Large-for-size orthotopic liver transplantation: a systematic review of definitions, outcomes and solutions

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Running Head: Large-for-size liver transplant

Category: Systematic Reviews

Disclosure: None

Author Contribution:

Substantial contributions to the conception or design of the work: PA, VN, BN, PB

Acquisition, analysis, or interpretation of data for the work; PA, VN, BN, PB

Drafting the work or revising it critically for important intellectual content: PA

Final approval of the version to be published PA, VN, BN, PB

Agreement to be accountable for all aspects of the work in ensuring that questions related to

the accuracy or integrity of any part of the work are appropriately investigated and

resolved. PA, VN, BN, PB

Abstract

Background: We systematically reviewed the literature on definitions and outcomes of large-for-size (LFS) syndrome in orthotopic liver transplantation (LT).

Methods: This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The Cochrane library, PUBMED, and Embase were searched (January 1990–January 2019) for studies reporting LFS in LT. Primary outcomes were definitions and mortality of LFS LT.

Results: Eleven studies reporting patients with LFS LT were identified. Four different formulas (Graft-recipient weight ratio (GRWR), Body surface area index (BSAi), Donor standardized total liver volume (sTLV)-recipient sTLV ratio, and Graft-weight/Right anteroposterior distance (RAP) ratio) with their critical thresholds were found. There were 81 patients (54% women) with a median weight and height of 62.5 kg (range, 40–105 kg) and 165 cm (range, 145–180 cm). The median graft weight was 1772 g (range, 1290–2400 g), and the median GRWR was 2.77% (range, 2.1–4.00%). Graft venous outflow obstruction was described in seven patients (8.6%). At the time of LT, fascial closure was not achieved in 24 patients (29.6%) and the graft size was reduced by a liver resection in three patients (3.7%). Thirteen deaths (16%) were reported in the first 90 postoperative days with two patients undergoing re-transplant.

Conclusions: LFS LT remains heterogeneously defined but characterized by high mortality rates despite the use of tailored surgical solutions (graft reduction and open abdomen). A composite definition is proposed in order to better describe LFS clinical syndrome.

Introduction

Currently, the allocation of a liver graft to a recipient is based on scores that give priority to the severity of liver disease more than to the anthropometrics of the donor and recipient¹. Discrepancies in appropriate matching between the donor and the recipient can lead to implantation of an excessively large liver graft into a small recipient cavity². This condition, known as large-for-size (LFS) liver transplantation (LT), has been widely described in pediatric LT³. The implantation of an LFS liver graft in babies was characterized by immediate hemodynamic instability, increased vascular complications and decreased survival³⁻⁵. When dealing with orthotopic LT in adults, the occurrence of an LFS LT remains theoretically rare because of a larger recipient cavity and the greater availability of adult deceased liver donors. However, transplant surgeons still can face an LFS graft because of the increased prevalence of obesity among the donor population, the urgent need for a liver graft (i.e. fulminant liver failure, urgent re-transplantation), and the inherent limitations given by the anthropometrics of some recipients. Recently, the occurrence of LFS has been described even in adult LTs as a possible consequence of an extreme anthropometrics mismatch between a donor and a recipient⁶. A recent study reported a postoperative mortality rate up to 40% for LFS LTs and other studies demonstrated a decreased graft and recipient survival⁶⁻⁸.

However, a uniform definition for LFS syndrome is currently lacking and little is known about outcomes of LFS LT in adults as well as technical solutions when facing this clinical scenario. The aim of this study was, therefore, to systematically review the literature regarding on LFS LTs in adults.

Patients and Methods

Search Strategy

The EMBASE, MEDLINE, and COCHRANE central databases were systematically searched from January 1990 through December 2018 for articles describing cases of LFS LTs in adult. The search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and limited to manuscripts written in English. The following phrases were used as search terms: “large-for-size,” “size mismatch,” each phrase was combined with “liver transplantation” or “orthotopic liver transplantation.”

Article Selection and Data Extraction

Potentially eligible articles were screened by two independent investigators. The exclusion criteria included articles describing: 1) LFS occurring after LT in pediatric patients; 2) LFS using a liver graft procured from a living donor in either an adult or pediatric recipient; 3) patients undergoing staged wound closure for causes other than donor-recipient size mismatch (e.g. bowel edema, massive coagulopathy and/or fluids resuscitations, and planned reoperation); and 4) registry studies. Discrepancies between the two investigators were resolved via consensus. The full text of the selected articles was analyzed for eligibility. The authors of the articles were contacted when additional information was needed. The primary outcomes of this review were definitions and mortality of LFS LT. Secondary outcomes were morbidity and solutions used in presence of LFS in LT. Data regarding the study period, number of patients, patients and donor characteristics, surgical complications, morbidity and mortality of LT were extracted from the included articles. All the data were extracted using a standardized extraction form.

Statistical Analysis

The methodological limitations and the volume of incomplete data hampered the meta-analysis. Continuous data were expressed as mean $\pm$ standard deviation (SD) and range or the median and range, as appropriate. Categorical variables were presented as numbers and percentages. Differences between groups were assessed using the chi-squared or Fisher's exact test (categorical variables) and the Wilcoxon rank sum test or the Student's *t*-test (continuous variables). This review is largely descriptive because of the small sample size.

Results

Physiopathology and Definitions

LFS in adult LT has been defined by the transplantation of a large liver graft into a small cavity. In both murine and porcine models, LFS transplantation has been characterized by higher serum levels of transaminases and potassium following reperfusion resulting from ischemic hepatocyte injury^{3,9-11}. These kinds of injuries have been related to the following: 1) poor liver reperfusion because of the large donor–recipient mismatch, which leaves a large poorly perfused area of liver parenchyma; 2) poor hemodynamic tolerance after unclamping the portal vein and the inferior vena cava; 3) kinking of the reconnected vessels because of the steric mismatch between a large donor graft and the recipient portal and inferior vena cava; 4) direct mechanical compression by the recipient abdominal cavity (costal margin, diaphragm, and nearby organs) over a large liver graft^{5,9-12}. These injuries have been thought to be responsible for severe allograft dysfunction with consequently poorer recipient and graft survival in both animals and humans (**Figure 1**). Four different formulas with their critical established threshold for defining LFS LT have been described and are reported in Table 1^{6,7,13,14}. Two of these formulas were based on a ratio between the donor graft weight and the recipient weight¹³ or the antero-posterior diameter of the abdominal cavity⁶. One formula was based

on a ratio between the standardized liver volume of the donor and the recipient¹⁴. The last formula used a ratio between the body surface area (BSA) of the donor and the recipient⁷.

A universally accepted definition of a clinical syndrome related to LFS was not available because these different formulas evaluated different main outcomes including early graft dysfunction¹⁵, pulmonary complications¹³, and graft and patient survival^{6,14}. Only one of these formulas combined the clinical condition represented by the impossibility of closing the abdominal wall because of a severe mismatch between the donor and recipient at the end of LT with early allograft dysfunction and/or death and/or the need for re-transplantation⁶.

Outcomes

The initial search resulted in 175 studies. However, only 11 studies (US [n=34], France [n=40], Korea [n=1], China [n=1], India [n=1], Japan [n=1], and Italy [n=3]) matched the inclusion criteria^{6,7,13,16-23} (Figure 2). The majority of the studies were published after the year 2010. There were 81 recipients with a median age of 48.5 years (range, 19–67 years) who underwent LFS LT. There were 39 women, which represented 54% of the recipients with available data regarding gender (39 out of 72). The median recipient weight and height were 62.5 kg (range, 40–105 kg) and 165 cm (range, 145–180 cm). Indications for LT are presented in Table 2, and fulminant liver failure and emergent liver re-transplantation were indications in ten patients (12.3%). The median graft weight was 1772 g (range, 1290–2400 g), the percentage of male donors ranged from 0 to 100%, and when reported, the median GWRW was 2.77% (range, 2.1–4.00). Table 3 shows postoperative outcomes of LT. To decrease the abdominal pressure, the abdominal wall was not closed in 24 patients and it was managed using negative pressure wound therapy in 12 patients, skin-only closure in three patients, and bridging mesh in seven patients (two were not described)^{6,13,16,18,19,21}. Three liver resections were performed to reduce the graft size (one right hepatectomy, one right posterior sectionectomy, one left lobectomy)^{17,20,22}. Venous outflow

obstruction by the large liver graft was described in seven patients intraoperatively (n=5)²¹ or in the immediate postoperative period (n=1), and it was managed by the placement of breast implants (n=2), pads (n=1), surgical gloves filled of saline solution (n=3), fascial closure with bridging mesh (n=1), or a “passing loop” caval anastomosis (n=1)^{17,21}. Thirteen deaths (16%) were reported in the first 90 postoperative days, with two patients undergoing re-transplantation.

Discussion

The current systematic review confirmed that LFS syndrome in adult LT patients remains rare but has a high related mortality despite tailored surgical solutions such as an open abdomen and graft reduction.

Appropriate matching between donors and recipients is of paramount importance to avoid LFS. From the analyzed pooled data LFSs appeared more frequently in small recipients (median height 165 cm) with large grafts (median weight 1772). The rare occurrence of this condition in adult LT compared to pediatric LT is related to the greater availability of adult liver grafts, the compliance of the abdominal cavity in adults, and the condition of the recipients, which may allow some waiting time to find a graft tailored to their abdominal cavity. However, the urgent need for a liver graft, such as in acute liver failure, can push the transplant team’s choice toward using larger liver grafts (**Figure 3**). In this review, acute or fulminant liver failure was the most frequent indication for LT in ten out of 13 patients who were reported in three studies^{6,16,22}. Patients with fulminant liver failure are more likely to have normal liver morphology and no ascites, which represents a favorable milieu for an anthropometric mismatch. LFS was also reported for re-transplantation where the previous surgery and strong adhesions could contribute to the shortage of space in the abdominal cavity^{6,16}.

There is currently no universally accepted definition of LFS. However the increasing number of the reports over the last ten years captured by the current review underlines probably the

increase awareness of this specific problem and reflects the more liberal policy in accepting larger liver grafts. This could be also reflecting the worldwide epidemic of obesity and metabolic syndrome. We found four different definitions related to the analysis of different outcomes. Three of these formulas, the BSAi, the GRWR, and the STLV, associated the presence of a larger liver graft with early liver graft dysfunction or an increased rate of pulmonary complications^{7,13,14}. In these three studies, no mention was made of the direct mechanical consequences that were related to the discrepancies between the small recipient abdominal cavity and the large graft. In addition, graft dysfunction and pulmonary morbidity can also be related to several other factors besides the presence of a large liver graft. Variability has also been reported when calculating the BSA, the STL, and the BMI ratio in predicting the occurrence of LFS because of the high variability of the recipient's weight in cirrhotic patients⁶. In fact all the studied morphological index (GWRW, STLV, BSAi) have their intrinsic limitation. For example, the weight of a given recipient (WR) can be largely influenced by the presence of diffuse edema and ascites or conversely by extreme malnutrition and sarcopenia. The BSA could be influenced also by the same weight variation. The formula using the standard liver volume could also be influenced by the variability in case of hypertrophic or hypotrophic cirrhotic liver and the presence of previous operation. Finally the presence of ascites could potentially increase the volume of a limited small abdominal cavity and challenge all these formulas (Figure 4). Imaging-based donor-recipient matching, whenever possible, should be pursued in order to avoid mismatch.

Recently, Allard et al. conducted a short study that showed a correlation between the clinical occurrence of the inability to close the abdomen at the end of the LT and a morphological mismatch between the donor and the recipient. They found that the combination of a female recipient and a male donor with a GW/RAP ratio >100 was associated with the highest risk of LFS syndrome, which is characterized by the highest mortality rate. This study was the first to introduce a morphological measure (RAP) that might anticipate the occurrence of a mismatch in the presence of

liver grafts. The same authors found that this ratio was better than the BSAi and the sTLV for predicting the occurrence of LFS syndrome⁶. However, the wide application of this method requires immediate access to the most recent CT scan results of a potential recipient.

A universal and easily applicable formula could not be proposed even after an extensive review of the literature also because the potential outcomes associated to the presence of large graft were different. Intuitively, when describing a clinical scenario associated to the presence of a large liver graft several conditions should be associated in a composite definition. First the presence of mechanical consequences related to a liver graft larger than the recipient liver cavity. These could include: the impossibility of closing the abdomen, and/or the presence of venous congestion (after having excluded all the other causes) and/or localized mechanical-associated liver areas of ischemia. Secondly, the presence of biological consequences should be present such as early allograft dysfunction, massive cytolysis and/or primary non-function. Third, the need for a graft-directed treatment such as re-laparotomy and/or graft reduction and/or open abdomen and/or retransplantation.

Anthropological differences between genders favor the occurrence of LFS. Previous studies demonstrated that male donors have larger liver grafts than females, and females usually have a smaller abdominal cavity than males²⁴. Not surprisingly, in the current systematic review, most LFS were reported in female recipients. Therefore, relatively low median recipient heights and weights were observed. Even if most donors were male in the current study, the lack of data did not allow us to quantify the exact incidence of the combination of a male donor graft that is used in a female recipient.

Transplanting a large graft into a small cavity can be associated with direct compression by nearby structures. Immediate outflow obstruction was reported in seven patients as a consequence of retrohepatic inferior vena cava compression by a large graft when performing a piggy-back LT with a side-to-side caval anastomosis^{21,23}. This complication was managed by rotating the graft and

releasing the compression on the IVC by mechanical means (prosthesis, pads, and filled gloves) and/or leaving the abdomen open²¹. Other authors described a systematic caval resection when implantation of a LFS graft was anticipated, which could be a reasonable technique¹³. Caval resection was still the technique used in six out of ten cases of extreme LFS, as reported by Allard et al.⁶ Another technical option could be of fashioning two caval anastomosis: one above and the other below the large liver graft (passing-loop technique).¹⁷

Definitely the alternative technical option could be to reduce the graft volume via liver resection. Not surprisingly, this was rarely performed, with only three cases reported in the current review, and the right liver resections (posterior section and the right liver) were the most prevalent. These resections were performed *in situ* and characterized by high blood losses (935 and 14,000 mL)^{17,20,22}. The scarce number of graft reductions could be explained certainly by the fact that LFS in these cases was described intraoperatively and maybe other cases of potential LFS were prevented by ex-situ reduction.

Leaving the abdomen open was the most prevalent method of managing the mismatch between a large graft and a small cavity. In some studies, a bridging mesh and exclusive cutaneous closure were the most frequently used technique, while more recently, negative pressure wound therapy (NPWT) was the most common technique that was used to manage the open abdomen^{6,16}. This technique immediately releases abdominal tension, avoids compartment syndrome, and postpones definitive closure of the fascial plane while allowing time for edema resorption. However, for severe LFS, definitive fascial closure was not possible in some cases⁶.

The current review found a high mortality rate (16%) in the first 90 days after LFS LT. Graft failure with multiorgan dysfunction and infections were the most common cause of death but vascular complications were not more common than in the general LT population. It is more likely that most of these deaths were related to the occurrence of an LFS syndrome with more prolonged

hospitalization and more infections and consequent multiorgan dysfunction because death related to graft necrosis and mechanical complications were rarely reported¹⁸.

From a practical point of view several approaches could be suggested after reviewing the literature. First, the chance of mismatch should be reduced by tailoring the choice of the graft to the recipient conditions. Predictive formulas of STL and CT scan of the donors should be used when facing the choice of a liver graft. Additionally, more recent images of the recipient should be reviewed in order to exactly determine the dimensions of the recipient's cavity which are related to several factors (liver volume, presence of ascites, adhesions, etc).

Secondly when size mismatch cannot be avoided because of the urgent need for a graft several technical tricks could be useful. First, in our opinion the abdominal incision should be lowered downward that will avoid that a large graft falls into the middle of high right subcostal incision. Secondly during recipient hepatectomy, in order to avoid bowel edema leading to further reduction of the abdominal space, a temporary portosystemic derivation could be performed whenever spontaneous shunts are hemodynamic inefficacious. Third, once at the end of hepatectomy transplant surgeons face a limited space for graft implantation, graft reduction should be planned ex-situ in order to reduce bleeding of in situ reduction. The choice of the liver segments to be resected will be based on the morphology of the liver and that of the recipient cavity. Left lobe or the right liver could be alternatively removed according to the morphology of the recipient.

Fourth, when LFS is evident at the end of the transplant NPWT with an open abdomen should be employed and the definitive closure of the fascia will be delayed in a progressive way. NPWT will allow sufficient time to adequately resuscitation of the patient to reduce edema. The current systematic review has several limitations. First, the relatively long interval of time that was analyzed and the small number of cases that were reported made a meaningful analysis difficult. Second, the lack of a uniform definition of LFS introduced a noteworthy selection bias. It is more likely that most of the patients with severe LFS were not even reported because of the rarity

of this condition. A multicentric study could help to determine the exact incidence and mortality of LFS. Third, a detailed morphological analysis of the recipients' abdominal cavity was lacking in all studies while the liver graft weight was available in most cases. An analysis of the recipients' abdominal cavity characteristics could have added more value to this analysis.

Conclusions

The LFS syndrome after LT remains an ill-defined but life-threatening condition despite the use of tailored surgical solutions (graft reduction and open abdomen). Its occurrence seems mostly prevalent in small-size recipients who have an acute need for a liver graft. Leaving the abdomen open could help in the acute setting to release the abdominal tension and avoid the occurrence of severe mechanical consequences. A composite definition is herein proposed in order to better define the LFS clinical syndrome. Once a uniform definition will be adopted, the exact threshold of the different anthropometric (BSA, STL, GWRW) and liver measures (Graft weight, Graft volume) associated with the LFS syndrome could be defined. Further multicentric studies gathering the data of patients with LFS LTs could help to extensively clarify risk factors and outcomes of this condition.

Acknowledgements

No funding.

Conflict of Interest

None.

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Figure 1: Schematic breakout of hypothesized mechanism leading to a clinical evident “large-for-size” liver transplantation syndrome.

Figure 2: PRISMA selection for study selection

Figure 3: Postoperative CT scan of a LFS LT in a 57-year-old man receiving an urgent re-transplantation for a late hepatic artery thrombosis. The GWRW, BSAi, and sTLV ratios were 3.3, 1.96, and 1.33, respectively. An extreme LFS was evident and immediately managed using negative pressure therapy. Red arrows indicate partial ischemic graft necrosis in the sagittal (left) and coronal (right) views.

Figure 4: Schematic breakout of the shortcomings of the current formulas in predicting LFS in a cirrhotic patient having large ascites. A large liver graft (2200 gr) with a GWRW, BSAi, and sTLV ratios of 2.8, 1.27, 1.41 respectively was transplanted uneventfully in presence of large ascites enabling uneventful postoperative outcomes.

Table 1: Definitions used for large-for-size liver transplantation.

Author	Year	Formulas	Definition	Outcomes
Fukazawa K	2011	Body surface area donor/ Body surface area recipient (BSAi)	BSA>1,24	Early allograft dysfunction and 90-day graft failure
Levesque E	2013	Graft-recipient weight ratio (GRWR)	GWRW>2.5%	Respiratory complications
Croome KP	2015	Donor standardized total liver volume (sTLV)-recipient sTLV ratio	sTLV ratio>1,25	Early allograft dysfunction
Allard MA	2017	Graft-weight/Right anteroposterior distance (RAP) ratio	GW/RAP>100	Impossibility to close the abdomen with 1) EAD and/or 2) death; and/or 3) urgent re-transplantation.

Author	Year of Publication	Country	N =	Gender	Age	HEIGHT	WEIGHT	Indications	Donor Gender	Graft weight	GWR W
Jafri MA	2007	US	6	NA	NA	NA	NA	NA	NA	NA	NA
Fukazawa K	2011	US	28	17F/11M	NA	NA	NA	NA	NA	NA	NA
Donataccio D	2011	Italy	3	NA	NA	NA	NA	NA	NA	NA	NA
Eldeen FZ	2013	China	1	F	49	148	40	Cirrhosis	na	NA	NA
Levesque E	2013	France	25	8F/17M	57*	171	60	Cirrhosis (10) Cancer(7) Other(8)	21M/4F	NA	2,75
Kim EY	2015	Korea	1	F	43		43	Cirrhosis	M	1710	3,98
Brustia R	2015	France	2	F	61	145	49	FLF	NA	1660	3,38
				F	24	168	48	Urgent re-LT	NA	1443	3,01
Allard MA	2017	France	10	F	39	180	70	FLF	M	1825	2,6
				F	19	160	50	Re-LT	M	1848	3,7
				F	47	155	77	Cirrhosis	M	1770	2,3
				F	59	170	105	Cirrhosis	M	2170	2,1
				F	32	170	70	FLF	M	1545	2,2
				F	37	165	60	FLF	M	2165	3,6
				F	48	158	60	Rendu-Osler	M	1675	2,8
				F	39	165	65	FLF	M	1848	2,8
				F	67	160	79	FLF	M	1865	2,4
				F	46	148	43	FLF	M	1725	4
Nagatsu A	2017	Japan	1	F	58	149	73	ALF	M	1290	2,74
Lim C	2018	France	1	F	55	150	72	Cirrhosis	M	1772	2,5
			1	M	49	171	70	Cirrhosis	M	2086	3
			1	M	53	178	100	Cirrhosis	F	2400	2,4
Jacob M	2018	India	1	M	58	165	60	NA	F	NA	

Table 2: Preoperative characteristics of patients undergoing liver transplantation developing LFS syndrome.

Author	Year of Publica tion	EA D	GWR W (%)	Open abdo men	Morbi dity	Vascular complicat ions	Biliary complicat ions	Retransplan tation	Dea th 90 day s	Dea th 1 yea r
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Table 3: Postoperative characteristics of patients undergoing liver transplantation developing LFS syndrome.

Jafri MA	2007	NA	NA	Yes(silastic mesh)	NA	NA	NA	NA	NA	NA
Fukaza wa K	2011	NA	NA	NA	NA	3.6%	0%	NA	6	NA
Donataccio D	2011	NA	NA	No	No	No	No	No	No	No
Eldeen FZ	2013	NA	NA	Non	No	No	No	No	Yes	Yes
Levesque E	2013	NA	2.75(2.5-3.63)	Yes(2)	Yes	1(4%)	1(4%)	Yes(1)	No	NA
Kim EY	2015	NA	3.98	Non	YES	No	No	No	No	No
Brustia R	2015	NA	3.38 3.01	Yes(N WP)	Yes	No	No	No	No	NA
				Yes(N WP)	Yes	No	No	No	No	NA
Allard MA	2017	NA	2.6	Yes(N WP)	NA	NA	NA	No	No	No
			3.7		NA	NA	NA	No	No	No
			2.3	Yes(N WP)	NA	NA	NA	No	Yes	-
			2.1	Yes(N WP)	NA	NA	NA	No	No	No
			2.2		NA	NA	NA	No	Yes	-
			3.6	Yes(N WP)	NA	NA	NA	No	Yes	-
			2.8	Yes(N WP)	NA	NA	NA	No	No	No
			2.8		NA	NA	NA	Yes	Yes	No
			2.4	Yes(N WP)	NA	NA	NA	No	No	-
			4.0							
				Yes(N WP)						
				Yes(N WP)						
				Yes(N WP)						
				Yes(N WP)						
Nagatsu A	2017	NA	2.74	No	No	No	No	No	No	No

Lim C	2018	NA	2.5	Yes(skin closure)	No	Yes (caval)	Yes	No	No	Yes
		NA	3.0	Yes(skin closure)	Yes	No	Yes	No	No	No
		Yes	2.4	Yes(skin closure)	Yes	No	No	Yes	Yes	-
Jacob M	2018	Yes	0%	Yes(mesh)	Yes	NA	NA	No	Yes	-