DR. JOHN RICHARD MONTGOMERY (Orcid ID : 0000-0001-7751-231X)

DR. CRAIG S. BROWN (Orcid ID : 0000-0002-2531-305X)

DR. CHRISTOPHER J SONNENDAY (Orcid ID : 0000-0002-1632-6529)

Article type : Original Articles

Graft Survival and Segment Discards Among Split-Liver and Reduced-Size Transplantations in the United States, 2008-2018

John R. Montgomery, MD MSc (ORCID 000-0001-7751-231X)[1,2]
Alexandra Highet (ORCID 0000-0002-4733-2825)[3]
Craig S. Brown, MD MSc (ORCID 0000-0002-2531-305X)[1,2]
Seth A. Waits, MD (ORCID 0000-0001-6570-5288)[2,4]
Michael J. Englesbe, MD (ORCID 0000-0001-8691-9111)[2,4]
Christopher J. Sonnenday, MD MHS (ORCID 0000-0002-1632-6529)[2,4]

[1] Department of Surgery, Michigan Medicine, Ann Arbor, MI.
[2] Center for Healthcare Outcomes & Policy, Michigan Medicine, Ann Arbor, MI.
[3] School of Medicine, University of Michigan, Ann Arbor, MI.
[4] Department of Surgery, Section of Transplantation, Michigan Medicine, Ann Arbor, MI.

Corresponding Author:
Christopher J. Sonnenday, MD, MHS

Department of Surgery, Section of Transplantation
University of Michigan
F6686 UH South
1500 E. Medical Center Drive
Ann Arbor, MI 48109
(P) 734-936-9623
(F) 734-763-3187
csonnend@umich.edu

Abbreviations:
ALT, Alanine Aminotransferase
AST, Aspartate Aminotransferase
BSA, Body Surface Area
CI, Confidence Interval
HCC, Hepatocellular Carcinoma
IQR, Interquartile Range
MELD, Model for End-Stage Liver Disease
OPO, Organ Procurement Organization
PELD, Pediatric End-Stage Liver Disease
STAR, Standard Transplant Analysis and Research
UNOS, United Network for Organ Sharing

Abstract

Split-liver transplantation has allocation advantages over reduced-size transplantation due to its ability to benefit two recipients. However, prioritization of split-liver transplantation relies on three major assumptions that have never been tested in the United States: similar long-term transplant recipient outcomes, lower incidence of segment discard among split-liver procurements, and discard of segments among reduced-size procurements that would be otherwise “transplantable.” We utilized UNOS-STAR data to identify all split-liver (n=1,831) and reduced-size (n=578) transplantation episodes in the United States between 2008-2018. Multivariable Cox proportional hazards modeling was used to compare 7-year all-cause graft loss between cohorts. Secondary analyses included etiology of 30-day all-cause graft loss events as well as incidence and anatomy of discarded segments. We found no difference in 7-year all-cause graft loss (aHR 1.09, 95%CI 0.82-1.46) or 30-day all-cause graft loss (aHR 1.13, 95%CI 0.70-1.80) between split-liver and reduced-size cohorts. Vascular thrombosis was the most common etiology of 30-day all-cause graft loss for both cohorts (56.4% vs 61.8% of 30-day graft losses, *P*=.85). Finally, reduced-size transplantation was associated with a significantly higher incidence of segment discard (50.0% vs 8.7%) that were overwhelmingly right-sided (93.6% vs 30.3%). Our results support the prioritization of split-liver over reduced-size transplantation whenever technically feasible.

1. Introduction

In the setting of an ongoing organ shortage in the United States, children and smaller-stature adults with end-stage liver disease are particularly disadvantaged in access to liver transplantation due to graft-to-patient size mismatch.[1–6] Transplantation of partial liver segments via split-liver or reduced-size transplantation are commonly used when whole-liver transplantation is too large for the intended recipient.[7–12] In each case, a portion of the donor liver is transplanted into the recipient, enabling appropriate segment-to-patient size matching. However, split-liver transplantation involves allocation of liver segments to two recipients at the time of the organ offer whereas reduced-size transplantation occurs when a single center procures the whole liver and then reduces it before transplantation, discarding the unused portion and benefiting only a single recipient.[12,13] As such, prioritization of split-liver transplantation over reduced-size transplantation has been advocated in order to benefit more patients and improve access to transplantation among children and smaller-stature adults.

However, the assumption of greater benefit to more patients after split-liver transplantation relies on three major assumptions that have never been tested in the United States. First, long-term post-transplantation recipient outcomes have never been compared between the practices. Concerns remain that split-liver transplantation outcomes may be inferior to those of reduced-size transplantation given the technical and anatomical challenges of splitting a liver for two separate recipients.[14,15] In particular, increased incidence of vascular thrombosis has been associated with short-term graft complications and failure among split-liver transplantation episodes.[16–19] Yet whether vascular thrombosis events and short-term graft loss are more common among split-liver versus reduced-size liver transplantation remain unknown. Second, incidence of segment discard has never been compared between split-liver and reduced-size transplantation. Should incidence segment discard among split-liver transplantation approach 50%, it would likely result in similar numbers of transplanted recipients as to reduced-size transplantation. Finally, the anatomy of segment discard has never been analyzed. If reduced-size transplant segment discards are generally left-sided segments from smaller-sized donors, these segments might be too small to allocate to another

recipient and split-liver transplantation for that procurement episode would be more challenging.

Therefore, we sought to investigate these questions by analyzing data from the United Network for Organ Sharing between 2008-2018. Our objectives were to compare whether either practice was associated with higher long-term all-cause graft loss (a measure of patient outcomes) or higher incidence of transplantable segment discard (a measure of potential allocation wastefulness). We hypothesized that split-liver transplantation episodes would have higher rates of 30-day graft loss due to technical factors, but that long-term graft survival would be similar. Furthermore, we hypothesized that split-liver transplantation would have a lower incidence of segment discard but that the anatomy of discarded segments would be similar between practices.

2. Materials and Methods

2.1. Data Source

This study represents an analysis of data from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research (STAR) file. This file was requested from UNOS and reflected the Organ Procurement and Transplantation Network database as of June 10, 2019 with procurements, transplants, and outcomes added through March 31, 2019. The data contained de-identified patient-level information for transplant recipients and wait-list candidates dating back to October 1, 1987 and is available online upon request.[20] This study was determined to be exempt by the Michigan Medicine Institutional Review Board because it contains all deidentified data from a quality improvement registry; informed consent was not required.

2.2. Study Population

All adult and pediatric liver procurement events with intention to transplant between January 1, 2008 and December 31, 2018 were identified from the UNOS-STAR file. This start date was chosen due to the November 2007 match run rule that defined “split eligibility” among deceased liver donors[21]; the end-date was chosen to ensure a

minimum of 6-months follow-up among transplantation episodes. The procurement events were linked with liver transplant recipient data. Episodes were excluded if the liver was not procured with intention to transplant (e.g. for research purposes only). Split-liver transplantation episodes were identified when two separate liver segment dispositions were listed in the deceased donor datafile. Reduced-size transplantation episodes were identified when partial liver transplantation was performed outside of an identified split-liver transplantation episode. A flow diagram of the study population is shown in Supplemental Figure.

2.3. Outcomes

The primary outcome was all-cause graft loss between split-liver and reduced-size transplantation episodes, defined as patient death or re-transplantation. The secondary outcome among transplant recipients was etiology of graft loss. Upon data exploration, it was discovered that there was extensive data missingness of graft loss etiology after 30-days of transplantation (missingness = 188/270 (69.6%) for graft loss events occurring >30 days from transplantation). Conversely, graft loss within 30-days of transplantation was better recorded (missingness = 57/156 (36.5%) for graft loss events within 30-days of transplantation). Therefore, the decision was made to only report etiology of graft loss within 30-days of transplantation. Graft loss etiologies were categorized as primary non-function, vascular thrombosis, acute rejection, and recipient death with a functioning graft. Vascular thrombosis included hepatic artery thrombosis, portal vein thrombosis, hepatic outflow occlusion, and other vascular thrombosis. Acute rejection episodes included cellular and antibody-mediated causes. Death with a functioning graft was determined when the patient died and variables for primary non-function, vascular thrombosis, and rejection were all negative and non-missing.

Secondary outcomes among procurement episodes included incidence, anatomy, and estimated volumes of discarded segments. Incidence of segment discard was computed by assuming that each split-liver and reduced-size procurement event could result in two transplantation episodes. Anatomy of discarded segments were classified according to the Couinaud classification system: left lateral (segments 2-3), left lobe (segments 2-

4), right lobe (segments 5-8), and right trisegment (segments 4-8).[22] The UNOS-STAR files does not contain data on liver segment volume or weight. Therefore, we estimated discarded segment volumes (in cm^3) by multiplying the total estimated liver volume (calculated per the Vauthey formula) by the median proportion of liver that each segment represents (per Abdalla *et al.*: 16% among left lateral segments, 33% among left lobes, 65% among right lobes, and 82% among right trisegments).[23–25]

2.4 Statistical Analysis

First, temporal trends in split-liver and reduced-size transplantation volume were compared. This was performed utilizing time series analysis with Newey-West standard errors for coefficients estimated by ordinary least squares regression. The Cumby-Huizinga test was used to test for autocorrelation within cohorts. As no autocorrelation was detected, the resulting analyses reflect linear regression models with robust standard errors. Given the possible clinical interchangeability of split-liver and reduced-size transplantation, the annual volume of each was correlated and the Pearson correlation coefficient (ρ) was reported.

Next, time-to-event analyses were performed with Kaplan-Meier and Cox proportional hazards modelling. Episodes were censored at time of last follow-up. Kaplan-Meier curves were compared with the log-rank test. Multivariable Cox regression models were created using stepwise, backward elimination to estimate the hazard of all-cause graft loss within 7-years of transplantation. The initial, full model included recipient age at transplantation, donor age at procurement, recipient sex, recipient race (Black versus non-Black), donor body surface area (in meters squared), pediatric end-stage liver disease score or laboratory model for end-stage liver disease score, hepatocellular carcinoma exception status, recipient history of portal vein thrombosis, insurance type (private versus other), listing status (1A/1B versus other), re-transplant status (re-transplant versus first-time transplant), year of transplantation, and blood-type incompatibility (compatible versus incompatible).[26] Body surface area was calculated using the Du Bois & Du Bois formula.[27] Covariates with the highest *P* values were sequentially eliminated from the model until all *P* values were <.15. The final model

included the following covariates: recipient age at transplantation, donor age at procurement, donor body surface area, insurance type, re-transplant status, and year of transplantation. Cox model standard errors were adjusted to account for clustering of outcomes within centers. Due to potential concerns of increased short-term graft loss among split-liver transplantation episodes, a sensitivity analysis of all-cause graft loss before and after 30-days of transplantation was conducted.

Next, etiologies of graft loss events within 30-days of transplantation were compared between cohorts. To address the outcome missingness in 57/156 (36.5%) of graft loss episodes within 30-days of transplantation, we elected to perform multiple imputation using a multinomial logistic function with 1,000 imputations based on recipient age, donor age, donor body surface area, donor terminal aspartate aminotransferase level, recipient history of portal vein thrombosis, previous transplantation status, status 1A/1B listing, blood-type incompatibility, time to graft loss (in days), and year of transplantation. Proportions with 95% confidence intervals were reported and compared with the *F*-test. Sensitivity analysis using complete-case approach was also performed in order to assess the robustness of our results.[28]

Finally, incidence of segment discard and anatomy of discarded segments were compared with χ^2 tests. A tornado plot was constructed to display these results. Due to concerns that donor height and weights would be different between split-liver and reduced-size transplantation episodes (thereby influencing the anatomy and resulting "transplantability" of discarded segments), figures of discarded segment anatomy by donor height and weight were constructed.

Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies were followed for data and analysis reporting.[29] Continuous data were compared by the non-parametric Wilcoxon rank-sum test and presented as medians with interquartile ranges (IQR); proportional data were compared by χ^2 test or Fisher's exact test when appropriate. A kernel density plot of recipient age at transplantation was used to highlight age distribution differences between split-liver and reduced-size

transplantation recipients. Two-sided *P*<.05 was used to indicate statistical significance for all comparisons. Demographic data missingness was minimal and noted in Table 1 footnotes. All analyses were conducted using STATA version 15.1 (StataCorp 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

3. Results

3.1. Characteristics of split-liver and reduced-size transplant episodes

In total, 2,409 partial-liver transplantation episodes were identified between January 1, 2008, and December 31, 2018. Of these, 1,831 (76.0%) were split-liver transplantation episodes and 578 (24.0%) were reduced-size transplantation episodes. Median annual volume of split-liver transplantation was 168 cases (minimum 137, maximum 203) (Figure 1). No temporal trend in annual split-liver transplantation volume was observed (slope +3.1 episodes/year, 95%CI -1.0 to +7.3 episodes/year). Median annual volume of reduced-size transplantation was 55 cases (minimum 38, maximum 63). There was a small but statistically significant temporal trend towards decreased annual volume of reduced-size transplantation (slope -1.6 episodes/year, 95%CI -3.1 to -0.1 episodes/year). Annual split-liver and reduced-size transplantation volumes were found to have a strong inverse correlation (ρ = -0.916, *P*<.001).

Donor, recipient, and transplant characteristics are listed in Table 1. Split-liver transplantation donors were older with larger body surface area. Split-liver transplantation recipients were older, had larger body surface area, more likely to receive hepatocellular carcinoma exception points, and spent more time on the waitlist. Split-liver transplantation recipient age followed a bimodal distribution whereas reduced-size transplantation recipient age was right-skewed (Figure 2). Reduced-size transplantation recipients were more likely to be status 1A/1B listing and have a history of previous liver transplantation. Split-liver transplantation episodes had a shorter cold ischemic time, although this difference was clinically small at a difference in median values of 0.6 hours.

3.2. All-Cause Graft Loss

Median follow-up was 4.8 years (interquartile range 2.0 to 7.7 years. Kaplan Meier estimates of all-cause graft failure among split-liver transplantation episodes was 11.8% at 1 year, 16.6% at 3 years, 19.3% at 5 years, and 22.4% at 7 years (Figure 3). Among reduced-size transplantation episodes, estimated incidence of all-cause graft failure was 10.6% at 1 year, 14.9% at 3 years, 17.0% at 5 years, and 20.0% at 7 years. This difference was not statistically-significantly different (*P*=.31). There was no statistical difference in 7-year all-cause graft loss between split-liver and reduced-size transplantation after adjusting for recipient age, donor age, donor body surface area, recipient insurance, re-transplant status, and year of transplantation (aHR 1.09, 95%CI 0.82-1.46) (Table 2). On sensitivity analysis, split-liver transplantation was not associated with increased hazard of all-cause graft loss within 30-days of transplantation (aHR 1.13, 95%CI 0.70-1.80) or beyond 30-days post-transplantation (aHR 1.08, 95%CI 0.77-1.51).

3.3. Etiology of All-Cause Graft Loss within 30-Days of Transplantation

A total of 426 all-cause graft loss events were observed over the study period; of these, 156 (33.6%) occurred within 30-days of transplantation. Vascular thrombosis was the most common etiology of all-cause graft loss within 30-days of transplantation, accounting for >50% in both split-liver and reduced-size transplantation cohorts (Table 3). There was no statistically-significant difference in etiology of all-cause graft loss within 30-days of transplantation between the cohorts (*P*=.85). Sensitivity analysis using a complete-case approach had similar results (Supplemental Table).

3.4. Incidence, Anatomy, and Volume of Segment Discards

Of 79,667 liver procurement episodes during the study period, 1,003 (1.3%) split-liver and 578 (0.7%) reduced-size procurements were identified. In total, 175/2,006 (8.7%) split-liver segments and 578/1,156 (50.0%) reduced-size segments were discarded (*P*<.001 for comparison). Split-liver discards were usually left-lateral segments (91/175, 52.0%) whereas reduced-size discards were usually right lobe (326/578, 56.4%) or right trisegment (215/578, 37.2%) (*P*<.001 for comparison) [Figure 4]. Volume of reduced-

size segment discards were statistically-significantly larger than split-liver segment discards [median (IQR) volume 745 (425-998) cm^3 vs 252 (199-699) cm^3, P<.001]. Anatomy of discarded segments by donor height and weight are displayed in Supplemental Figure. Distribution of donor heights and weights appeared similar between split-liver and reduced-size segment discards.

4. Discussion

Between 2008-2018, we found no difference in long-term all-cause graft loss between split-liver and reduced-size transplantation episodes. Additionally, there was no evidence of increased hazard of all-cause graft loss within 30-days of transplantation among split-liver transplantation episodes. Etiology of all-cause graft loss within 30-days of transplantation was similar between cohorts, with the majority of graft losses being secondary to vascular thrombosis. Finally, reduced-size procurements resulted in a significantly higher incidence of segment discards that were usually right-sided.

Similar incidence of short- and long-term all-cause graft loss between split-liver and reduced-size transplantation episodes further underscores the need to prioritize split-liver transplantation over reduced-size transplantation whenever technically feasible. This study demonstrates that reduced-size transplantation overwhelmingly results in discard of right-sided liver segments (right lobe and right trisegment), which are generally larger and should be usable for transplant into an appropriate size recipient. Similar donor height and weight distributions among discarded segments further rejects the hypothesis that differential donor size leads to use of reduced-size over split-liver transplantation on a population level. Finally, the lack of a bimodal distribution among reduced-size transplantation episodes (compared to split-liver transplantation episodes) suggests that reduced-size transplantations occur when a pediatric center is allocated a whole liver that they intend to reduce, without consideration of allocation of the residual segment to a second recipient. Taken together, these data suggest that continued use of reduced-size transplantation when split-liver transplantation is technically feasible represents a potentially wasteful practice.

While there is national agreement that split-liver transplantation needs to be better utilized in order to increase the number of liver transplantations performed annually, there is debate as to the means.[30] Logistical challenges of allocating split-liver segments to different centers has been identified as a major barrier to split-liver transplantation. As such, multiple split-liver allocation variances (Region 8, Region 2, and a single Organ Procurement Organization (OPO) in Region 5) have been attempted to incentivize split-liver transplantation by allocating both segments to the same center. Proponents maintain that such variances solve logistical problems, encourage centers to perform more split-liver transplants, and allow for optimal anatomical splitting of the liver for the center's two recipients. However, opponents are concerned that these variances disadvantage centers without institutionally-affiliated pediatric programs due to match run rules that favor allocation to pediatric recipients. Furthermore, there is concern that increasing split-liver transplantation among adults will have poorer patient outcomes compared to whole-liver transplantation and centers will be penalized for these outcomes. Given that split-liver transplantation represents <2% of all liver transplants performed annually, we contend that concerns over disadvantaging individual centers by increasing split-liver transplantation is overstated.[31] The transplant community should prioritize performing the greatest number of transplants to save the greatest number of lives, even if this is at the marginal expense of a small number of transplant centers. We advocate for any split-liver variances that accomplishes more split-liver transplants and prevents the unnecessary wasting of reduced-size transplant discards.

Current transplantation policies require OPOs to exercise equal effort and resources to place each segment of a split-liver procurement; however, there is little accountability among OPOs or transplant centers for converting reduced-size transplantation episodes to split-liver transplantation. While our analysis suggested a higher potential acuity among reduced-size transplantation recipients (more likely to be status 1A/1B listing, retransplants, and higher Pediatric End-Stage Liver Disease scores), these factors alone should not absolve transplant centers or organ procurement organizations from their dual responsibility to facilitate placement of the unused segment. In clinical practice, the decision to reduce or split a liver is delegated to the accepting center for

the primary recipient. Transplant centers should be required to report their intention to perform reduced-size transplantation at time of organ-offer acceptance, which should trigger the OPO to exercise equal effort and resources to place the unused segment. Ongoing emphasis on creating best practices and standards in split-liver transplantation is needed to facilitate decision-making as it relates to assignment of blood vessels and bile ducts between the two allografts, and procurement technique. Such standards will help facilitate collaboration between transplant centers and OPOs that may convert more appropriate donors to split-liver transplantation.

In addition to similar short and long-term all-cause graft loss between split-liver and reduced-size transplantation episodes, we found similar etiologies of 30-day graft loss between the practices. Vascular thrombosis was associated with the majority of graft losses within this timeframe. This highlights the increased technical complexity of these procedures and identifies vascular complications as the key challenge to target for improvement in outcomes for either split-liver or reduced-size transplants. Further analysis of center-level variation in practice may identify best practices to decrease vascular thrombosis events among split-liver and reduced-size transplantation episodes.

Our study has limitations. First, etiology of graft loss was missing in 36.6% of graft loss episodes within 30-days of transplantation. Multiple imputation was utilized to estimate the graft loss etiology, but it is possible that technical causes of graft loss could have been under- or overestimated. Even so, the robustness of our results was supported by a sensitivity analysis using a complete-case approach. Second, biliary and vascular anatomic characteristics between split-liver and reduced-size transplantation episodes are not captured in the UNOS-STAR file and therefore cannot be compared. We were not able to compare biliary or vascular anatomy between split-liver and reduced-size transplantation episodes and cannot say with certainty that all of the reduced-size transplantation donors had anatomy amenable to splitting. However, it is highly unlikely that biliary and vascular anatomy alone would explain the choice to perform reduced-size transplantation in all 578 cases. Third, this study is limited by its retrospective

nature and utilization of registry data that is prone to residual confounding and misclassification bias. However, this data is the best available to study these rare events on a national basis. Finally, this study does not address the larger proportion of whole-liver transplantations that might be amendable to split-liver transplantation. This potential population of split-liver transplants must be addressed with future studies to realize a substantial impact on split-liver transplant utilization.

In conclusion, 25% of partial-liver transplants are reduced-size transplant episodes, which leads to the discard of generally right-sided segments that likely could have been used to transplant another candidate. Our analysis revealed similar incidence of short and long-term all-cause graft loss between split-liver and reduced-size transplantation, suggesting that a presumed advantage in outcomes does not support the use of reduced-size transplantation. It is critically important to develop best practices and policies that encourage transplant centers and OPOs to prioritize split-liver transplantation when technically feasible and minimize the use of reduced-size transplantation, thus optimizing the impact of each deceased organ donor.

Acknowledgements

John R. Montgomery and Craig S. Brown had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. John R. Montgomery is supported by the Obesity Surgery Scientist Fellowship Award administered from the National Institute of Diabetes and Digestive and Kidney Diseases T32-DK108740. Alexandra Highet is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health TL1TR002242. Craig S. Brown is supported by the Ruth L. Kirschstein Postdoctoral Research Fellowship Award administered from the National Institute on Drug Abuse F32-DA050416.

Disclosures

The authors of this manuscript have no conflicts of interest to disclose as described by the *Liver Transplantation*.

Data Availability Statement

The data that supports the findings of this study are publicly available at the United States Department of Health & Human Services website: https://optn.transplant.hrsa.gov/data/request-data/.

References

1. Ge J, Hsu EK, Bucuvalas J, Lai JC. Deceased Pediatric Donor Livers: How Current Policy Drives Allocation and Transplantation. *Hepatology*. 2019;69(3):1231-1241. doi:10.1002/hep.30295
2. Cullaro G, Sarkar M, Lai JC. Sex-based disparities in delisting for being "too sick" for liver transplantation. *Am J Transplant*. 2018;18(5):1214-1219. doi:10.1111/ajt.14608
3. Mathur AK, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Sex-based disparities in liver transplant rates in the United States. *Am J Transplant*. 2011;11(7):1435-1443. doi:10.1111/j.1600-6143.2011.03498.x
4. Bowring MG, Ruck JM, Haugen CE, Massie AB, Segev DL, Gentry SE. Deceased-Donor Liver Size and the Sex-Based Disparity in Liver Transplantation. *Transplantation*. 2017;101(11):e329. doi:10.1097/TP.0000000000001898
5. Lai JC, Terrault NA, Vittinghoff E, Biggins SW. Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system. *Am J Transplant*. 2010;10(12):2658-2664. doi:10.1111/j.1600-6143.2010.03326.x
6. Mindikoglu AL, Emre SH, Magder LS. Impact of estimated liver volume and liver weight on gender disparity in liver transplantation. *Liver Transpl*. 2013;19(1):89-95. doi:10.1002/lt.23553
7. Ge J, Perito ER, Bucuvalas J, et al. Split liver transplantation is utilized infrequently and concentrated at few transplant centers in the United States. *Am J Transplant*. 2020;20(4):1116-1124. doi:10.1111/ajt.15696
8. Ge J, Lai JC. Split-Liver Allocation: An Underused Opportunity to Expand Access to Liver Transplantation. *Liver Transplant*. 2019;25(5):690-691. doi:10.1002/lt.25458
9. Emond JC, Whitington PF, Thistlethwaite JR, Alonso EM, Broelsch CE.

Reduced-size orthotopic liver transplantation: Use in the management of children with chronic liver disease. *Hepatology*. 1989;10(5):867-872. doi:10.1002/hep.1840100520

10. Otte JB, De Ville De Goyet J, Reding R, et al. Pediatric liver transplantation: From the full-size liver graft to reduced, split, and living related liver transplantation. *Pediatr Surg Int*. 1998;13(5-6):308-318. doi:10.1007/s003830050328
11. Otte JB, Ville de Goyet J, Sokal E, et al. Size Reduction of the Donor Liver Is a Safe Way to Alleviate the Shortage of Size-Matched Organs in Pediatric Liver Transplantation. *Ann Surg*. 1990;211(2):146-157. doi:10.1097/00000658-199002000-00006
12. Gong N, Chen X. Partial liver transplantation. *Front Med China*. 2011;5(1):1-7. doi:10.1007/s11684-010-0105-7
13. Houssin D, Soubrane O, Boillot O, et al. Orthotopic liver transplantation with a reduced-size graft: An ideal compromise in pediatrics? *Surgery*. 1992;111(5):532-542.
14. Liu H, Li R, Fu J, He Q, Li J. Technical Skills Required in Split Liver Transplantation. *Ann Transplant*. 2016;21:408-415. doi:10.12659/aot.896351
15. Lauterio A, Di Sandro S, Concone G, De Carlis R, Giacomoni A, De Carlis L. Current status and perspectives in split liver transplantation. *World J Gastroenterol*. 2015;21(39):11003-11015. doi:10.3748/wjg.v21.i39.11003
16. Gavriilidis P, Roberts KJ, Azoulay D. Right lobe split liver graft versus whole liver transplantation: A systematic review by updated traditional and cumulative meta-analysis. *Dig Liver Dis*. 2018;50(12):1274-1282. doi:10.1016/j.dld.2018.08.025
17. Elsabbagh AM, Williams C, Girlanda R, et al. The impact of intercenter sharing on the outcomes of pediatric split liver transplantation. *Clin Transplant*. 2017;31(12). doi:10.1111/ctr.13138
18. Mourad MM, Liossis C, Kumar S, et al. Vasculobiliary complications following adult right lobe split liver transplantation from the perspective of reconstruction techniques. *Liver Transplant*. 2015;21(1):22-28. doi:10.1002/lt.24015
19. Wan P, Li Q, Zhang J, Xia Q. Right lobe split liver transplantation versus whole liver transplantation in adult recipients: A systematic review and meta-analysis.

Liver Transpl. 2015;21(7):928-943. doi:10.1002/lt.24135

20. Request Data - OPTN. https://optn.transplant.hrsa.gov/data/request-data/. Accessed January 16, 2020.
21. Ethics - Split Versus Whole Liver Transplantation - OPTN. https://optn.transplant.hrsa.gov/resources/ethics/split-versus-whole-liver-transplantation/. Accessed January 16, 2020.
22. Couinaud C. The parabiliary venous system. *Surg Radiol Anat*. 1988;10(4):311-316. doi:10.1007/bf02107904
23. Vauthey JN, Abdalla EK, Doherty DA, et al. Body surface area and body weight predict total liver volume in western adults. *Liver Transplant*. 2002;8(3):233-240. doi:10.1053/jlts.2002.31654
24. Olthof PB, van Dam R, Jovine E, et al. Accuracy of estimated total liver volume formulas before liver resection. *Surg (United States)*. 2019;166(3):247-253. doi:10.1016/j.surg.2019.05.003
25. Abdalla EK, Denys A, Chevalier P, Nemr RA, Vauthey JN. Total and segmental liver volume variations: Implications for liver surgery. *Surgery*. 2004;135(4):404-410. doi:10.1016/j.surg.2003.08.024
26. Montgomery JR, Berger JC, Warren DS, James NT, Montgomery RA, Segev DL. Outcomes of ABO-incompatible kidney transplantation in the United States. *Transplantation*. 2012;93(6). doi:10.1097/TP.0b013e318245b2af
27. Burton RF. Estimating body surface area from mass and height: Theory and the formula of du Bois and du Bois. *Ann Hum Biol*. 2008;35(2):170-184. doi:10.1080/03014460801908439
28. Childers CP, Maggard-Gibbons M. Same Data, Opposite Results? *JAMA Surg*. November 2020. doi:10.1001/jamasurg.2020.4991
29. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *UroToday Int J*. 2009;2(2). doi:10.4038/jccpsl.v13i2.2965
30. Split liver variance - OPTN. https://optn.transplant.hrsa.gov/governance/public-comment/split-liver-variance/. Accessed November 17, 2020.

31. Kwong AJ, Kim WR, Lake JR, et al. OPTN/SRTR 2019 Annual Data Report: Liver. *Am J Transplant*. 2021;21(S2):208-315. doi:10.1111/ajt.16494

	Split-Liver Transplantation	Reduced-Size Transplantation	P value
Donor characteristics			
Procurements, n	998	578	N/A
Age, median (IQR), y	19 (16, 26)	13 (7, 18)	<.001
Male sex, n (%)	669/998 (67.0)	368/578 (63.7)	.18
Body mass index, median (IQR), kg/m^2 [a]	23.1 (20.8, 25.5)	20.2 (17.0, 23.5)	<.001
Body surface area, median (IQR), m^2	1.79 (1.64, 1.93)	1.48 (0.91, 1.78)	<.001
Hypertension, n (%)	46/993 (4.6)	26/577 (4.5)	.91
Diabetes, n (%)	10/994 (1.0)	15/577 (2.6)	.015
Smoker, n (%)	31/990 (3.1)	8/576 (1.4)	.033
Intravenous drug use, n (%)	38/988 (3.8)	13/575 (2.3)	.089
Donation after circulatory death, n (%)	0/998 (0.0)	3/578 (0.5)	.049
Terminal ALT, median (IQR), IU/L [a]	31 (20, 54)	35 (21, 65)	.005
Terminal AST, median (IQR), IU/L	43 (27, 73)	48 (28, 81)	.021
Recipient characteristics			
Number of recipients, n	1,831	578	N/A
Age, median (IQR), y	9 (1, 56)	1 (0, 4)	<.001
Male sex, n (%)	879/1,831 (48.0)	297/578 (51.4)	.16
Race, n (%)			.17
White	987/1,831 (53.9)	315/578 (54.5)	
Black	233/1,831 (12.7)	74/578 (12.8)	
Hispanic	430/1,831 (23.5)	118/578 (20.4)	
Asian	140/1,831 (7.6)	49/578 (8.5)	
Other [b]	41/1,831 (2.2)	22/578 (3.8)	
Body mass index, median (IQR), kg/m^2 [a]	19.5 (16.6, 24.8)	16.9 (15.5, 18.7)	<.001
Body surface area, median (IQR), m^2 [a]	1.02 (0.44, 1.74)	0.44 (0.34, 0.71)	<.001
Laboratory MELD score, median (IQR)	17 (11, 24)	20 (13, 25)	.41
PELD score, median (IQR)	13 (-1, 25)	16 (3, 24)	.029
Private insurance, n (%)	808/1,831 (44.1)	236/578 (40.8)	.16
Status 1A or 1B listing, n (%)	380/1,831 (20.8)	210/578 (36.3)	<.001
HCC exception points, n (%)	268/1,831 (14.6)	9/578 (1.6)	<.001
Previous transplantation, n (%)	87/1,831 (4.8)	51/578 (8.8)	<.001
Previous portal vein thrombosis, n (%)	155/1,829 (8.5)	48/578 (8.3)	.90
Days on waitlist, median (IQR), d	94 (26, 271)	42 (11, 108)	<.001
Transplant characteristics			
Number of transplants, n	1,831	578	N/A
Cold ischemia time, median (IQR), h [a]	6.8 (5.1, 8.5)	7.4 (6.2, 9.0)	<.001

Blood-type incompatible, n (%)	44 (2.4)	35 (6.1)	<.001

Table 1. Donor, recipient, and transplantation characteristics.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; PELD, Pediatric End-Stage Liver Disease.

[a] Missingness <1.0% for split-liver and reduced-size transplantation cohorts.

[b] Other races include American Indian/Alaska Native, Native Hawaiian or Other Pacific Islander, and multiracial.

	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	***P value***	***aHR (95% CI)***	***P value***
Split-liver transplantation	1.12 (0.80-1.58)	.50	1.09 (0.82-1.46)	.55
Recipient age at transplantation (*per 5-year increase*)	1.02 (1.00-1.04)	.10	1.02 (1.00-1.04)	.035
Donor age at procurement (*per 5-year increase*)	1.11 (1.05-1.16)	<.001	1.13 (1.08-1.19)	<.001
Donor body surface area (*per 0.1 m^2 increase*)	1.01 (0.98-1.04)	.59	0.96 (0.93-0.99)	.019
Private insurance	0.85 (0.68-1.06)	.15	0.79 (0.65-0.96)	.020
History of previous liver transplant	2.04 (1.49-2.79)	<.001	2.18 (1.57-3.03)	<.001
Year of transplantation (*per 1-year increase*)	0.97 (0.93-1.01)	.10	0.96 (0.93-1.00)	.042

Table 2: Cox proportional hazards analysis of all-cause graft loss between split-liver and reduced-size transplantation episodes in the United States, 2008-2018. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

	Split-Liver Transplantation	Reduced-Size Transplantation	*P* value
Vascular thrombosis	56.4% (45.9-66.9%)	61.8% (43.6-79.9%)	.85
Primary non-function	30.3% (20.4-40.2%)	23.9% (8.2-39.6%)	
Acute rejection	7.7% (1.5-13.8%)	5.8% (0.0-15.9%)	
Death with functioning graft	5.6% (0.0-11.9%)	8.5% (0.0-19.5%)	

Table 3. Etiology of graft loss within 30-days of transplantation between split-liver and reduced-size transplantation episodes. Data presented as proportions with 95% confidence intervals.

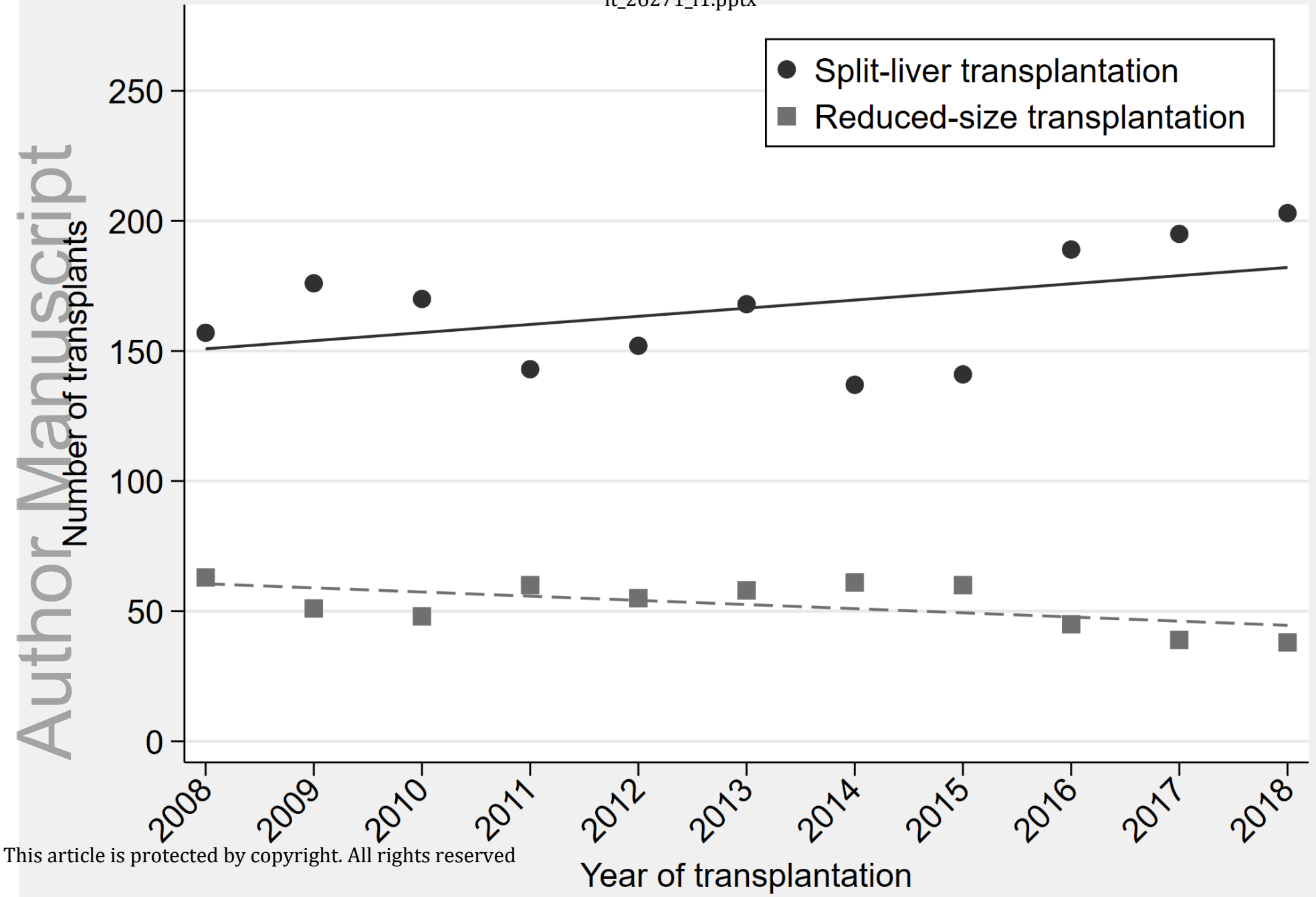
FIGURE LEGENDS

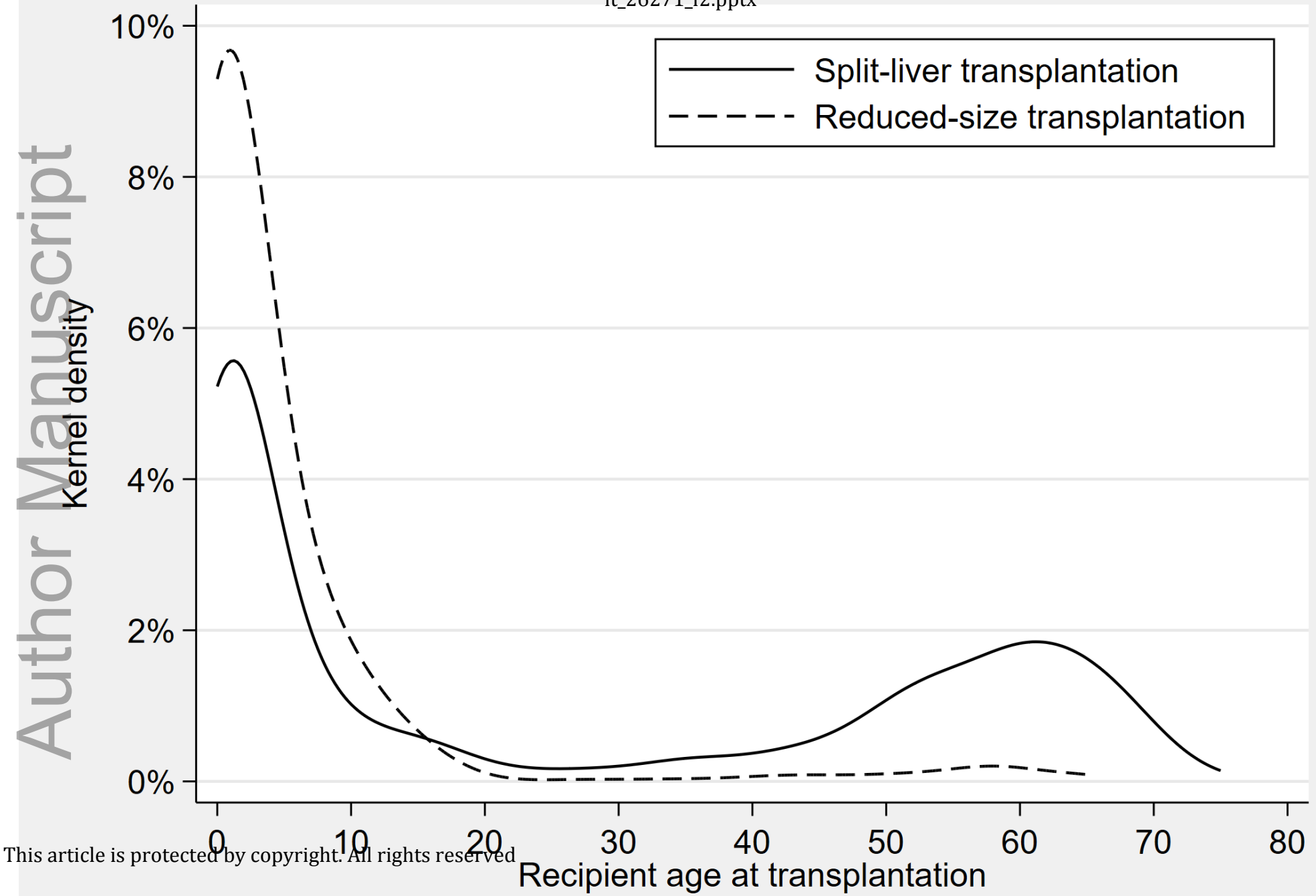
Figure 1. Annual volume of split-liver and reduced-size transplantation episodes in the United States, 2008-2018. Dots represent annual number of split-liver and reduced-size transplantation episodes, respectively. Lines are the linear fits of these volumes over time. Pairwise correlation (ρ) between split-liver and reduced-size liver transplantation by year was -0.916 (*P*<.001).

Figure 2. Smoothed kernel density plots of recipient age at transplantation between split-liver and reduced-size transplantation episodes. As shown, recipient age at transplantation among split-liver transplantation episodes (blue line) follows a bimodal distribution whereas recipient age at transplantation among reduced-size transplantation episodes (red line) follows a right-skewed distribution.

Figure 3. Kaplan-Meier curves of all-cause graft loss between split-liver and reduced-size transplantation episodes. There was no statistical difference between the curves on log-rank test (*P*=.31). Abbreviations: SLT, split-liver transplantation; RST, reduced-size transplantation.

Figure 4. Tornado plot of discarded segment anatomy between split-liver and reduced-size transplantation episodes. The anatomy of discarded segments was statistically-significantly different on χ^2 test (*P*<.001).





lt_26271_f3.pptx

Number at risk

SLT	1831	1394	1145	970	832	687	551	427
RST	578	477	413	371	317	258	202	158

lt_26271_f4.pptx