and consent was obtained through voluntary survey participation.

**Table 1.** Global distribution of LDLT.

	Global population	Million people (%)
		7220.4 (100)
Part A: global distribution of liver transplantation		
Number of countries with reported LDLT cases		68
Global population with access to LDLT		5634.4 (78.2)
Global population with access to DDLT Only		111.2 (1.5)
Global population with access to LDLT Only		753.7 (10.4)
Global population with no access to LT		1372.5 (19.0)
Part B: survey response		
Total countries responded	41	
Responses by UN geographic region (no. of countries with ≥10 LDLT/year)		
	No. of countries with completed surveys (%)	Population represented by completed surveys (million)
Africa (2)	2 (100)	146.5
Asia (18)	17 (94.4)	3420.8
Europe (12)	11 (91.7)	557.9
Latin America (4)	4 (100)	320.8
North America (3)	3 (100)	490.3
Oceania (0)	0 (0)	0
Additional surveys from countries with <10 LDLT/year		
	No. of LDLT/year	Population represented by completed surveys (million)
Africa (none)	n/a	0
Asia (Viet Nam, Qatar)	3, 3	95.6
Europe (none)	n/a	26.9
Latin America (Costa Rica)	2	4.9
North America (none)	n/a	0
Oceania (New Zealand)	3	4.7
Completed surveys from high volume LDLT countries (>50 cases/year)		
	No. LDLT/year	No. of centers responded
India	1200	11
Turkey	1004	4
South Korea	942	5
Egypt	450	2
China	408	2
Japan	381	3
United States	359	43
Brazil	186	2
Pakistan	177	1
Jordan	174	2
Saudi Arabia	147	2
Russia	130	1
Canada	61	2
Germany	61	3
Kazakhstan	57	2

Population and LT volume data are based on the most recently reported year for each country in the WHO Global Observatory on Donation and Transplantation.

### Data handling and analysis

Data from each respondent were automatically extracted and manually reviewed for inconsistencies. For duplicate

responses from a single center, the most complete survey was included, and the duplicate was excluded from the final analysis. The individual responses were combined into a single file for subsequent analysis.

Responses were summarized by content area using a descriptive statistical approach, and data were reported as counts and percentages or median and interquartile ranges, where appropriate. The Fisher's exact test was used to compare categorical variables, and the t-test was used to compare differences in means of continuous variables. Nonparametric variables in independent samples were compared by the Mann-Whitney *U* test. An analysis of variance (ANOVA) was used to compare differences in means in survey respondent categories. A *P*-value <0.05 was considered to be significant. Statistical analysis was performed with R 4.0.3 and figures were generated using Tableau Desktop 2019.1.

## Results

### Part I: global prevalence of LDLT

The global utilization of LDLT was examined to identify countries to include in our survey distribution. Overall, 68 countries were identified with LDLT activity, representing 78.2% of the global population (Table 1). Among these, 15 countries reported  $\geq 50$  LDLT. Nineteen percent of the global population does not have an LT program in their country, primarily in Sub-Saharan Africa, the Middle East, and the parts of Southeast Asia (Fig. 1).

### Part II: survey response

During the study period, 143 survey links were accessed, and 124 were completed and included in the final analysis, representing a click-through rate of 86.7%. Survey responses were obtained from 41 countries with LDLT activity. Among "high-volume countries", at least two unique centers responded except in Pakistan and Russia, where, to our knowledge, there is only one active program for each (Table 1). For U.S.-based programs, 43/44 (97.7%) responded.

Among the 124 respondents, 47 were from Asian and Middle Eastern programs (A/ME), 20 were from Europe, and 57 were from programs in North and South America ("Americas"; Table 2). A/ME perform more LDLT per year [median 30 (95% CI: 30, 50), range up to 400] when compared to Europe [median 8 (95% CI: 8, 15), range up to 80] or the Americas [median 10 (95% CI: 10,15), range up to 110]  $P < 0.01$ . In parallel, A/ME programs evaluate more potential living donors [median 30 (95% CI: 25, 40), range up to 1000] versus Europe [median 20 (95% CI: 20, 30), range up to 200] and the Americas [median 30 (95% CI: 30, 36), range up to 300,  $p = <0.01$ ]. Most survey respondents were

affiliated with programs offering LDLT to both adult and pediatric recipients. Overall, 66% of programs were operational  $\geq 10$  years.

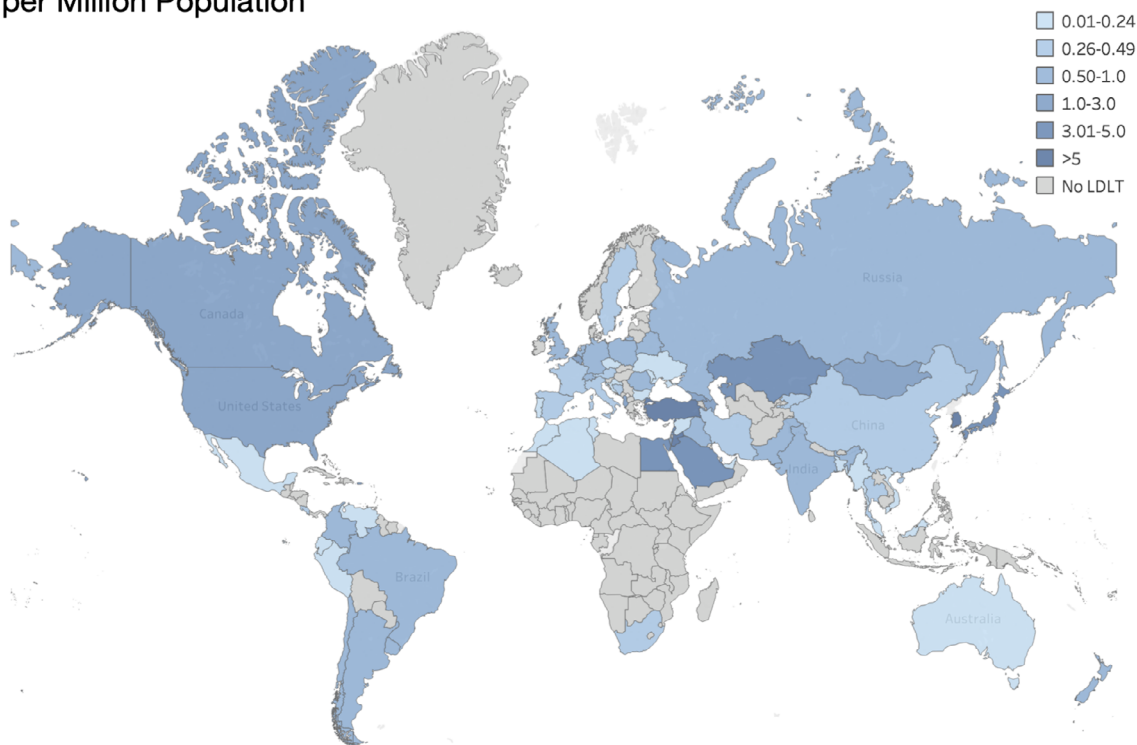
### Part III: living donor and recipient screening criteria

The majority of programs (82.3%) reported having a defined living liver donor acceptable age range, with a median range of 18 to 60 years (Table 3). European programs were less likely to have a defined age range [60% vs. 85.1% of A/ME programs ( $P = 0.05$ ) and 87.7% of the Americas programs ( $P = 0.02$ )]. Only 44.8% of all programs will evaluate ABO-incompatible living donors, with the top indication being for 'any blood group recipient' versus 'fulminant failure'. Two thirds of all respondents reported having donor BMI criteria for eligibility. For programs with defined cut-offs, European centers have a lower acceptable upper limit of BMI (median 30 [95% CI: 30, 30]) versus A/ME (median 31 [95% CI: 31, 34],  $P = 0.02$ ) and the Americas (median 32 [95% CI: 32, 35],  $P = 0.01$ ). A/ME programs are less likely to consider anonymous non-directed living donors (27.7%) versus programs from Europe (60.0%) or the Americas (56.1%). Several respondents, particularly from A/ME, indicated that anonymous donation is not permitted in their country. Willingness to consider 'transfusion-free' living donors (i.e., Jehovah's Witness patients) was infrequent (25.8%), particularly among programs in the Americas (15.8%).

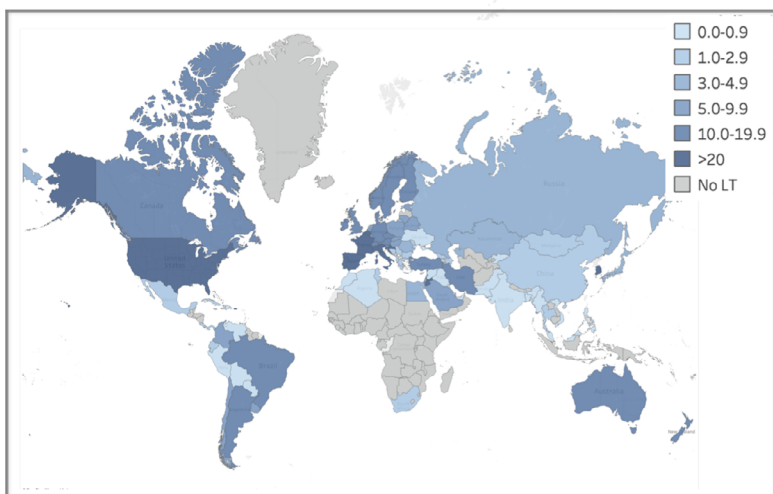
Due to potential heritability, some programs may be reluctant to proceed with first-degree relatives as living liver donors in recipients with certain heritable etiologies of chronic liver disease. Four recipient diagnoses were queried: non-alcoholic Steatohepatitis (NASH), primary biliary cholangitis (PBC), primary sclerosing Cholangitis (PSC), and Alpha-1-Antitrypsin Deficiency (A1AT). Some indicated that these recipient diagnoses could factor into living donor candidacy, with A1AT (41.8%) and PSC (41.0%) being the most likely to lead to exclusion of potential first-degree relative donors (Table 3).

Criteria for LDLT recipients were also examined (Table 3). Nearly half (45.2%) of respondents indicated their program has no pre-defined MELD caps for recipient candidacy, with 59.6% of A/ME programs reporting no MELD caps versus 55.0% of European programs ( $P = 0.74$ ) and 29.8% of programs in the Americas ( $P = 0.01$  vs. A/ME). For programs reporting a MELD cap, there were no regional differences, and the median upper MELD limit was 28 (95% CI: 25, 30). The majority of programs (83.9%) are willing to consider LDLT in fulminant liver failure.

### LDLT per Million Population



### LT per Million Population



**Figure 1** Global distribution of liver transplantation (inset) and living donor liver transplantation.

#### Part IV: living donor evaluation components

Four components of the living liver donor evaluation were examined: routine imaging, assessment of hepatic steatosis, supervised weight loss programs, and hypercoagulable testing (Table 3). The most common imaging studies for donor evaluation were (magnetic resonance imaging) MRI (92.7%), (computed tomography) CT (92.7%), and ultrasound (52.4%), with 46.0% of all centers routinely using all three approaches. European

programs most often use all three modalities (75.0%) versus 59.6% of A/ME programs ( $P = 0.59$ ) and 24.6% of the Americas programs ( $P < 0.01$ ). Liver biopsy remains the gold standard for assessment of liver steatosis (71.8%), followed by MRI (55.6%) and ultrasound (40.3%). The overall mean maximal acceptable degree of macrosteatosis was  $18.2 \pm 8.8\%$  (range 5–40%), with A/ME indicating a higher cut-off of  $20.2 \pm 9.2\%$  than the Americas programs ( $16.5 \pm 8.4$ ,  $P = 0.04$ ). The majority of programs offer potential living donors

Table 2. Survey respondents.

Individual respondents	Total: 124		Asia/middle east: 47		Europe: 20		Americas: 57	
	Median [95% CI]	Range	Median [95% CI]	Range	Median [95% CI]	Range	Median [95% CI]	Range
No. LDLT/year	15 [15,20]	(1–400)	30 [30,50]	(2–400)	8 [8,15]	(1–80)	10 [10,15]	(1–110)
No. potential donors evaluated/year	30 [25,40]	(1–1000)	60 [60,100]	(5–1000)	20 [20,30]	(1–200)	30 [30,36]	(1–300)
Years LDLT activity (N, %)								
#1–5	21 (16.9)		9 (19.1)		1 (5.0)		11 (19.3)	
#6–10	21 (16.9)		11 (23.4)		2 (10.0)		8 (14.0)	
≥10	82 (66.1)		27 (57.4)		17 (85.0)		38 (66.7)	
Recipient population (N, %)								
Pediatric only	15 (12.1)		2 (4.3)		5 (25.0)		8 (14.0)	
Adult only	33 (26.6)		14 (29.8)		5 (25.0)		14 (24.6)	
Adult and pediatric	76 (61.3)		31 (66.0)		10 (50.0)		35 (61.4)	

supervised weight loss programs for both obesity (60.2%) and hepatic steatosis (59.7%).

The components of the living liver donor hypercoagulable assessment have not been well defined but are often considered to minimize the risk of postoperative thromboembolic events in both the donor and the recipient. Overall, programs from Europe and the Americas often complete a more comprehensive hypercoagulable evaluation for potential donors when compared to A/E, with most European and Americas programs testing INR (international normalized ratio), PTT (partial thromboplastin time), Factor V Leiden, Protein C, Protein S, Antithrombin III, and Prothrombin gene mutations (Table 3).

### Part V: anatomic and surgical considerations for LDLT

Anatomic features of the partial allograft and surgical considerations were assessed (Table 4). Most programs are willing to use allografts with multiple arteries, bile ducts, and portal venous branches. A/ME programs more often use microscopic arterial reconstruction (66.0%) compared to Europe (40.0%,  $P = 0.06$ ) and the Americas (38.6%,  $P = 0.01$ ), and both transplant surgeons and plastic surgeons may perform this part of the procedure. Similarly, 63.8% of A/ME programs use  $>3.5\times$  Magnification, which was more common than European (30.0%,  $P = 0.02$ ) or Americas (43.9%,  $P = 0.03$ ) programs. Most programs reconstruct middle hepatic vein branches, with 69.5% reconstructing branches  $\geq 5$  mm, 16.1% reconstructing all branches, and only 14.5% not routinely reconstructing these branches. The majority of programs perform living donor hepatectomy via an open approach (75.8%), with no geographic variation. Most living liver donors receive venous thromboembolism (VTE) prophylaxis postoperatively (73.4%). Overall, 94.7% of all programs follow living liver donors for at least one year post-donation.

### Discussion

To our knowledge, this study represents the first systematic evaluation of the global practice of assessment, selection, and management of living liver donors. Our analysis determined that 68 countries have LDLT centers, suggesting that up to 78% of the global population has local LDLT availability. Even with continued expansion, 19% of the population does not have any access to LDLT or DDLT in their country. A high survey

**Table 3.** Living donor screening criteria and evaluation.

	Total: 124		Asia/middle East: 47		Europe: 20		Americas: 57		P-values			
	N	%	N	%	N	%	N	%	Overall	A/ME vs. Europe	A/ME vs. Americas	Europe vs. Americas
Donor screening												
Defined donor age range, yes	102	82.3	40	85.1	12	60.0	50	87.7	0.03	0.05	0.78	0.02
Lower age limit, median (95% CI)	18 [18,18]		18 [18,18]		18 [18,18]		18 [18,18]		0.49	0.35	0.34	0.69
Upper age limit, median (95% CI)	55 [55,60]		55 [55,60]		60 [60,60]		55 [55,60]		0.29	0.17	0.22	0.98
ABO-i living donors, yes	55	44.4	24	51.1	9	45.0	22	38.6	0.44	0.79	0.24	0.79
If yes, for which recipients?												
Any blood group	33	26.6	19	40.4	6	30.0	8	14.0	0.01	0.58	<0.01	0.17
Fulminant	18	14.5	4	8.5	3	15.0	11	19.3	0.3	0.42	0.16	0.99
Defined donor BMI range, yes	83	67.5	31	67.4	14	70.0	38	66.7	0.86	0.99	0.64	0.99
Lower BMI Limit, Median (95% CI)	18 [18,19]		18 [18,20]		18 [18,19]		18.5 [18.5,20]		0.37	0.28	0.65	0.16
Upper BMI limit, median (95% CI)	30 [30,32]		31 [31,34]		30 [30,30]		32 [32,35]		0.04	0.02	0.79	0.01
Special situations												
Anonymous nondirected donors, yes	57	46.0	13	27.7	12	60.0	32	56.1	0.01	0.03	0.01	0.8
Transfusion-free (i.e. Jehovah's Witness) donors, yes	32	25.8	15	31.9	8	40.0	9	15.8	0.04	0.58	0.06	0.03
Recipient screening												
May exclude donors of first-degree relative recipients with												
Non-alcoholic steatohepatitis	24	19.8	7	15.6	4	20.0	13	23.2	0.68	0.73	0.45	0.99
Primary biliary cholangitis	42	34.7	13	28.9	7	35.0	22	39.3	0.55	0.77	0.3	0.79
Primary sclerosing cholangitis	50	41.3	23	51.1	6	30.0	21	37.5	0.22	0.18	0.23	0.6
Alpha-1-antitrypsin deficiency	51	42.1	15	33.3	7	35.0	29	51.8	0.14	0.99	0.07	0.3
MELD cut off for LDLT												
None pre-defined	56	45.2	28	59.6	11	55.0	17	29.8	0.03	0.74	0.01	0.14
If pre-defined, median [95% CI]	28 [25,30]		30 [30,35]		26 [26,26]		28 [28,30]		0.48	0.39	0.24	0.6
LDLT in fulminant liver failure, yes	104	83.9	42	89.1	19	95	43	75.4	0.07	0.66	0.08	0.1

Table 3. Continued.

	Total: 124		Asia/middle East: 47		Europe: 20		Americas: 57		P-values			
	N	%	N	%	N	%	N	%	Overall	A/ME vs. Europe	A/ME vs. Americas	Europe vs. Americas
Donor evaluation												
Routine imaging modalities												
MRI	115	92.7	42	89.4	19	95.0	54	94.7	0.65	0.66	0.46	0.99
CT	115	92.7	47	100	20	100	48	84.2	<0.01	0.99	<0.01	0.1
Ultrasound	65	52.4	30	63.8	16	80.0	19	33.3	<0.01	0.26	<0.01	<0.01
Other	11	8.9	3	6.4	5	25.0	3	5.3	0.03	0.05	0.99	0.02
Imaging patterns												
MRI + CT + US	57	46.0	28	59.6	15	75.0	14	24.6	<0.01	0.59	<0.01	<0.01
MRI + CT	49	39.5	14	29.8	4	20.0	31	54.4				
MRI only	7	5.6	0	0.0	0	0.0	7	12.3				
Other	11	8.9	5	10.6	1	5.0	5	8.8				
Approach to assess liver steatosis												
MRI	69	55.6	19	40.4	12	60.0	38	66.7	0.02	0.18	0.01	0.6
Liver biopsy	89	71.8	31	66.0	13	65.0	45	78.9	0.25	0.99	0.18	0.24
Ultrasound	50	40.3	21	44.7	11	55.0	18	31.6	0.14	0.59	0.22	0.11
Other	22	17.7	15	31.9	2	10.0	5	8.8	0.01	0.07	0.01	0.99
Max. macrosteatosis, mean $\pm$ SD [range]	18.2 $\pm$ 8.9 [5–40]		20.2 $\pm$ 9.2 [5–40]		18.0 $\pm$ 9.1 [5–35]		16.5 $\pm$ 8.4 [5–35]		0.13	0.39	0.04	0.52
Supervised weight loss programs												
Weight loss for BMI cut off, yes	74	60.2	32	69.6	11	55.0	31	54.4	0.25	0.27	0.15	0.99
Weight loss for hepatic steatosis, yes	74	59.7	31	66.0	13	65.0	30	52.6	0.39	0.99	0.23	0.44
Hypercoagulable evaluation												
INR	109	87.9	38	80.9	19	95.0	52	91.2	0.21	0.26	0.15	0.99
PTT	104	83.9	35	74.5	19	95.0	50	87.7	0.09	0.09	0.12	0.67
Factor V Leiden	70	56.5	16	34.0	14	70.0	40	70.2	<0.01	0.01	<0.01	0.99
Protein C	75	60.5	24	51.1	15	75.0	36	63.2	0.17	0.1	0.24	0.42
Protein S	70	56.5	21	44.7	15	75.0	34	59.6	0.06	0.03	0.17	0.28
Antithrombin III	73	58.0	23	48.9	16	80.0	34	59.6	0.06	0.03	0.32	0.11
Prothrombin gene mutations	49	39.5	13	27.7	9	45.0	27	47.4	0.1	0.26	0.05	0.99
Fibrinogen	63	50.8	19	40.4	18	90.0	26	45.6	<0.01	<0.01	0.69	<0.01
Anticardiolipin antibody	46	37.1	13	27.7	9	45.0	24	42.1	0.24	0.26	0.15	0.99
Homocysteine	38	30.6	9	19.1	8	40.0	21	36.8	0.09	0.12	0.05	0.8
Factor VIII	34	27.4	8	17.0	8	40.0	18	31.6	0.09	0.06	0.11	0.59
Other	5	4.0	1	2.1	1	5.0	3	5.3%	0.71	0.51	0.62	0.99



**Table 4.** Anatomic and surgical considerations.

	Total: 124		Asia/middle east: 47		Europe: 20		Americas: 57		P-values			
	N	%	N	%	N	%	N	%	Overall	A/ME vs. Europe	A/ME vs. Americas	Europe vs. Americas
Anatomic considerations												
Arterial anatomy (acceptable)												
1 artery only	33	26.6	13	27.7	3	15.0	17	29.8	0.44	0.36	0.83	0.25
>1 artery	91	73.4	34	72.3	17	85.0	40	70.2				
Microscopic arterial reconstruction												
Utilized	61	49.2	31	66.0	8	40.0	22	38.6	0.01	0.06	0.01	0.99
If yes, surgeon type:												
Transplant surgeon	43	34.7	23	48.9	6	30.0	14	24.6	0.03	0.19	0.01	0.77
Plastic surgeon	27	21.8	13	27.7	4	20.0	10	17.5	0.45	0.76	0.24	0.75
Case by case	14	11.3	5	10.6	1	5.0	8	14.0	0.6	0.66	0.77	0.43
Magnification level												
2.5x	19	15.3	8	17.0	4	20.0	7	12.3	0.02	0.02	0.03	0.46
3.5x	44	35.5	9	19.1	10	50.0	25	43.9				
>3.5x	61	49.2	30	63.8	6	30.0	25	43.9				
Portal venous anatomy (acceptable)												
1 PV only	37	29.8	9	19.1	10	50.0	18	31.6	0.04	0.02	0.18	0.18
>1 PV	87	70.2	38	80.9	10	50.0	39	68.4				
Hepatic venous anatomy (acceptable)												
1 HV only	13	10.6	4	8.7	2	10.0	7	12.3	0.92	0.99	0.75	0.99
>1 HV	110	89.4	42	91.3	18	90.0	50	87.7				
Reconstruction of MHV branches												
No	18	14.5	2	4.3	5	25.0	11	19.3	0.08	0.05	0.05	0.73
Yes, >5 mm	86	69.4	35	74.5	12	60.0	39	68.4				
Yes, all branches	20	16.1	10	21.3	3	15.0	7	12.3				
Biliary anatomy (acceptable)												
1 bile duct only	10	8.1	3	6.4	1	5.0	6	10.5	0.24	0.14	0.22	0.64
2 bile ducts	80	64.5	26	55.3	16	80.0	38	66.7				
3+ bile ducts	34	27.4	18	38.3	3	15.0	13	22.8				
Surgical considerations												
Surgical approach												
Open	94	75.8	34	72.3	13	65.0	47	82.5	0.56	0.74	0.51	0.25
Laparoscopic, left lateral segments only	11	8.9	5	10.6	3	15.0	3	5.3				
Laparoscopic, left or right lobe	15	12.1	7	14.9	3	15.0	5	8.8				
Post-operative thromboprophylaxis												

Table 4. Continued.

	Total: 124		Asia/middle east: 47		Europe: 20		Americas: 57		P-values			
	N	%	N	%	N	%	N	%	Overall	A/ME vs. Europe	A/ME vs. Americas	Europe vs. Americas
None	24	19.4	17	36.2	1	5.0	6	10.5	<0.01	0.01	<0.01	0.76
Heparin prophylaxis	91	73.4	27	57.4	18	90.0	46	80.7				
Therapeutic anticoagulation	6	4.8	3	6.4	0	0.0	3	5.3				
Duration of post-donation follow up												
3 months	11	8.9	8	17.0	1	5.0	2	3.5	0.01	0.5	0.01	0.02
6 months	8	6.5	4	8.5	3	15.0	1	1.8				
1 year	31	25.0	13	27.7	7	35.0	11	19.3				
>1 year	74	59.7	22	46.8	9	45.0	43	75.4				

response rate was achieved, with respondents from 41 countries, including 100% of those with >50 LDLT/year. Our data support the concept that geographic variation in the availability of deceased donors impacts LDLT practice, and some programs are evaluating up to 1000 potential living donors each year. We observed geographic variations in practice, specifically related to donor age ranges, donor BMI cut-offs, acceptable graft steatosis percent, recipient MELD caps, and donor evaluation components including imaging and hypercoagulable workup.

A recent survey of 24 predominantly high-volume centers in ten countries from Asia, Europe, and North America with LDLT activity examined several features of living liver donor evaluation [21]. This study supports several of our findings, including an acceptable donor age range, willingness to consider variant anatomy, approach to liver biopsy, and acceptable macrosteatosis percent. With 124 respondents from 41 countries and six continents with a more comprehensive assessment of donor candidacy, surgical issues, and recipient selection, our survey expands upon this important work and allows for comparison across geographic regions. Key parameters of living donor screening, evaluation, surgical care, and recipient candidacy are summarized in Table 5 and provide a framework for policy development as LDLT continues to expand worldwide.

Society guidelines for living liver donation uniformly emphasize donor safety, but specific criteria have not been widely established [14–23]. The most recent ILTS Guidelines suggest that donors are “generally between 18 and 60 years of age”, which is in keeping with the majority of our respondents and prior reports including the Adult-to-Adult Living Donor Liver Transplantation (A2ALL) cohort [7–21]. However, nearly 20% of those surveyed in this study indicated that they presently have no formal age cut-off, even among North American centers. Similarly, some programs indicated they would consider a donor as young as 16 years if the intended recipient was the donor’s biological child and the donor received medical and psychosocial clearance. Our data suggest that donors >60 years old who are medically suitable may be considered on a case-by-case basis.

The recent ILTS Guidelines state that “>30% macrosteatosis is an absolute contraindication to donation,” and our survey indicates that most programs follow this recommendation. Interestingly, one A/ME center reported that they would accept up to 40% macrosteatosis, while one U.S. program reported a cut-off of 33%. The largest experience using macrosteatosis livers (10–20%) in 92 LDLT recipients in India reported

**Table 5.** Summary of donor evaluation and LDLT candidacy based on survey data.

Screening of potential living liver donors	
Age range	18–60 years; consideration of older donors on a case-by-case basis
ABO-incompatibility	Evaluate in countries with limited access to deceased donors, programs with ABO-incompatibility protocols, and/or when potential donors are willing to consider a paired exchange
Acceptable BMI	18–35 kg/m <sup>2</sup> ; Consideration of higher BMI candidates on a case-by-case basis
Anonymous donation	If permitted by local regulations and program has parameters for evaluation and allocation
Transfusion-free donation	If permitted by local regulations and program has parameters for evaluation and allocation
Recipient candidacy for LDLT	
MELD cutoff	Judicious use of LDLT in recipients with MELD >30. At discretion of program based on experience and availability of deceased organ donors
Fulminant liver failure	Acceptable; at discretion of program based on experience and availability of deceased organ donors
Living donor evaluation	
Imaging	Minimum: MRI + CT Scan. Additional modalities per program preference
Hepatic steatosis	Assessed via biopsy versus MRI depending on local resources Grafts with ≤20% macrosteatosis may be considered.
Medically supervised weight loss programs	Widely used to support donors who do not meet BMI and/or steatosis criteria for donation
Hypercoagulable workup	At a minimum: INR, PTT, Fibrinogen, Factor V Leiden, Protein C, Protein S, Anti-thrombin III
Anatomic features	
Arterial anatomy	≥2 widely considered acceptable, microscopic reconstruction at discretion of surgeon/program
Biliary anatomy	≥2 widely considered acceptable
MHV branch reconstruction	Performed by most centers, especially for branches ≥5 mm
Postoperative management of living liver donors	
VTE prophylaxis	Chemical per guidelines for major surgical procedures
Follow up	≥1 year

acceptable donor and recipient outcomes, but this donor population was relatively young (median age  $36 \pm 10$  years) and not obese (BMI  $26.7 \pm 3.0$ ) [24]. In practice, several factors, including donor age, donor liver remnant volume, GRWR, recipient age, and recipient underlying chronic liver disease are collectively examined when considering a fatty living donor allograft. Our data provide a reference point for acceptable macrosteatosis percent in the current practice of living liver donor selection.

In terms of BMI, the Vancouver Consensus and UK Guidelines both suggested that BMI >30 may increase the risk of surgical complications and that a liver biopsy may/should be considered if the BMI >30 [15–23]. In our study, only 67.5% of respondents reported an upper BMI cut-off, indicating that programs increasingly recognize that obesity is not always associated with hepatic steatosis and may not preclude living donor candidacy [24,25]. Among respondents with BMI criteria, A/ME and Americas programs have a higher median acceptable BMI of 35 and 30, respectively, versus 26 for European programs, likely reflecting the challenge of obesity

among potential donors in these regions. Indeed, in the A2ALL cohort, 16% of living liver donors had BMI  $\geq 30$ , which was only associated with one post-donation complication on multivariable analysis: an increased risk of hernia formation [7]. As well, we observed that 60% of programs have adopted medically supervised weight loss programs to improve candidacy for potential donors with obesity and/or fatty livers, which has been shown to convert previously unacceptable candidates into successful donors without an increase in adverse perioperative outcomes [26]. Our survey supports the concept of evaluating higher BMI donor candidates on a case-by-case basis.

Important lessons can be learned from the international experience in the application of LDLT in higher-risk situations, including high MELD recipients, fulminant liver failure, and ABO-incompatible donor and recipient pairs. Our data confirm that centers from countries with limited access to DDLT (A/ME) have more liberal approaches to donor age, graft steatosis, recipient MELD. High-volume LDLT centers in Taiwan and India have demonstrated that graft and patient

survival for LDLT with MELD >30 is comparable to the outcome in patients with lower MELD scores [27,28]. A recent retrospective review of the more extreme situation of acute liver failure from India, involving >400 LDLT, demonstrated that acceptable donor and recipient outcomes can be achieved, even with urgent time constraints, and a critically ill recipient [29]. With the development of rituximab-based induction and desensitization protocols, ABO-incompatible LDLT has been expanded, particularly in South Korea and Japan. A meta-analysis examining nearly 4000 patients determined that there was no difference in graft or patient survival for ABO-incompatible LDLT when compared to ABO-compatible cases, although there was a higher rate of biliary complications [30]. Our survey findings confirm that many programs will consider LDLT under these circumstances, assuming that a recipient has limited access to a deceased donor organ and a willing and otherwise compatible living donor.

Despite variances in practice and case volumes, there are many similarities across the global experience. Nearly all programs use MRI and CT scans to evaluate donor anatomy, and liver biopsy is the preferred modality to assess hepatic steatosis when required. Most programs are comfortable with complex anatomical considerations, including multiple arteries, bile ducts, and portal veins. Respondents from A/ME more often reported the use of microscopic arterial reconstruction, which has been associated with decreased rates of hepatic artery thrombosis [31–33]. The need for the reconstruction of MHV branches to prevent outflow congestion has been controversial [34–36]. Our data indicate that 85.5% of all centers surveyed routinely reconstruct these branches, most often for those  $\geq 5$  mm. Other similarities include offering supervised weight loss programs to potential living liver donors to improve their candidacy and the inclusion of a hypercoagulable workup. Finally, despite continued innovation of minimally invasive donor hepatectomy, the majority of respondents (75.8%) indicated that the procedure is performed via an open approach at their center, regardless of geography. This is likely related to surgeon experience, emphasis on donor safety via the ability to control unexpected bleeding through an open operation, and the observation that most donors do not have negative feelings about their surgical scar [37].

Expansion of the potential living liver donor pool through anonymous donation was first performed in the U.S. in 2000 at our center and has since been reported by centers in the U.S., Canada, and Belgium [38–40]. Over the past three years, there has been a rapid expansion of

anonymous donation in both the U.S. and Canada, with >40 anonymous living liver donors in the U.S. in 2019 alone [38]. However, the ethics surrounding this donor population and potential for coercion have led to restrictive policies, particularly among high volume LDLT countries (reviewed in Ref. [38]). This is reflected in our survey response, where only 27.7% of centers in A/ME would consider an anonymous donation, with some respondents indicating that existing regulations forbid it (Table 3). On the other hand, 60% of European survey respondents indicate that they would consider anonymous donors, which is in keeping with a recent review of global policies indicating that anonymous living organ donation is permitted in Sweden, Italy, Belgium, Denmark, England, Latvia, the Netherlands, Portugal, Scotland, Spain, and Switzerland, while it is prohibited in Bulgaria, the Czech Republic, Estonia, Finland, France, Germany, Hungary, and Lithuania as of 2013 [41]. As centers gain experience using anonymous liver donors, consensus guidelines surrounding donor selection and graft allocation will provide standards to guide the ethical use of this unique donor population.

Although our survey was developed in a structured manner by transplant physicians and vetted through professional societies, it was not validated using principle components analysis [42]. The impact of each respondent's program-specific protocol component was not linked to post-transplant donor and recipient outcomes. Relationships between various components of the living donor evaluation that might impact overall candidacy, such as age, BMI, and macrosteatosis, could not be determined. Also, components of the psychosocial evaluation, cardiovascular evaluation, and consequence of abnormal testing during the hypercoagulable workup, such as heterozygous Factor V Leiden, were not assessed.

## Conclusions

Presently, >80% of the global population lives in a country with LT activity, and 68 countries have active LDLT programs. Through the distribution of an international survey with a high response rate, key components of the living donor evaluation and recipient LDLT have been summarized and can inform policy development, particularly as LDLT continues to expand (Table 5). Importantly, our data provide reference points to key aspects of the donor evaluation, which should continue to emphasize donor safety. While there are considerable variations in LDLT practice and case volume, this study has confirmed that, with experience, surgeons are more comfortable with complex

anatomical variations, and programs are increasingly willing to consider higher-risk donors and recipients. As donor and recipient selection criteria continue to evolve, ongoing close follow-up will be necessary to minimize donor morbidity and maintain acceptable outcomes after both donation and transplantation.

## Authorship

JE, LS and YG: involved in the conception or design of the work. JE, CC, MK and PS: data acquisition. JE, BS, CN, YK, LS and YG: analysis and interpretation of data. JE, CC, MK and LS: drafted the article. Critically revised the article: All contributing authors. Finally approved the version to be published: All contributing authors.

## Funding

No grant or financial support was received for this study.

## Conflicts of interest

The authors in this manuscript have no conflicts of interest to disclose.

## Acknowledgments

The authors would like to recognize the American Society of Transplant Surgeons Scientific Study Committee and the executive leadership of the International Liver Transplant Society for their input into the survey instrument and study distribution. We are grateful to the American Society of Transplantation Liver and Intestinal Community of Practice for sharing the list of U.S. Liver Transplant Program Directors. We also appreciate Dr. Christiane Lane for her critiques of our survey instrument and preliminary analysis of survey data.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Population and liver transplant data utilized in this study.

**Data S1.** Living donor liver transplantation program survey to identify trends in living donor candidate evaluation.

## REFERENCES

- Ueda M, Oike F, Ogura Y, *et al.* Long-term outcomes of 600 living donor liver transplants for pediatric patients at a single center. *Liver Transplant* 2006; **12**: 1326.
- Bonanno AP, Saad WA, Ribeiro MA Jr. Pediatric liver transplantation: comparison between results from deceased and living related transplantation. *Transpl Proc* 2008; **40**: 720.
- Yankol Y, Fernandez LA, Kanmaz T, *et al.* Results of pediatric living donor compared to deceased donor liver transplantation in the PELD/MELD era: experience from two centers on two different continents. *Pediatr Transplant* 2016; **20**: 72.
- Laurence JM, Sapisochin G, DeAngelis M, *et al.* Biliary complications in pediatric liver transplantation: Incidence and management over a decade. *Liver Transpl* 2015; **21**: 1082.
- Olthoff KM, Smith AR, Abecassis M, *et al.* Defining long-term outcomes with living donor liver transplantation in North America. *Ann Surg* 2015; **262**: 465; discussion 473–5.
- Barbetta A, Aljehani M, Kim M, *et al.* Meta-analysis and meta-regression of outcomes for adult living donor liver transplantation versus deceased donor liver transplantation. *Am J Transplant* 2021; **21**: 2399–2412.
- Abecassis MM, Fisher RA, Olthoff KM, *et al.* Complications of living donor hepatic lobectomy – a comprehensive report. *Am J Transplant* 2012; **12**: 1208.
- Simpson MA, Pomfret EA. Checking the harness: Safety for living liver donors. *Liver Transplant* 2012; **18**: S15.
- Sharma A, Ashworth A, Behnke M, Cotterell A, Posner M, Fisher RA. Donor selection for adult-to-adult living donor liver transplantation. *Transplant J* 2013; **95**: 501.
- Valentín-Gamazo C, Malagó M, Karliova M, *et al.* Experience after the evaluation of 700 potential donors for living donor liver transplantation in a single center. *Liver Transplant* 2004; **10**: 1087.
- Wu M-K, Hsu L-W, Huang K-T, *et al.* Assessment of relevant factors with respect to psychosocial properties in potential living donor candidates before liver transplantation. *Neuropsychiatr Dis Treat* 2018; **14**: 1999.
- Nugroho A, Kim O-K, Lee K-W, *et al.* Evaluation of donor workups and exclusions in a single-center experience of living donor liver transplantation. *Liver Transplant* 2017; **23**: 614.
- Erim Y, Beckmann M, Kroencke S, *et al.* Psychological strain in urgent indications for living donor liver transplantation. *Liver Transpl* 2007; **13**: 886.
- Miller CM, Durand F, Heimbach JK, *et al.* The international liver transplant society guideline on living liver donation. *Transplantation* 2016; **100**: 1238.
- Manas D, Burnapp L, Andrews PA. Summary of the British transplantation society UK guidelines for living donor liver transplantation. *Transplantation* 2016; 1184.
- Tulla KA, Jeon H. Living donor liver transplantation. *Gastroenterol Clin North Am* 2018; **47**: 253.
- World Health Organization Transplant Observatory [Internet]. 2018 [cited 2018 Jan 6]. Available from: <http://www.transplant-observatory.org/export-database/>.
- International Registry in Organ Donation and Transplantation (IRODAT) [Internet]. [cited 2018 Jan 6]. Available from: <http://www.irodat.org/?p=database&c=CO#data>.

19. United Nations. Geographic subregions [Internet]. 2018 [cited 2018 Jan 6]. Available from: <https://unstats.un.org/unsd/methodology/m49/>.
20. Stevens GA, Alkema L, Black RE, *et al*. Guidelines for accurate and transparent health estimates reporting: the GATHER statement. *Lancet* 2016; **388**: e19.
21. Soin AS, Chaudhary RJ, Pahari H, Pomfret EA. A worldwide survey of live liver donor selection policies at 24 centers with a combined experience of 19 009 adult living donor liver transplants. *Transplantation* 2019; **103**: e39.
22. Miller CM, Quintini C, Dhawan A, *et al*. The international liver transplantation society living donor liver transplant recipient guideline. *Transplantation* 2017; **101**: 938.
23. Pruett TL, Tibell A, Alabdulkareem A, *et al*. The ethics statement of the Vancouver forum on the live lung, liver, pancreas, and intestine donor. *Transplantation* 2006; **81**: 1386.
24. Bhangui P, Sah J, Choudhary N, *et al*. Safe use of right lobe live donor livers with up to 20% macrovesicular steatosis without compromising donor safety and recipient outcome. *Transplantation* 2020; **104**: 308.
25. Gaba RC, Knuttinen MG, Brodsky TR, *et al*. Hepatic steatosis: correlations of body mass index, CT fat measurements, and liver density with biopsy results. *Diagn Interv Radiol* 2011; **18**: 282.
26. Choudhary NS, Saraf N, Saigal S, *et al*. Rapid reversal of liver steatosis with life style modification in highly motivated liver donors. *J Clin Exp Hepatol* 2015; **5**: 123.
27. Poon K-S, Chen T-H, Jeng L-B, *et al*. A high model for end-stage liver disease score should not be considered a contraindication to living donor liver transplantation. *Transplant Proc* 2012; **44**: 316.
28. Yadav SK, Saraf N, Saigal S, *et al*. High MELD score does not adversely affect outcome of living donor liver transplantation: experience in 1000 recipients. *Clin Transplant* 2017; **31**: e13006.
29. Pamecha V, Vagadiya A, Sinha PK, *et al*. Living donor liver transplantation for acute liver failure: donor safety and recipient outcome. *Liver Transplant* 2019; **25**: 1408.
30. Yadav DK, Hua YF, Bai X, *et al*. ABO-incompatible adult living donor liver transplantation in the era of rituximab: a systematic review and meta-analysis. *Gastroenterol Res Pract* 2019; **2019**: 1.
31. Lee C-F, Lu J-Y, Zidan A, *et al*. Microscope-assisted hepatic artery reconstruction in adult living donor liver transplantation-A review of 325 consecutive cases in a single center. *Clin Transplant* 2017; **31**: e12879.
32. Li P-C, Thorat A, Jeng L-B, *et al*. Hepatic artery reconstruction in living donor liver transplantation using surgical loupes: achieving low rate of hepatic arterial thrombosis in 741 consecutive recipients-tips and tricks to overcome the poor hepatic arterial flow. *Liver Transplant* 2017; **23**: 887.
33. Okazaki M, Asato H, Takushima A, *et al*. Hepatic artery reconstruction with double-needle microsuture in living-donor liver transplantation. *Liver Transplant* 2006; **12**: 46.
34. Kamei H, Fujimoto Y, Nagai S, Suda R, Yamamoto H, Kiuchi T. Impact of non-congestive graft size in living donor liver transplantation: new indicator for additional vein reconstruction in right liver graft. *Liver Transplant* 2007; **13**: 1295.
35. Pomposelli JJ, Verbesey J, Simpson MA, *et al*. Improved survival after live donor adult liver transplantation (LDALT) using right lobe grafts: program experience and lessons learned. *Am J Transplant* 2006; **6**: 589.
36. Cattral MS, Molinari M, Vollmer CM, *et al*. Living-donor right hepatectomy with or without inclusion of middle hepatic vein: comparison of morbidity and outcome in 56 patients. *Am J Transplant* 2004; **4**: 751.
37. Raza MH, Kim MH, Ding LI, *et al*. Long-term financial, psychosocial, and overall health-related quality of life after living liver donation. *J Surg Res* 2020; **253**: 41.
38. Raza MH, Aziz H, Kaur N, *et al*. Global experience and perspective on anonymous nondirected live donation in living donor liver transplantation. *Clin Transplant* 2020; **34**: e13836.
39. Goldaracena N, Jung J, Aravinthan AD, *et al*. Donor outcomes in anonymous live liver donation. *J Hepatol* 2019; **71**: 951.
40. Braun HJ, Torres AM, Louie F, *et al*. Expanding living donor liver transplantation: report of first US living donor liver transplant chain. *Am J Transplant* 2021; **21**: 1633.
41. Lopp L. Regulations regarding living organ donation In Europe [Internet]. Regulations Regarding Living Organ Donation in Europe: Possibilities of Harmonisation. Berlin, Heidelberg: Springer Berlin Heidelberg, 2013. Available from: <http://link.springer.com/10.1007/978-3-642-33799-4>.
42. Jolliffe IT. Principal component analysis and factor analysis. In: *Principal Component Analysis*. New York, NY: Springer, 1986; 115–128. [https://link.springer.com/chapter/10.1007/978-1-4757-1904-8\\_7](https://link.springer.com/chapter/10.1007/978-1-4757-1904-8_7).