



Universiteit
Leiden
The Netherlands

Liver discard rate attributable to conservative estimations of steatosis: an inference-based approach

Guo, H.; Gala-Lopez, B.L.; Alwayn, I.P.J.; Hewitt, K.C.

Citation

Guo, H., Gala-Lopez, B. L., Alwayn, I. P. J., & Hewitt, K. C. (2025). Liver discard rate attributable to conservative estimations of steatosis: an inference-based approach. *Transplantation*, 109(10), e609-e618. doi:10.1097/TP.0000000000005401

Version: Publisher's Version
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/4301364>

Note: To cite this publication please use the final published version (if applicable).

Liver Discard Rate Attributable to Conservative Estimations of Steatosis: An Inference-based Approach

Hao Guo, PhD,^{1,2} Boris L. Gala-Lopez, MD, PhD,³ Ian P.J. Alwayn, MD,⁴ and Kevin C. Hewitt, PhD¹

Background. On-site conservative estimations of steatosis could result in the unnecessary discard of donor livers. This study applied the body mass index as an independent statistical indicator to determine the extent of this problem. We aimed to quantitatively evaluate if decisions based nonbiopsy donor liver assessments are more conservative (inclined to reject marginal fatty livers) than biopsy-based evaluations. **Methods.** The study processed intradatabase comparisons using 177 081 datasets from Organ Procurement and Transplantation Network spanning 2004 to 2022 September in the United States. Postmatching body mass index was applied as an independent indicator of statistical risk of hepatic steatosis (HS). **Results.** A total of 7420, 4990, 5994, and 7523 pair of donors with/without biopsy records were matched in 2004–2010, 2011–2014, 2015–2018, and 2019–2022 September, respectively. Consistent with our hypothesis, absent biopsies and evaluations before and during organ procurement were observed to be more conservative, leading to the discard of 16.4% (2004–2010), 16.9% (2011–2014), 10.6% (2015–2018), and 10.3% (2019–2022 September) of potential donor livers. **Conclusions.** The study concludes that there was a significant (10.3%–16.9%) disparity caused by on-site nonbiopsy assessments of HS, leading to the unnecessary discard of potential donor livers. The findings emphasize the need to develop more accurate intraoperative techniques for assessing HS to optimize donor liver procurement.

(*Transplantation* 2025;109: e609–e618).

INTRODUCTION

Hepatic steatosis (HS), especially moderate and severe macrovesicular steatosis (MaS) of donor livers, is associated with an increased risk of graft dysfunction after liver transplantation (LT).^{1,4} Although transplant centers have been increasingly using marginal donor livers to expand the organ pool, HS remains a critical reason for discard.⁵ Livers with severe MaS ($\geq 60\%$) are usually considered high risk for graft dysfunction and are often discarded outright.⁶ Livers with microvesicular steatosis (MiS) and mild (5%–30%) MaS are usually safe for LT, but transplanting livers with moderate (30%–60%) MaS is still controversial.^{6–9} Furthermore, there seems to be disagreement between transplant physicians on

the exact risk attributed to this steatosis. As a result, surgeons from different centers act differently when offered a steatotic organ.¹⁰ Therefore, accurate classification and quantification of steatotic donor livers with a solid cutoff are essential.

The current qualification of HS of donor livers relies on semisubjective and subjective methods.¹¹ Liver biopsy, though with limitations such as invasiveness, sampling errors, interobserver variability, weak reproducibility, and occasional low on-site availability, is currently the “gold standard” for assessing HS of donor’s livers.^{7,12,13} However, a biopsy is only performed in a portion of donor surgeries. The most widely used method is the surgeon’s visual quality inspection during organ procurement surgeries. An online

Received 17 June 2024. Revision received 9 January 2025.

Accepted 21 January 2025.

¹ Department of Physics and Atmospheric Science, Dalhousie University, Halifax, NS, Canada.

² Department of Medical Physics, Nova Scotia Health Authority, Halifax, NS, Canada.

³ Department of Surgery, Dalhousie University, Halifax, NS, Canada.

⁴ Department of Surgery, LUMC Transplant Center, Leiden University Medical Center, Leiden, the Netherlands.

H.G. is supported by the Vitamin Scholarship, Dalhousie University and the Research Nova Scotia Doctoral Award, Research Nova Scotia.

The authors declare no conflicts of interest.

H.G. conceived of the study and its design; acquisition, analysis, and interpretation of data; and drafting and critically revising the article for important

intellectual content. K.C.H. provided oversight of the work in their supervisory capacity of the trainee. H.G., K.C.H., B.L.G.-L., and I.P.J.A. were involved in the critical revision of the article. All authors approved the final version to be published.

Visual abstract is available online at doi.org/10.1097/TP.0000000000005401.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal’s Web site (www.transplantjournal.com).

Correspondence: Kevin C. Hewitt, PhD, Department of Physics and Atmospheric Science, Dalhousie University, 6310 Coburg Rd, PO Box 15000, Halifax, NS B3H 4R2, Canada. (kevin.hewitt@dal.ca).

Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 0041-1337/20/10910-e609

DOI: 10.1097/TP.0000000000005401

survey indicated that one-third of surgeon members of the American Society of Transplant Surgeons replied that visual inspection played a critical role in their decision to transplant >50% of donor livers.¹⁴ In contrast with visual estimation, only 30% of donors after circulatory death had data from biopsies between 2004 and 2010 in the United States.³

Surgeon’s visual quality inspection is based on the stiffness and macroscopic appearance of livers during organ procurement surgeries. Experienced surgeons can accurately predict <30% MaS; however, surgeons’ prediction of ≥30% MaS was correct only for 52.2% of the cases, according to a prospective, double-blind study of 201 procured donor livers.¹⁵ Compared with the visual quality inspection, the degree of HS in biopsies is assessed more quantitatively, though it shows a considerable variation among assessments of pathologists.¹³

The low accuracy and high variability of the degree of HS assessed by the visual inspection and biopsies bring uncertainties to transplanting livers with MaS ranging 20%–60%. A natural hypothesis is that to ensure LT’s safety, transplant centers tend to estimate the degree of HS and make the decision of LT using a conservative (inclined to reject marginal fatty livers) approach, especially in cases without the availability of liver biopsies. Assuming this hypothesis is true, a considerable percentage of donor livers with “actual” MaS <30% are rejected before and/or during organ procurement. Because the “actual” degree of HS cannot be determined using the current gold standard, an alternative method is needed to quantify the discrepancies between the prevalence of HS and the frequency of HS of donor livers based on on-site assessments.

Because the information on the degree of HS is unavailable from donors who did not receive liver biopsies, the body mass index (BMI) can be used as an indirect intermediate parameter to statistically describe “potential” HS in each group of analyses. The risks of HS have been found significantly and independently correlated with increasing BMI in a nonlinear fashion.^{16–18} BMI was also found an independent predictor of the extent of fat infiltration.¹⁹ As a predictor for HS, the receiver operating characteristic curve analysis of BMI was reported with an area under the ROC curve ranging from 0.77 to 0.84.^{20,21}

In this study, by adopting BMI as an independent indicator of the statistical HS risk, we applied an inference-based approach to quantify unrecovered steatotic donor livers impacted by on-site conservative decisions based on biopsy and nonbiopsy assessments. The analysis is supported by data from publicly available national clinical registries.

MATERIALS AND METHODS

We analyzed the Organ Procurement and Transplantation Network (OPTN) data in 2004–September 2022 in the United States. This research does not require research ethics board review because it relies exclusively on information that is publicly available through a mechanism set out by regulation and that is protected by law, according to the 2018 Tri-Council Policy Statement for the Ethical Conduct for Research Involving Humans.

Ninety-seven percent of the donor deaths collected by OPTN in 2009–2020 were caused by anoxia, stroke, head trauma, or central nervous system tumor, the incidence of which are stochastic and independent from BMI or liver diseases.²² Considering that the online database developed by OPTN contains data about every organ donation and transplant event in the United States since 1987,²³ the OPTN data can be regarded as nationally representative. Starting from 2004, all variables (Table 1) used for analysis in this study were recoded in the OPTN database.

All statistical data analyses using the OPTN data (Table 1) were performed using Stata Version 17.0-Basic Edition (StataCorp LLC, TX). *P* values of <0.05 were considered statistically significant.

In 2004–September 2022, the OPTN database recorded 177 081 deceased donors from whom at least 1 solid organ was recovered.

Exclusion and Matching of Data

As described in Figure 1, deceased liver donations were included in the present study if (1) an authorization of liver donation was obtained, (2) the donor was at least 18 y of age, (3) the donor was not found to be a heavy alcohol user (defined as consuming >2 drinks per day),²⁴ (4) the participant did not carry viral hepatitis, (5) the information of liver disposition was specified, and (6) the donor liver was either recovered, transplanted, or not recovered for reasons related to steatosis.

To eliminate potential interference of risk factors other than HS and BMI on this study, according to the definition of a liver donor marginal by European Association for the Study of the Liver Clinical Practice Guidelines,²⁵ deceased liver donations were excluded from this study if any of the following criteria was met: age >65 y, serum sodium >165 mmol/L, alanine aminotransferase (ALT) > 105 U/L, aspartate aminotransferase > 90 U/L, or serum bilirubin >3 mg/dL.

In our study, we applied propensity score matching to match sex, age, BMI, ALT, aspartate aminotransferase,

TABLE 1.
Variables of retrieved data from OPTN registries

OPTN variable		Description	OPTN variable		Description
RECOVERY_DATE_DON	Recovery date (sent to the operating room)		LI_REASON_CD	Liver disposition reason	
BMI_DON_CALC	Donor body mass index		HCV_NAT	Hepatitis C nucleic acid amplification testing	
GENDER_DON	Donor gender		HBV_SUR_ANTIGEN_DON	Hepatitis B surface antigen status	
AGE_DON	Age in years		ALCOHOL_HEAVY_DON	Heavy alcohol use (heavy = 2+ drinks per day)	
MACRO_FAT_LI_DON	Macrovesicular fat (%)		SGOT_DON	Terminal laboratory aspartate aminotransferase	
MICRO_FAT_LI_DON	Microvesicular fat (%)		SGPT_DON	Terminal laboratory alanine aminotransferase	
LI_BIOPSY_DON	Liver biopsy		TBILI_DON	Terminal laboratory total bilirubin	
LI_DISPOSITION	Liver disposition		SODIUM170_VAL_DON	Last serum sodium	

OPTN, Organ Procurement and Transplantation Network.

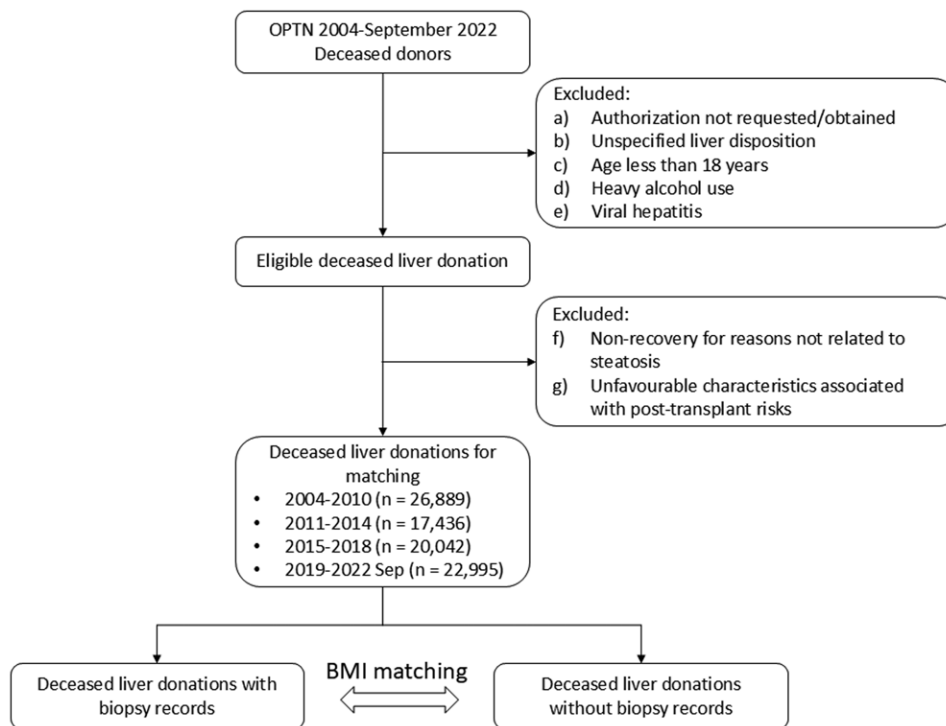


FIGURE 1. Flowchart of the study. Donation registrations were excluded before BMI matching when an authorization was not requested or obtained (A), the organ disposition information was not available (B), the donor was <18 y of age (C), the donor consumed >2 drinks per day (D), the test result of any of hepatitis B surface antigen, hepatitis C RNA, hepatitis D antibody, and hepatitis E IgM is positive (E), 1 of the following reasons (which are not related to steatosis) was recorded: cardiac arrest, positive hepatitis, positive HIV, anatomical abnormalities, vascular damage, no recipient located, donor medical history, donor social history, surgical damage in the operating room, hemodynamically unstable donor, trauma to the organ, time constraints, medical examiner restricted recovery, and other specify (F), and at least 1 of the following criteria was met: age >65 y, serum sodium >165 mmol/L, ALT >105 U/L, AST >90 U/L, or serum bilirubin >3mg/dL (G). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index.

total bilirubin, and sodium of donors with and without ALT biopsy records. As donor livers with marginal biochemical indicators had been excluded before matching, BMI was the only characteristic being matched for comparing donations with and without biopsy records. Propensity scores were calculated based on multivariable logistic regressions, where the dependent variable was whether a biopsy result was recorded, and the independent variables to be matched was BMI.

After the estimation of propensity scores, we used the “psmatch2” module in Stata to perform nearest-neighbor 1-to-1 matching.²⁶ We assessed the quality of the BMI matches by checking the balance of the covariates across the treated and untreated groups after matching using the “pctest” (paired ttest) command, which evaluates whether the average of BMI differences within each pair is 0. For the parameters other than BMI, “ttest” (unpaired ttest) command was used to evaluate if there is no significant difference between the means of 2 groups.

Deceased liver donations were classified into several categories for matching and analyses, as Table 2 describes. The categories “biopsy” and “nonbiopsy” act as a group indicator separating donations to a group with liver biopsy records and a group without liver biopsy records. The category “for transplant” includes transplanted donor livers and donor livers recovered for transplantation but not transplanted. The category “not for transplant” includes donor livers that were not

recovered and donor livers recovered not for the purpose of transplantation.

Based on codes of liver disposition reasons, nonrecovery for reasons not related to steatosis was excluded from the matching, with detailed explanations shown in Table S1 (SDC, <http://links.lww.com/TP/D253>). Specifically, code 218 (ruled out after evaluation in the operating room), though not directly related to steatosis, was analyzed as an independent category, as it indicates liver discard during the recovery surgeries.

RESULTS

The pre- and postmatching population characteristics of included donors registered in OPTN are shown in Table 3 and Tables S2–S5 (SDC, <http://links.lww.com/TP/D253>), with the reporting of pre- and postmatching p values of the “pctest” (null hypothesis: the average BMI difference between each matched pair of the biopsy and nonbiopsy groups is 0) and “ttest” (null hypothesis: the difference between the means of the biopsy and non-biopsy groups is 0). As Table 3 shows, 7420, 4990, 5994, and 7523 pair of donors with/without biopsy records were matched in year 2004–2010, year 2011–2014, year 2015–2018, and year 2019–2022 September, respectively. The postmatching paired donors with and without biopsy records had no statistically significant difference ($P > 0.05$) in the distribution of covariate between BMIs, indicating excellent BMI matching in this intragroup comparison. Although this less

TABLE 2.
Classification of liver donations registered in OPTN

Category	OPTN variable	Value
Biopsy	LI_BIOPSY_DON	"Y"
Nonbiopsy	LI_BIOPSY_DON	"N"
For transplant	LI_DISPOSITION	5 and 6
Not for transplant	LI_DISPOSITION	3 and 4
Nonrecovery for reasons not related to steatosis	LI_REASON_CD	201, 202, 203, 204, 206, 207, 208, 209, 210, 211, 213, 214, 220, 221, 222, 223, 224, 225, 226, 295, and 299
Ruled out after evaluation in the operating room	LI_REASON_CD	218

OPTN, Organ Procurement and Transplantation Network.

rigorous matching solely targeted BMI, the values of other risk factors, no matter their statistical differences were significant or not, were all within the safe ranges because the donations including unfavored characteristics had already been excluded before matching.

Figure 2 compares the distributions of postmatching BMIs for donors with and without biopsy records. The kernel density curves nearly overlap, indicating that postmatching BMI distributions between the biopsy and nonbiopsy groups are statistically identical across all 4 time categories.

Figure 3 compares postmatching BMI distributions between donors with and without biopsy records in the “for transplant” group. Among these donors, those with biopsy records were more widespread in the “high BMI” range which is defined by the higher intersection of 2 overlapping BMI distribution curves.

From 2004 to 2010, when BMI exceeded the threshold of 32.10 kg/m², 2,346 donor livers with biopsy records (32.1% of 7300) were procured “for transplant,” compared with 1768 without biopsy records (27.6% of 6405). From 2011 to 2014 (at the same threshold 32.10 kg/m²), 1600 livers with biopsy records (34.2% of 4681) and 1256 without biopsy records (29.9% of 4199) were procured “for transplant.” In 2015–2018, at a threshold of 32.80 kg/m², 1,839 livers with biopsy records (33.1% of 5,549) were procured, compared with 1478 without biopsy records (29.7% of 4973). Finally, from 2018 to September 2022, with a threshold at 33.25 kg/m², 2252 livers with biopsy records (32.8% of 6867) were procured, against 1448 without biopsy records (25.9% of 5584). These findings indicate a consistent trend over time: “high BMI” donor livers procured for transplant are more likely to have biopsy records.

Among donor livers classified as “not for transplant,” those in the high BMI range were more likely to lack biopsy records. Figure 4 compares postmatching BMI distributions for donors with and without biopsy records in this group. From 2004 to 2010, when BMI exceeded 34.10 kg/m², 43 donor livers with biopsy records (35.5% of 121) were classified as “not for transplant,” compared with 533 without biopsy records (51.9% of 1026). From 2011 to 2014, with a threshold of 33.60 kg/m², 111 livers with biopsy records (35.9% of 309) and 418 without biopsy records (52.8% of 791) were classified as “not for

transplant.” In 2015–2018, with a threshold of 33.50 kg/m², 182 livers with biopsy records (40.9% of 445) were classified as “not for transplant,” compared with 523 without biopsy records (51.5% of 1021). Finally, from 2018 to September 2022, with a threshold of 33.15 kg/m², 230 livers with biopsy records (35.1% of 656) were classified as “not for transplant,” compared with 880 without records (45.4% of 1939).

Figure 5 compares postmatching BMI distributions between donors with biopsy records and those without biopsy records who were ruled out after evaluation in the operating room. From 2004 to 2010, all donor livers ruled out after operating room evaluation lacked biopsy records. From 2011 to 2014, using a high BMI threshold of 31.95 kg/m² (determined by the crosspoint of kernel density curves), 45 donor livers (44.6% of 101) with biopsy records were ruled out, compared with 145 without biopsy records (63.0% of 210). From 2015 to 2018, with a threshold of 30.91 kg/m², 91 livers (49.7% of 183) with biopsy records were ruled out, versus 122 without biopsy records (64.6% of 189). Finally, from 2018 to September 2022, using a threshold of 33.75 kg/m², 109 livers (40.2% of 271) with biopsy records were ruled out, compared with 142 without biopsy records (49.7% of 286).

Table 4 quantifies frequency differences in donor liver disposition (based on area differences under the curves on the higher BMI side of the dashed line) between those with and without biopsy records at similar statistical risks of HS. For donor livers classified as “for transplant,” those with biopsy records were 3.4%–6.9% more likely to fall in the “high BMI” (high HS risk) range (indicated by a negative difference). In cases classified as “not for transplant,” those with biopsy records were 10.3%–16.9% less likely to be in the “high BMI” range (indicated by a positive difference). For livers “ruled out after operating room evaluation,” those with biopsy records were 9.5%–18.4% less likely to fall into the “high BMI” range.

DISCUSSION

Understanding the potential to expand the use of marginally steatotic livers is essential for maximizing donor liver recovery. However, there is no quantification of how many discarded steatotic livers could actually be salvaged, as we lack definitive preknowledge of whether a discarded liver is truly unusable. To address this, we analyzed the OPTN registry, using cases with liver biopsy records as a benchmark to quantify the relative conservativeness of nonbiopsy assessment methods.

The decision to accept or discard a marginal donor is based on a structured evaluation of steatosis severity (via biopsy and nonbiopsy methods), recipient urgency and health status, donor characteristics (age, BMI, intensive care unit duration), and preservation method (favoring machine perfusion for high-fat livers). Institutional policies and experience with higher-risk transplants also guide acceptance. If risks are deemed manageable and align with recipient needs, the liver is accepted; otherwise, it is discarded. Because grafts require vigilant monitoring for safety, greater uncertainty in risk assessment (such as estimating HS without biopsy) necessitates wider safety margins, prioritizing patient safety over maximizing

TABLE 3.

Pre- and postmatching population characteristics of donors registered in OPTN, categorized into year 2004–2010, year 2011–2014, year 2015–2018, and year 2019–2022 September

Characteristics	Prematching			Postmatching		
	Biopsy	Nonbiopsy	<i>P</i>	Biopsy	Nonbiopsy	<i>P</i>
Year 2004–2010 (Matched n = 7420)						
Sex, n (%)						
Female	6695 (45.7)	15 771 (39.3)		3718 (50.1)	3339 (45.0)	
Male	7941 (54.3)	24 392 (60.7)		3702 (49.9)	4082 (55.0)	
Age, y, mean ± SD						
Mean ± SD	49.6 ± 15.5	37.2 ± 18.7	<0.001	47.9 ± 11.9	41.0 ± 13.9	<0.001
Median (IQR)	51 (41–60)	38 (21–52)		50 (41–57)	43 (28–53)	
BMI, kg/m ²						
Mean ± SD	29.0 ± 7.1	26.0 ± 6.3	<0.001	29.7 ± 6.8	29.7 ± 6.8	0.961
Median (IQR)	27.8 (24.0–32.8)	25.3 (22.0–29.2)		28.8 (24.8–34.8)	28.8 (24.8–34.8)	
Year 2011–2014 (Matched n = 4990)						
Sex, N (%)						
Female	4796 (46.0)	8684 (38.2)		2490 (49.9)	2161 (43.3)	
Male	5633 (54.0)	14 021 (61.8)		2500 (50.1)	2829 (56.7)	
Mean ± SD	48.8 ± 14.8	36.0 ± 17.8	<0.001	47.4 ± 12.0	40.5 ± 13.5	<0.001
Median (IQR)	50 (39–59)	36 (25–51)		50 (39–57)	41 (28–52)	
BMI, kg/m ²						
Mean ± SD	30.1 ± 7.6	26.3 ± 6.5	<0.001	30.0 ± 6.8	30.0 ± 6.8	0.961
Median (IQR)	28.9 (24.8–34.2)	25.6 (22.1–29.7)		29.3 (25.2–34.0)	29.3 (25.2–34.0)	
ALT, U/L, median (IQR)						
Year 2015–2018 (Matched n = 5994)						
Sex, n (%)						
Female	6223 (44.8)	9696 (37.1)		2912 (48.6)	2624 (43.8)	
Male	7673 (54.3)	16 465 (62.9)		3082 (51.4)	3370 (56.2)	
Age, y, mean ± SD						
Mean ± SD	47.6 ± 15.0	35.9 ± 17.2	<0.001	47.1 ± 12.2	40.0 ± 13.3	<0.001
Median (IQR)	49 (36–59)	35 (23–50)		49 (38–57)	40 (28–52)	
BMI, kg/m ²						
Mean ± SD	30.4 ± 7.8	26.7 ± 6.6	<0.001	30.6 ± 7.0	30.6 ± 7.0	0.944
Median (IQR)	29.2 (24.8–34.5)	25.9 (22.3–30.1)		29.9 (25.5–34.5)	29.9 (25.5–34.6)	
Year 2019–2022 September (matched n = 7523)						
Sex, N (%)						
Female	6993 (42.2)	11 595 (36.8)		3417 (45.4)	3066 (40.8)	
Male	9564 (57.8)	19 924 (63.2)		4106 (54.6)	4457 (59.2)	
Age, y, mean ± SD						
Mean ± SD	47.4 ± 14.5	39.1 ± 16.9	<0.001	46.5 ± 12.1	41.6 ± 13.2	<0.001
Median (IQR)	48 (37–58)	39 (27–53)		48 (37–56)	42 (30–53)	
BMI, kg/m ²						
Mean ± SD	30.4 ± 7.7	27.8 ± 7.3	<0.001	31.0 ± 7.4	31.0 ± 7.4	0.932
Median (IQR)	29.3 (24.9–34.6)	26.7 (22.9–31.4)		30.2 (25.7–35.1)	30.2 (25.7–35.1)	

The median CAP scores classify S₀–S₃. Null hypothesis: there is no statistically significant difference in the distribution of a covariate between the treated and control groups after matching. The bold values indicate that the evidence is not enough to reject the null hypothesis at the 5% significance level.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; IQR, interquartile range; OPTN, Organ Procurement and Transplantation Network; S₀, nonsteatosis; S₁, mild steatosis; S₂, moderate steatosis; S₃, severe steatosis.

organ recovery and imbuing conservativeness in the risk assessments.

This present study adopted BMI as an independent indicator of the statistical risk of HS and tested if decisions based on nonbiopsy donor liver assessments are more conservative than those based on biopsies. The evaluation bases on a BMI matching strategy. Given that both the biopsy and non-biopsy data originated from the same OPTN registry, and that liver donors on the marginal fringe had been excluded before matching, the matching

process was solely dependent on the donors' BMI. As BMI is a positively correlated independent risk factor of HS,^{16–18} it was used as a surrogate to estimate the statistical risks of HS impacting the liver discard rates, specifically in the context of non-biopsy assessments of steatosis.

The analysis of postmatching OPTN data corroborated that on-site nonbiopsy evaluations of donor livers tended to be more conservative than their biopsy-inclusive counterparts. Notably, donor livers with biopsy records were 3.4%–6.9% more frequently selected for

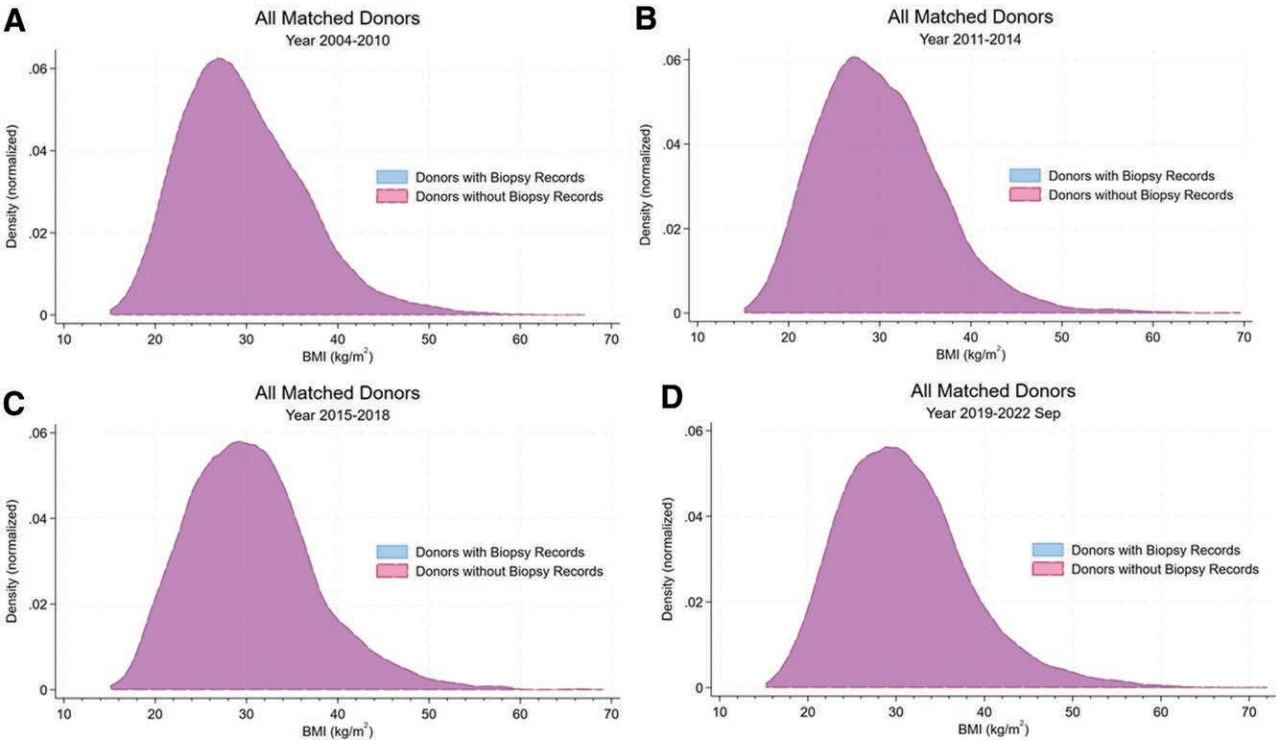


FIGURE 2. Comparison of postmatching BMIs between the donor groups with and without biopsy records on univariate kernel density estimations in year 2004–2010 (A), year 2011–2014 (B), year 2015–2018 (C), and year 2019–2022 September (D). BMI, body mass index.

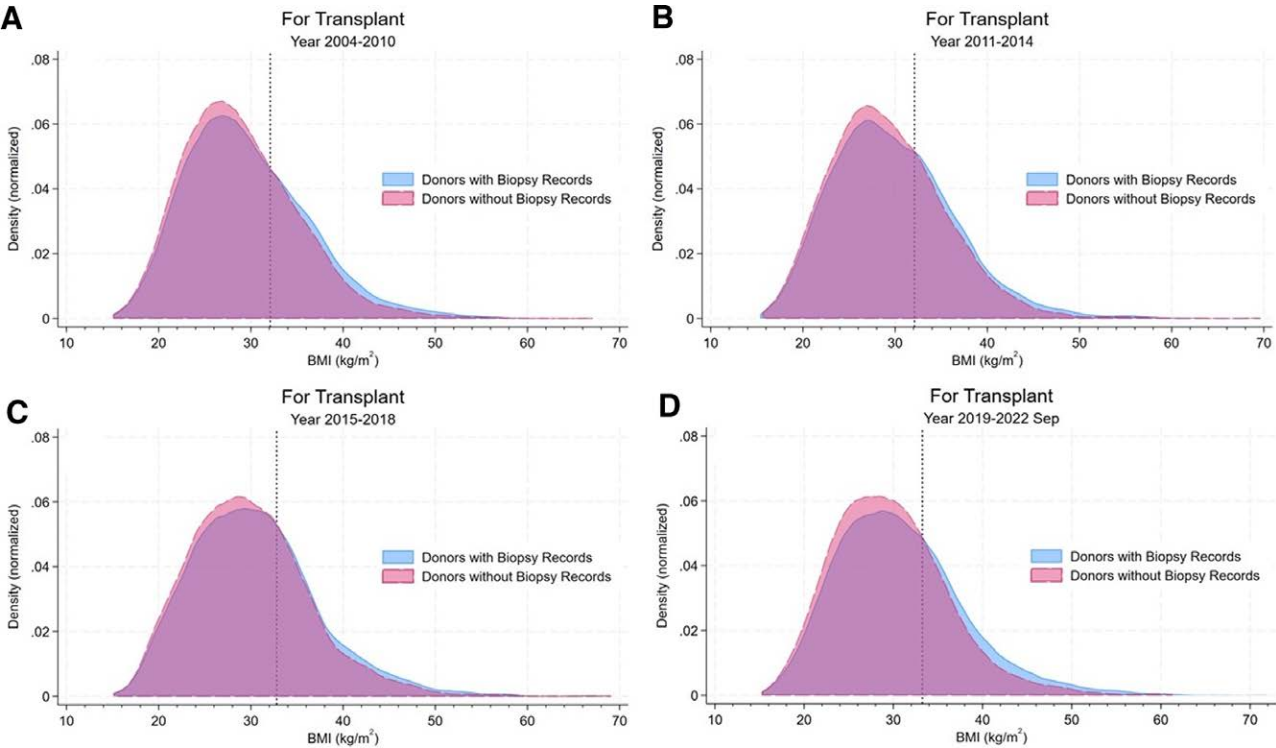


FIGURE 3. Comparison of postmatching BMIs between the donor groups with and without biopsy records on univariate kernel density estimations in the group “for transplantation” in year 2004–2010 (A), year 2011–2014 (B), year 2015–2018 (C), and year 2019–2022 September (D). The vertical dashed line at 32.10 (A), 32.10 (B), 32.80 (C), and 33.25 kg/m² (D), indicated the corresponding BMI value at the crosspoints of the kernel density curves in each subfigure. BMI, body mass index.

transplantation when BMI (statistical risks of HS) is relatively high, compared with those without biopsy records. Conversely, among the discarded donor livers (livers “not

for transplant”), donor livers with biopsy records were 10.3%–16.9% less frequently in the “high BMI” range than those without biopsy records.

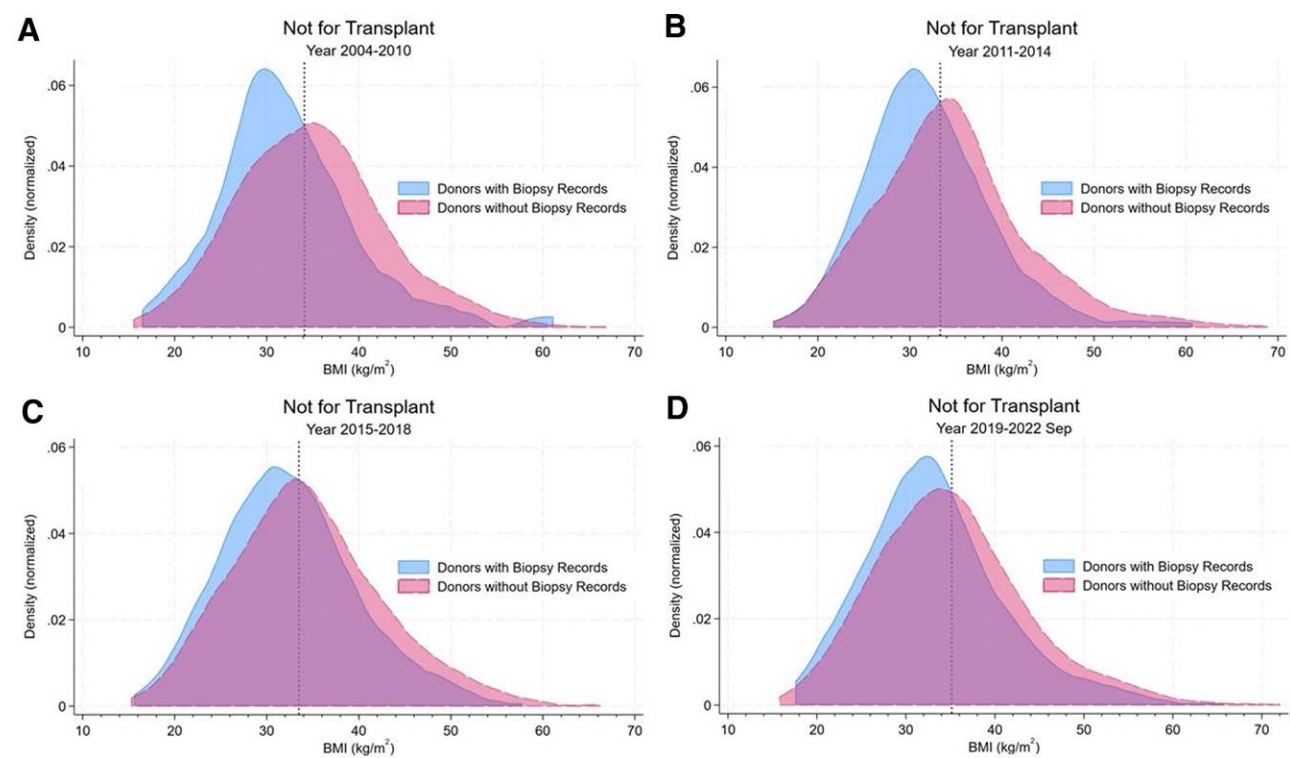


FIGURE 4. Comparison of postmatching BMIs between the donor groups with and without biopsy records on univariate kernel density estimations in the group “not for transplantation” in (A) year 2004–2010 (A), year 2011–2014 (B), year 2015–2018 (C), and year 2019–2022 September (D). The vertical dashed line at 34.10 (A), 33.60 (B), 33.50 (C), and 35.15 kg/m² (D), indicated the corresponding BMI value at the crosspoints of the kernel density curves in each subfigure. BMI, body mass index.

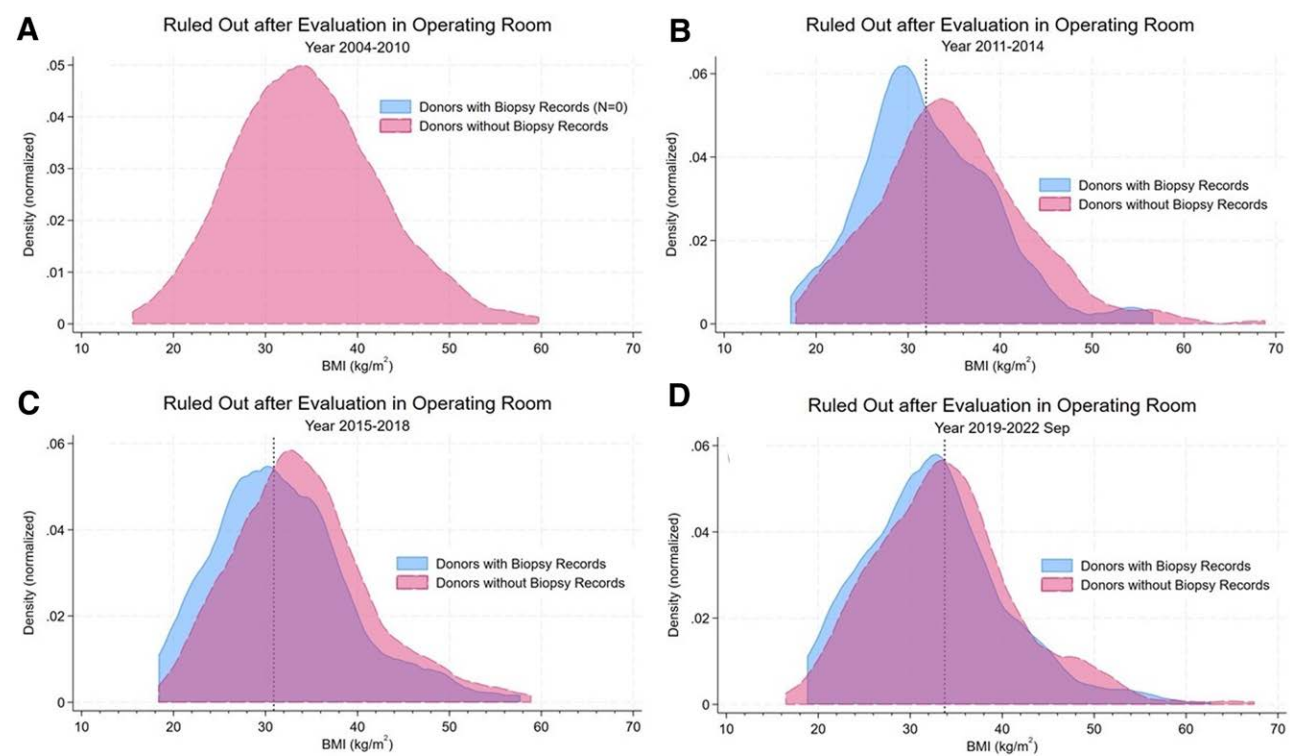


FIGURE 5. Comparison of postmatching BMIs between the donor groups with and without biopsy records on univariate kernel density estimations in the group “ruled out after evaluation in operating room” in year 2004–2010 (A), year 2011–2014 (B), year 2015–2018 (C), and year 2019–2022 September (D). The vertical dashed line at n/a (A), 31.95 kg/m² (B), 30.91 kg/m² (C), and 33.75 kg/m² (D), indicated the corresponding BMI value at the crosspoints of the kernel density curves in each subfigure. BMI, body mass index; n/a, not applicable.

TABLE 4.
Frequency differences in donor liver disposition by liver biopsy records

Category	Year 2004–2010	Year 2011–2014	Year 2015–2018	Year 2019–2022 September
For transplant				
“High BMI” threshold (kg/m ²)	32.10	32.10	32.80	33.25
Biopsy, all BMI, n (%)	7300 (100)	4681 (100)	5549 (100)	6867 (100)
Biopsy, high BMI, n (%)	2346 (32.1)	1600 (34.2)	1839 (33.1)	2252 (32.8)
Nonbiopsy, all, n, (%)	6405 (100)	4199 (100)	4973 (100)	5584 (100)
Nonbiopsy, high BMI, n (%)	1768 (27.6)	1256 (29.9)	1478 (29.7)	1448 (25.9)
Frequency discrepancy, %	−4.5	−4.3	−3.4	−6.9
Not for transplant, n				
“High BMI” threshold (kg/m ²)	34.10	33.60	33.50	35.15
Biopsy, all BMI, n (%)	121 (100)	309 (100)	445 (100)	656 (100)
Biopsy, high BMI, n (%)	43 (35.5)	111 (35.9)	182 (40.9)	230 (35.1)
Nonbiopsy, all, n, (%)	1026 (100)	791 (100)	1021 (100)	1,939 (100)
Nonbiopsy, high BMI, n (%)	533 (51.9)	418 (52.8)	526 (51.5)	880 (45.4)
Frequency discrepancy, %	16.4	16.9	10.6	10.3
Ruled out after evaluation in operating room				
“High BMI” threshold (kg/m ²)	n/a	31.95	30.91	33.75
Biopsy, all BMI, n (%)	0 (100)	101 (100)	183 (100)	271 (100)
Biopsy, high BMI, n (%)	n/a	45 (44.6)	91 (49.7)	109 (40.2)
Nonbiopsy, all, n, (%)	341 (100)	230 (100)	189 (100)	286 (100)
Nonbiopsy, high BMI, n (%)	n/a	145 (63.0)	122 (64.6)	142 (49.7)
Frequency discrepancy, %	n/a	18.4	14.9	9.5

BMI, body mass index; n/a, not applicable.

A prominent disparity caused by on-site nonbiopsy assessments HS could be observed in the operating room. Analysis of the postmatching BMI distributions between donors with and without biopsy records revealed that donors without biopsy records were discarded 9.5%–18.4% more frequently compared with donors with biopsy records and comparably high BMIs.

All the above-mentioned evidence suggests that evaluations based on nonbiopsy donor liver assessments are generally more conservative than those based on biopsies. Donor livers with similarly high BMIs were consistently more likely to be classified “for transplant” and less likely to be discarded as “not for transplant” when assessed without biopsy.

Taking year 2019–2022 September as an example, the conservative on-site evaluations based on non-biopsy assessment of HS inadvertently led to the loss of 200 (10.3% of 1939) donor livers in the United States, including 27 (9.4% of 286) donor livers directly ruled out in the operating room. This suggests that an additional 200 livers could potentially have been recovered without surpassing the accepted risk threshold for HS.

A limitation of this study is that to fulfill data matching criteria, most of the data (up to 56.9%, in year 2015–2018) remained untreated (unmatched), which negatively affected the data volume. This study also purposefully omitted considerations of compound factors influencing donor liver quality. Although we excluded nonrecoveries because of nonsteatosis-related reasons, livers classified as “not for transplant” could be attributed to numerous factors, including poor quality of blood vessels, malignancies, fibrosis, technical procurement issues, and HS. However, these factors might not be thoroughly considered when extrapolating statistical HS risks to BMIs.

Another limitation of our study is the inability to incorporate type 2 diabetes as a controlled risk variable during data cleaning and BMI matching. Although we acknowledge type 2 diabetes as an important risk factor, the OPTN database structures type 2 diabetes data separately from LT records, and because of the database’s deidentified nature, linking individual cases across data-sheets is not feasible. However, we have applied relatively strict criteria (as shown in Figure 1) based on biochemical variables to most possibly isolate other risk factors other than BMI to compensate this limitation. Future studies may benefit from using databases that integrate comorbidity data within a unified dataset, allowing for a more comprehensive evaluation of risk factors associated with LT outcomes.

The OPTN dataset offers the advantage of a large, comprehensive sample size, encompassing all liver donations across the United States. However, because the decision to discard an organ is made on a case-by-case basis and cannot be fully captured in aggregate data, the analyses based on the OPTN registration lack the granularity necessary to accurately quantify how many organs empirically discarded in the non-biopsy group could have been safely transplanted based on biopsy findings. Despite this imperfection, the conclusions are meaningful, as the large sample size strengthens the statistical power of the analyses which highlight systemic issues in LT.

In this study, we translated comparisons between HS degrees in donor livers with and without biopsy records into comparisons of HS risks, using BMI as an indirect intermediate parameter to statistically depict HS risks. The inference logic chain in our present study is as follows:

1. Foundation: Solid evidence shows that the risk of HS is independently correlated with increasing BMI.¹⁶⁻¹⁹

2. Inference 1: Statistically, donors with higher BMI are more likely to have HS.
3. Supporting evidence:
 - a. In the “for transplant” group, donors with biopsy records were more likely in the high BMI range.
 - b. Conversely, in the “not for transplant” group, donors in the high BMI range were less likely to have biopsy records.
4. Inference 2:
 - a. In the “for transplant” group, livers with biopsy records were more likely to be steatotic.
 - b. In the “not for transplant” group, livers at higher risk of steatosis were more often not assessed by biopsy.

CONCLUSIONS

Decision-making based on nonbiopsy assessments appears statistically more conservative compared with decisions made using biopsy-based assessments when considering the risks of HS.

One advantage of this inferential approach is that it allowed us to quantify the impact of conservative on-site steatosis estimations on unrecovered donor livers on a statistical level. Nevertheless, the current research did not disclose how on-site assessments, including both biopsies and nonbiopsy evaluations, impact liver recovery for individual donors. Individual case discrepancies might exceed statistical discrepancies because of uncertainties inherent in current subjective and semi-subjective HS assessment methods.

Although the OPTN data did not enable us to track if a biopsy was operated before or during the organ procurement surgeries, the majority of the recorded biopsies were believed intraoperative biopsies, since most organ procurement organizations reported that 5%–10% of their donors received a prerecovery liver biopsy, according to a study in 2017.²⁷ On-site donor liver biopsy interpretation on frozen sections reliably distinguishes transplantable from risky livers. Even a pathologist with minimal training and experience can generally assess the degree MaS (>60%, 30%–60%, or <30%). with reasonable accuracy. However, most donors (up to 63.6%) did not have biopsy records according on our study on the OPTN registrations (further discussion is beyond this study's scope).

Based on the findings in this study, we propose several recommendations to improve liver transplant practices. First, given that biopsy rates have shown little improvement throughout the study period (2004 to September 2022), increasing the use of donor liver biopsy in pretransplant assessments is the most direct way to reduce unnecessary organ discards. Because increasing the utilization of liver biopsy might be affected by complex factors, updating guidelines to ensure appropriate use of more marginal fatty livers based on nonbiopsy assessments would be valuable. Conducting further research to validate nonbiopsy predictive factors would provide stronger foundation for such guidelines. Furthermore, developing (alternative) accurate and easy-to-use intraoperative techniques for assessing HS and MaS (potentially, through utilizing elastography²⁸⁻³⁰ or spectroscopy³¹⁻³³) in the future will be vital to mitigate the impacts of conservative on-site estimations.

REFERENCES

1. Mergental H, Laing RW, Kirkham AJ, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun*. 2020;11:1–12.
2. Moosburner S, Gassner JMGV, Nösser M, et al. Prevalence of steatosis hepatitis in the eurotransplant region: Impact on graft acceptance rates. *HPB Surg*. 2018;2018:6094936.
3. Orman ES, Barritt AS, Wheeler SB, et al. Declining liver utilization for transplant in the United States and the impact of donation after cardiac death. *Liver Transpl*. 2013;19:59–68.
4. Spitzer AL, Lao OB, Dick AAS, et al. The biopsied donor liver: Incorporating macrosteatosis into high-risk donor assessment. *Liver transplant*. 2010;16:874–884.
5. Jackson KR, Motter JD, Haugen CE, et al. Temporal trends in utilization and outcomes of steatotic donor livers in the United States. *Am J Transplant*. 2020;20:855–863.
6. Linares I, Hamar M, Selzner N, et al. Steatosis in liver transplantation: Current limitations and future strategies. *Transplantation*. 2019;103:78–90.
7. Mikolasevic I, Filipce-Kanizaj T, Mijic M, et al. Nonalcoholic fatty liver disease and liver transplantation - Where do we stand? *World J Gastroenterol*. 2018;24:1491–1506.
8. McCormack L, Dutkowski P, El-Badry AM, et al. Liver transplantation using fatty livers: Always feasible? *J Hepatol*. 2011;54:1055–1062.
9. Deroose JP, Kazemier G, Zondervan P, et al. Hepatic steatosis is not always a contraindication for cadaveric liver transplantation. *HPB*. 2011;13:417–425.
10. Imber CJ, St. Peter SD, Lopez I, et al. Current practice regarding the use of fatty livers: a trans-Atlantic survey. *Liver transplant*. 2002;8:545–549.
11. Neil DAH, Minervini M, Smith ML, et al. Banff consensus recommendations for steatosis assessment in donor livers. *Hepatology*. 2022;75:1014–1025.
12. Ratzu V, Charlotte F, Heurtier A, et al; LIDO Study Group. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology*. 2005;128:1898–1906.
13. El-Badry AM, Breitenstein S, Jochum W, et al. Assessment of hepatic steatosis by expert pathologists: the end of a gold standard. *Ann Surg*. 2009;250:691–697.
14. Volk ML, Roney M, Merion RM. Systematic bias in surgeons' predictions of the donor-specific risk of liver transplant graft failure. *Liver transplant*. 2013;19:987–990.
15. Yersiz H, Lee C, Kaldas FM, et al. Assessment of hepatic steatosis by transplant surgeon and expert pathologist: a prospective, double-blind evaluation of 201 donor livers. *Liver transplant*. 2013;19:437–449.
16. Fan R, Wang J, Du J. Association between body mass index and fatty liver risk: a dose-response analysis. *Sci Reports*. 2018;8:1–7.
17. Loomis AK, Khabadi S, Preiss D, et al. Body mass index and risk of nonalcoholic fatty liver disease: two electronic health record prospective studies. *J Clin Endocrinol Metab*. 2016;101:945–952.
18. Miyake T, Kumagi T, Hirooka M, et al. Body mass index is the most useful predictive factor for the onset of nonalcoholic fatty liver disease: a community-based retrospective longitudinal cohort study. *J Gastroenterol*. 2013;48:413–422.
19. Angulo P, Keach JC, Batts KP, et al. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. *Hepatology*. 1999;30:1356–1362.
20. Rehm JL, Connor EL, Wolfgram PM, et al. Predicting hepatic steatosis in a racially and ethnically diverse cohort of adolescent girls. *J Pediatr*. 2014;165:319–325.e1.
21. Abeysekera KWM, Orr JG, Gordon FH, et al. Evaluating future risk of NAFLD in adolescents: a prediction and decision curve analysis. *BMC Gastroenterol*. 2022;22:1–13.
22. Israni AK, Zaun D, Gauntt K, et al. OPTN/SRTR 2020 annual data report: DOD. *Am J Transplant*. 2022;22:519–552.
23. OPTN. About data. Available at <https://optn.transplant.hrsa.gov/data/about-data/>. Accessed January 1, 2023.
24. White J. Public Comment Proposal Data Collection to Evaluate Organ Logistics and Allocation OPTN Operations and Safety Committee. Available at <https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/data-collection-to-evaluate-organ-logistics-and-allocation/>. Accessed June 14, 2023.
25. Association for the Study of the Liver E. EASL clinical practice guidelines: liver transplantation q. *J Hepatol*. 2016;64:433–485.
26. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support

- graphing, and covariate imbalance testing. 2018. Available at <https://econpapers.repec.org/RePEc:boc:bocode:s432001>. Accessed June 14, 2023.
27. Oliver JB, Marcus AF, Paster M, et al. Organ procurement organization survey of practices and beliefs regarding prerecovery percutaneous liver biopsy in donation after neurologic determination of death. *Transplantation*. 2017;101:821–825.
28. de Lédinghen V, Wong GLH, Vergniol J, et al. Controlled attenuation parameter for the diagnosis of steatosis in non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2016;31:848–855.
29. Park CC, Nguyen P, Hernandez C, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Gastroenterology*. 2017;152:598–607.e2.
30. Feuille C, Kari S, Patel R, et al. Utility and impact of magnetic resonance elastography in the clinical course and management of chronic liver disease. *Sci Reports*. 2024;14:1–5.
31. Guo H, Zions VS, Law BA, et al. Potential of Raman-Reflectance combination in quantifying liver steatosis and fat droplet size: Evidence from Monte Carlo simulations and phantom studies. *J Biophotonics*. 2024;17:e202400156.
32. Guo H, Tikhomirov AB, Mitchell A, et al. Real-time assessment of liver fat content using a filter-based Raman system operating under ambient light through lock-in amplification. *Biomed Opt Express*. 2022;13:5231–5245.
33. Guo H, Stueck AE, Doppenberg JB, et al. Evaluation of minimum-to-severe global and macrovesicular steatosis in human liver specimens: a portable ambient light-compatible spectroscopic probe. *J Biophotonics*. 2024;17:e202400292.