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Review article

The effect of donor body mass index on graft function in liver transplantation: A systematic review



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ABSTRACT

The impact of donor body mass index (BMI) on graft function outcomes in liver transplantation (LT) is still controversial. The aim of this study was to review the current evidence investigating the effect of donor BMI on outcomes in patients undergoing LT. A systematic review was performed to evaluate relevant outcomes such as the availability of data on donor BMI as well as graft and patient survival after LT. Screening of 901 articles resulted in 11 observational studies for data extraction. In adult deceased donor after brain death and living donor LT, donor BMI was not associated with graft and patient survival. However, high donor BMI was associated with a higher chance of macrosteatosis besides a significantly higher incidence of declined livers. In pediatric LT, severe obesity in adult donors with BMI ≥ 35 was associated with graft loss and mortality, whereas obesity in pediatric donors was not associated with graft loss and mortality. Accordingly, donor BMI is not associated with long-term outcomes in adult patients undergoing LT. However, further research should be conducted to identify the effect of donor BMI on outcomes in LT.

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Abbreviations: ECD, extended criteria donor; BMI, body mass index; LT, liver transplantation; DRI, Donor Risk Index; UNOS, United Network for Organ Sharing; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; OR, odds ratio; PNF, primary non-function; DBD, donors after brain death; DCD, donors after circulatory death; HR, hazard ratio; CI, confidence interval.

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1. Introduction

In the past three decades obesity has become a pandemic; global obesity prevalence is foreseen to reach 21% in women and 18% in men by 2025 [1,2]. A recent study has shown that the prevalence of age-standardized obesity increased from 6.4% in 1975 to 14.9% in 2014 in women and from 3.2% to 10.8% in men [3]. The increasing prevalence of overweight and obesity will inherently lead to an increasing number of obese organ donors.

Strict donor pool selection criteria, especially from extended criteria donors (ECDs) such as high body mass index (BMI) donors, are crucial to obtain good clinical outcomes after liver transplantation (LT). The common index to predict post-transplant outcomes in LT is the Donor Risk Index (DRI). However, DRI does not include donor BMI as a risk factor [4,5]. In contrast, several ECDs include donor BMI as risk factor where acceptable outcomes from extended criteria donors have been reported [6–8].

The impact of donor BMI on graft function in LT was first reported in 2003 based on the United Network for Organ Sharing (UNOS) database, showing no influence for outcomes in LT [9]. Several studies on donor BMI in LT have been conducted after that, with conflicting results reported [10–12]. Moreover, the effect of donor BMI differs per field in LT, including deceased donor LT (DDLT), living donor LT (LDLT), and pediatric LT.

To date, the effect of donor BMI on graft function outcomes in LT has not yet been systematically reviewed. Therefore, the aim of this systematic review was to investigate the association of donor BMI with post-transplant outcomes in patients undergoing DDLT, LDLT, and pediatric LT, focusing on comparing outcomes between lower and higher donor BMI.

2. Material and methods

2.1. Literature search strategy

A systematic literature search of Embase, Medline Ovid, Web of Science, and Cochrane CENTRAL was performed on the 1st of February 2020 using the following key words: liver transplantation, donor, and body mass index. The full search terms are available in Supplementary Table 1. The search was limited to the English language without limitations of the publication year. This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13].

2.2. Inclusion and exclusion criteria

The present study included articles investigating the association of donor BMI with outcomes in patients undergoing DDLT, LDLT, and pediatric LT, focusing on comparing outcomes between lower and higher donor BMI. Review articles, records without abstract, articles without sufficient data, conference abstracts, and case reports were excluded.

2.3. Data extraction

First duplicate records were removed. Subsequently abstracts were screened to determine eligible studies for further analysis, and full-text articles of the remaining records were subsequently reviewed independently by two investigators (KT and RdW). The extracted data were as follows: study information (year, study design, study period, and number of patients included), donor and recipient information (type of donor, donor BMI, and recipient characteristics), post-transplant outcomes (donor and recipient complications including primary non-function [PNF] and retransplantation, and long-term outcomes such as graft and patient survival), and follow-up period.

2.4. Assessment of study quality

The methodological quality of the included studies was evaluated using the Newcastle-Ottawa quality assessment scale for cohort studies [14]. Studies with a total score with 6 or higher were considered as high-quality [15].

3. Results

A systematic literature search identified 901 articles (Fig. 1). After excluding duplicate articles and screening the abstracts, 15 full-text articles were reviewed. Finally, 11 articles [9–12,16–22] were included in the present study since necessary data were not available from 4 articles.

The characteristics of the included studies are summarized in Table 1. Out of 11 studies, ten were retrospective series and one was prospective study using the UNOS database. Different cut-off values of BMI were used in each study.

The assessment of methodological quality of the included studies was demonstrated in Table 2. Out of 11 studies, 10 were evaluated as high-quality with a total score of 6 or higher.

3.1. Impact of donor BMI on graft function in adult deceased donor liver transplantation

Three studies from the UNOS database have been published to investigate the effect of donor BMI in adult DDLT. Yoo et al. analyzed 22,303 LT recipients in the period 1987–2001 for which four groups were defined based on donor BMI: BMI <25 ($n = 11,660$), 25 to 29.9 ($n = 7418$), 30 to 34.9 ($n = 2301$), and ≥ 35 ($n = 924$) [9]. They observed that the incidence of PNF and early retransplantation rates were similar among the groups, and concluded that donor BMI or moderate steatosis did not influence short-term and long-term outcome of LT. A second prospective observational study by Bloom et al. was conducted from 2008 to 2011 in the UNOS Region 5 [12]. During this period, 730 livers were transplanted from 961 donors (76%) where donor BMI was identified as one of independent predictors of liver use (odds ratio [OR] 0.94, $P = 0.001$). Multivariable analysis found that lower donor BMI (OR 0.91, $P = 0.009$) was associated with improved graft survival. A third study by Steggerda et al. evaluated trends in the utilization and outcomes based on donor BMI and the potential role of liver biopsy in

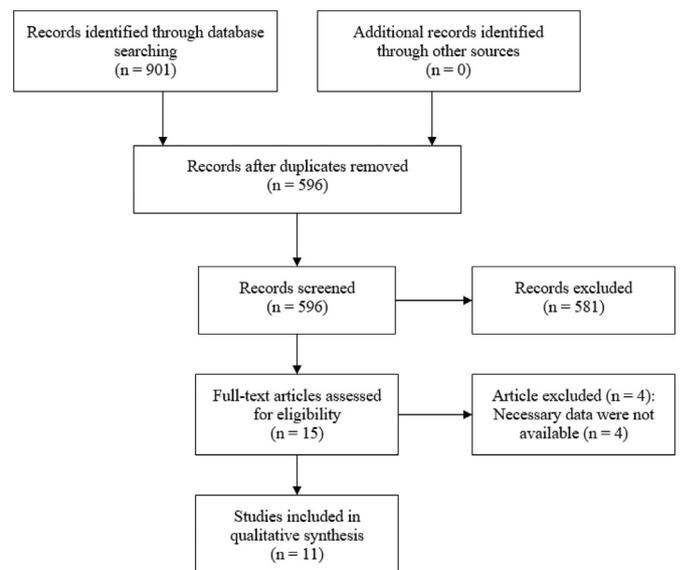


Fig. 1. PRISMA 2009 Flow Diagram.

Table 1
Literatures reporting the effect of donor body mass index on outcomes in liver transplantation.

Study	Year	Study design	Study period	Number	Type of donor	Recipients	Cut-off of donor BMI	Reported outcome	Follow-up
Yoo et al. [9]	2003	UNOS Retrospective	1988–2001	22,303	Deceased (DBD)	Adults	<25 (n = 11,660) 25–30 (n = 7418) 30–35 (n = 2301) >35 (n = 924)	PNF Retransplantation Graft survival Patient survival	n.a.
García et al. [10]	2004	Single center Retrospective	1982–1999	301	Deceased (DBD)	Adults PBC	<25 (n = 203) 25–29.9 (n = 90) 30–39.9 (n = 7) >40 (n = 1)	PNF Graft survival Patient survival	56 months (mean)
Moss et al. [16]	2005	Single center Retrospective	1998–2003	68	Living	Adults	<30 (n = 52) >30 (n = 16)	Donor complications Recipient complications Patient survival	25 months (median)
Wigg et al. [11]	2005	Single center Retrospective	1992–2004	110	Deceased (DBD)	Adults ALF	n.a.	Early mortality Patient survival	n.a.
Perito et al. [17]	2012	UNOS Retrospective	1990–2010	3788	Living Deceased (DBD)	Pediatric	<25 25–35 >35	Mortality Graft survival Patient survival	n.a.
Bloom et al. [12]	2015	UNOS Prospective	2008–2011	730	Deceased (DBD)	Adults	<25 (n = 167) 25–30 (n = 125) 30–35 (n = 61) >35 (n = 25)	Graft survival	74 ± 73 days
Andert et al. [18]	2016	Single center Retrospective	2010–2014	163	Deceased (DBD)	Adults	<30 (n = 111) 30–39 (n = 31) >40 (n = 15)	PNF Retransplantation Mortality Graft survival Patient survival	n.a.
Knaak et al. [19]	2017	Single center Retrospective	2000–2014	469	Living	Adults	<30 (n = 364) 30–35 (n = 105)	Donor complications Recipient complications Retransplantation Mortality Graft survival Patient survival	n.a.
Pischke et al. [20]	2017	Single center Retrospective	1997–1999	114	Deceased (DBD)	Adults	<24 >24	Graft survival Patient survival	171 months (median)
Molina et al. [21]	2019	Single center Retrospective	2006–2014	225	Deceased (DBD)	Adults	<30 (175) >30 (50)	Complications Retransplantation Graft survival Patient survival	n.a.
Steggerda et al. [22]	2019	UNOS Retrospective	2006–2016	60,200	Deceased (DBD)	Adults	<30 >30	Graft survival	n.a.

UNOS, United Network for Organ Sharing; DBD, donors after brain death; PNF, primary non-function; PBC, primary biliary cirrhosis; ALF, acute liver failure; n.a., not available.

donor evaluation between 2006 and 2016 using the UNOS database (n = 60,200) [22]. Utilization rates from higher donor BMI (≥ 30) and lower BMI (< 30) were 73.7% and 84.3% ($P < 0.001$), respectively. Pretransplant biopsy was performed more frequently in high BMI donors (52.1% versus 33.1%, $P < 0.001$) and macrosteatosis ($\geq 30\%$) was identified more often compared to lower BMI donors (21.1% versus 12.2%, $P < 0.001$). Nonetheless, graft survival showed no significant

difference between recipients with lower donor BMI and higher donor BMI ($P = 0.44$). However, grafts from higher donor BMI were transplanted much less frequently.

Several single center retrospective studies have been reported regarding the effect of donor BMI in LT. Andert et al. evaluated the outcome of 163 patients undergoing LT at the University Hospital Aachen according to donor BMI categorized as < 30 , 30–39, and ≥ 40 [18].

Table 2
The Newcastle-Ottawa scale for quality assessment of include studies [14].

Study	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study		Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	
Total score	1	1	1	1	2	1	1	1	9
Yoo et al. [9]	1	1	1	0	0	1	0	1	5
García et al. [10]	1	1	1	0	0	1	1	1	6
Moss et al. [16]	1	1	1	0	1	1	1	1	7
Wigg et al. [11]	1	1	1	0	1	1	1	1	7
Perito et al. [17]	1	1	1	0	1	1	1	1	7
Bloom et al. [12]	1	1	1	0	1	1	0	1	6
Andert et al. [18]	1	1	1	0	1	1	0	1	6
Knaak et al. [19]	1	1	1	0	1	1	1	1	7
Pischke et al. [20]	1	1	1	0	1	1	1	1	7
Molina et al. [21]	1	1	1	0	1	1	1	1	7
Steggerda et al. [22]	1	1	1	0	1	1	1	1	7

Although the BMI 30–39 group had a higher incidence of early allograft dysfunction compared to BMI <30 and BMI ≥40 group (64.5%, 33.3% vs 26.7%, $P = 0.005$), the incidence of PNF ($P = 0.72$) and retransplantation ($P = 0.07$) was not significantly different between the groups. In addition, patient and graft survival did not differ significantly between the groups (patient survival, $P = 0.4$). In a different study, Molina et al. compared outcomes between grafts from BMI ≥30 ($n = 50$) and BMI <30 donors ($n = 175$) [21]. The Kaplan-Meier survival curve showed no significant differences between the groups in terms of patient survival ($P = 0.50$) and graft survival ($P = 0.44$). In addition, multivariable analysis found that donor BMI was not associated with post-transplant mortality. Pischke et al. revealed that recipient BMI was a predictor of long-term survival after LT, whereas donor BMI was not associated with decreased survival [20].

Concerning the effect of donor BMI on disease-specific outcomes, Garcia et al. conducted a retrospective analysis of 301 patients with primary biliary cirrhosis (PBC) following LT [10]. They observed that high donor BMI ≥30 was not associated with overall graft and patient survival. In a study by Wigg et al. 110 patients with seronegative acute liver failure transplanted between 1992 and 2004 were evaluated [11]. The multivariable analysis identified that donor BMI was the most predictive parameter associated with early death (OR 1.2, $P = 0.009$).

In summary, donor BMI was not associated with graft and patient survival in adult DDLT. However high donor BMI was associated with a higher incidence of macrosteatosis and the graft declination rate was significantly higher. Notably, these results are based on donors after brain death (DBD) and the effect of BMI in donors after circulatory death (DCD) remains unknown.

3.2. Impact of donor BMI on graft function in living donor liver transplantation

Two studies have reported the impact of donor BMI on outcome in LDLT [16,19]. First, Moss et al. evaluated 68 adult-to-adult LDLTs between 1998 and 2003 comparing 52 donors with BMI <30 and 16 donors with BMI >30 [16]. With regard to recipient outcome, there was no significant difference between grafts from donors with BMI >30 and < 30. Recipient survival was 80% with non-obese donors and 100% with obese donors with a median follow-up of 25 months ($P = 0.1$). The authors concluded that donors with BMI >30 may undergo donor hepatectomy with acceptable recipient outcomes, and have the potential to safely increase the donor pool.

In a different study by Knaak et al., the outcome of 469 adult LDLTs encompassing donors with BMI <30 ($n = 364$) and donors with BMI ≥30 ($n = 105$) was reported [19]. In this study, donors with evidence of >10% liver steatosis in the liver biopsy, regardless of their BMI, were excluded from being donor candidates. Regarding recipient short-term outcomes, overall complications during the first 30 days after LDLT were significantly higher in the non-obese group (44% vs. 30%, $P = 0.013$), whereas major complications (Clavien-Dindo ≥3b) were similar (25% vs. 20%, $P = 0.30$). The incidence of 30-day mortality was not different between the two groups (2% vs. 3%, $P = 0.72$). Long-term recipient outcome following LDLT showed no significant differences between the BMI <30 and BMI ≥30 with respect to the incidence of biliary complication (25% vs. 20%, $P = 0.30$), graft rejection (16% vs. 10%, $P = 0.16$), and retransplantation (5% vs. 5%, $P = 1$). Furthermore, graft survival from donors with BMI <30 and ≥30 was similar at 1 year (91% vs. 87%), 5 years (81% vs. 75%) and 10 years (70% vs. 61%) ($P = 0.12$). Likewise, no difference in patient survival was found between the groups at 1-year (93% vs. 90%), 5 years (83% vs. 78%) and 10-year follow-up (76% vs. 67%) ($P = 0.12$). The authors concluded that donor BMI ≥30 in the absence of graft steatosis is no contraindication for LDLT.

In summary, donor BMI was not associated with graft and patient survival in LDLT. Donor BMI should not be considered a

contraindication for living liver donation when the presence of steatosis is within limits.

3.3. Impact of donor BMI on graft function in pediatric liver transplantation

The UNOS data for pediatric LT in the United States was reported in 2012 [17]. Between 2004 and 2010, 3788 pediatric LTs were performed in the United States of which 1259 had adult donors, and 2529 had pediatric donors. Thirty percent of the adult donors were overweight (BMI 25–30), 8% were obese (BMI 30–35), and 2% were severely obese (BMI ≥35). Among pediatric donors, 16% were overweight, 6% were obese, and 3% were severely obese. For pediatric recipients receiving adult donor livers multivariate analysis showed (grafts from a living donor, 30%; deceased whole graft, 50%; deceased split graft, 20%), a donor BMI of 25 to <35 was not associated with graft survival (overweight donors, hazard ratio [HR] 1.00, 95% confidence interval [CI] 0.73–1.36, $P = 0.98$; obese donors, HR 0.84, 95% CI 0.49–1.42, $P = 0.50$) and patient survival (overweight donors, HR 1.20, 95% CI 0.81–1.78, $P = 0.36$; obese donors, HR 0.95, 95% CI 0.48–1.89, $P = 0.89$). However, severely obese donors were associated with increased risk of graft loss (HR 2.54, 95% CI 1.29–5.01, $P = 0.007$) and death (HR 3.56, 95% CI 1.64–7.72, $P = 0.001$). Donor BMI of pediatric donors was not associated with graft loss or mortality in uni- or multivariate analysis. Furthermore, an overweight or obese adult or pediatric donor was not a risk factor for post-transplant obesity in recipients.

In summary, the evidence on the effect of donor BMI on graft function outcomes in pediatric LT is limited. Though, severe obesity in adult donors (BMI ≥35) was associated with graft loss and mortality.

4. Discussion

There seems to be a growing trend of utilizing overweight and obese donors for LT due to the increasing prevalence of overweight people [23]. BMI is commonly used as a simple and objective index which categorizes overweight and obese [1,2], therefore we performed the preset systematic review to gain a better understanding on the relationship between donor BMI and graft function after LT. After a systematic literature review, eleven observational studies were included. To the best of our knowledge, the present systematic review is the first to evaluate the current evidence regarding the effect of donor BMI on outcomes in LT, including DDLT, LDLT, and pediatric LT.

Although the increasing demand of organs in patients on waiting lists and the shortage of organs have forced to utilize ECDs for graft selection in LT, the assessment of liver grafts is still a difficult task [24]. A previous study demonstrated that liver grafts with macrosteatosis ≥30% was a risk factor of early graft dysfunction and PNF, and utilization rates of grafts with macrosteatosis ≥30% were low [22]. It is a well-known fact that the degree of histologically determined liver steatosis is a more reliable biomarker to predict graft suitability compared to donor BMI, however a problem is that histological evaluation is not always available in clinical practice due to time limitations [18]. In addition, the quantification of macrosteatosis using biopsy is strongly dependent on individual pathologists and not reproducible [25]. Therefore it should make sense to take donor BMI into account as a surrogate for hepatic macrosteatosis as it is always available in clinical setting.

Based on our results, donor BMI was not associated with graft and patient survival in adult DBD DDLT. However, high donor BMI was associated with a higher chance of macrosteatosis besides a significantly higher incidence of declined livers. In LDLT, donor BMI was not associated with graft and patient survival provided that pretransplant liver biopsy did not reveal >10% steatosis. BMI itself should not be considered a contraindication for donorship in LDLT, necessitating strict selection including the absence of steatosis and donor comorbidities should be required. In pediatric LT, grafts from severely obese adult donors were associated with increased risk of graft loss and mortality whereas for

obese pediatric donors there was no association. Accordingly, the evidence of donor BMI on outcomes in LDLT and pediatric LT is limited and the effect of BMI in DCD donors remains unknown.

Recent topic is how to improve the quality of organ from ECD including older donor age, higher BMI, steatosis, and DCD by using machine perfusion as well as regional perfusion techniques [26–28]. Machine perfusion has been recognized as an evolving technology that may not only enhance the performance of extended criteria donor but might lead to optimized donor pool utilization [27]. Therefore, recent developments in normothermic machine perfusion might be beneficial (i.e. reversal of steatosis) to so-called ‘high-risk’ obese donor livers [29,30].

There are several limitations in the present study. Most of included studies were retrospective data, therefore there might exist publication bias. Regarding studies from the UNOS database, there exists a certain overlapping between the studies by Bloom et al. [12] and by Steggerda et al. [22], which might cause an elevated risk of overlapping for these data. In addition, different cut-off values for BMI were used in each study. Lastly, BMI could reflect a wide range of physical and clinical conditions including obesity, malnutrition, and comorbidities. Therefore BMI might be an anthropometric parameter with heterogeneous clinical applicability. However we believe that BMI is a useful parameter which is always available in clinical practice.

5. Conclusions

The present systematic review represents the clinical significance of donor BMI on graft function outcome in LT. In adult DDLT, donor BMI was not associated with graft and patient survival. In LDLT, donor BMI itself should not be considered a contraindication for donorship after strict donor selection. In pediatric LT, grafts from severely obese adult donors were associated with increased risk of graft loss and mortality, while no association was found from obese pediatric donors. The evidence of donor BMI on outcomes in LDLT and pediatric LT is still limited, therefore further research is warranted to clarify the clinical significance of donor BMI on outcomes in the field of LT and explore the possibilities of organ recovery in high risk livers.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

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