ORIGINAL ARTICLE

# Obesity does not significantly impact outcomes following simultaneous liver kidney transplantation: review of the UNOS database - a retrospective study

Jonathan W. Yu[1], Gaurav Gupta[2], Le Kang[1], Dipankar Bandyopadhyay[1], Mohammed S. Siddiqui[3], Chandra S. Bhati[4], Richard T. Stravitz[3], Marlon Levy[4] & Trevor W. Reichman[4]

1 Department of Biostatistics, Virginia Commonwealth, University, Richmond, VA, USA
2 Division of Nephrology, Department of Medicine, Virginia Commonwealth, University, Richmond, VA, USA
3 Division of Hepatology, Department of Medicine, Virginia Commonwealth, University, Richmond, VA, USA
4 Division of Transplantation, Department of Surgery, Virginia Commonwealth University, Richmond, VA, USA

**Correspondence**
Trevor W. Reichman MD, PhD, Division of Transplant Surgery, Department of Surgery, Virginia Commonwealth University, PO Box 980057, Richmond, VA 23298-0057, USA.
Tel.: 804 828 2461;
fax: 804 828 4858;
e-mail:
trevor.reichman@vcuhealth.org

## SUMMARY

Simultaneous liver kidney transplantation (SLK) is the only curative option for patients with combined end stage liver and kidney disease. With the global obesity epidemic, an increasing number of obese patients are in need of SLK. However, the impact of pre-transplant obesity on outcomes after SLK is unknown. An analysis of the United States OPTN registry (Oct 1987 – June 2016) identified 7205 SLK transplants. Of these, 1677 patients were overweight/obese (OW, BMI 30–39) and 183 were morbidly obese (MO, BMI ≥40). 29% of patients had NASH in the MO group versus 16.4% and 4.7% in the OW and normal weight (NW) groups, respectively. The 1, 3 and 5 year overall patient survival, kidney and liver graft survivals were comparable between the three groups. Numerically higher rates of acute kidney rejection were reported in the MO group at 1 year [12.73%, 8.59%, and 10.05% for MO, OW and NW, respectively ($P = 0.22$)]. Multivariate analysis identified diagnosis of hepatitis C, donor age, diabetes mellitus, and delayed kidney transplant function but not BMI as risk factors for poor patient and both liver and kidney graft survival. Based on these findings, obesity should not be a contraindication for SLK even for patients with BMIs ≥ 40.

*Transplant International* 2019; 32: 206–217

**Key words**
liver transplantation, obesity, outcomes, simultaneous liver kidney transplantation

Received: 28 December 2017; Revision requested: 19 February 2018; Accepted: 13 September 2018; Published online: 30 October 2018

## Introduction

Simultaneous liver kidney transplantation (SLK) is life saving for patients with concomitant end stage liver (ESLD) and end stage renal disease (ESRD). With improving patient outcomes, the rates of SLK have been steadily increasing in the United States [1]. Indications for SLK in the U.S. have been evolving with nonalcoholic steatohepatitis (NASH) cirrhosis becoming the leading indication for SLK in the United States [2,3]. NASH represents a unique challenge to the transplant community, as it is closely associated with metabolic syndrome [4]. This syndrome has been linked to pre-, peri- and post-operative clinical outcomes in liver transplant recipients. However, the impact of the metabolic syndrome, particularly, the component of obesity on SLK is relatively unknown.

The global obesity epidemic already affects >40% of the population of the United States [5]. Obesity, which




doi:10.1111/tri.13352

is associated with the metabolic syndrome, is a constellation of symptoms/disorders including diabetes, cardiovascular disease, liver steatosis, and hyperlipidemia [4]. As patients progress to cirrhosis, these metabolic comorbidities can also impact renal function. End stage liver disease is known to have an effect on kidney function with many patients developing significant kidney disease as hepatic function declines both in the form of hepatorenal syndrome but also chronic kidney disease [6]. Interestingly, a recent report implicates NASH as an independent risk factor for chronic kidney dysfunction (CKD) and is also an independent risk factor for the deterioration in renal function after liver transplantation [7].

There are currently no accepted national guidelines for BMI cut-off and there is significant heterogeneity in clinical practice across transplant centers in the U.S. In addition, the impact of obesity on SLK is largely lacking. Thus, the UNOS database was queried to determine the impact of obesity and degree of obesity on graft loss and patient survival in patients receiving SLK.

## Methods

A retrospective analysis of the UNOS STAR files that encompassed patients transplanted from Oct 10, 1987 – June 30, 2016. Data was requested through the following URL: https://optn.transplant.hrsa.gov/data/request-data/#.

BMIs used for analysis were recorded at the time of transplant. When BMI was not available, it was calculated based on the patient's height and weight. All patients that underwent SLK were selected for the analysis. The compiled demographic, pathologic and clinical variables included: gender, age, waiting time, physiological MELD, cold and warm ischemia times, and graft steatosis. The kidney donor risk index (KDRI) was also calculated for all kidney grafts [8]. The measured outcome variables included: treated acute rejection of the liver and kidney allografts as well as graft and patient survival.

### Statistical analysis

All means were expressed as mean ± standard deviation for continuous variables. Comparisons of continuous measures were assessed by the Kruskal–Wallis test. Categorical variables were analyzed by the Proportion test. Survival probabilities were estimated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analysis was performed using shared frailty Cox regression models, with region as a random effect, where graft or patient survival was used as an outcome [9]. In order to avoid any bias, all preoperative variables deemed important were selected for multivariate analysis. However, re-transplants and post-operative variables (except delayed graft function (DGF) were excluded from the analysis. Interactions between BMI and NASH, albumin and MELD with known risk factors were considered. The *P*-values for significant covariates from the final multivariate model and their corresponding univariate *P*-values are shown in the tables. The resulting hazard ratios and their 95% confidence limits from the multivariate analyses can be shown in a forest-plot. Descriptive summaries and forest plot were created in R 3.3.2 (URL: https://www.r-project.org/) while statistical analysis was performed using SAS v9.4 (SAS Institute, Cary, NC, USA). All analyses used a 5% level of statistical significance.

To accommodate variation over time of BMI on the patient mortality and/or graft failure, we also used a shared frailty Cox proportional hazards survival regression model using cubic B-splines to model the hazard ratio as a flexible function over time. The number of knots used was determined by the model with highest log-likelihood and the location of these interior knots were based on the quartiles of the observed time events to approximate equal number of events in each interval. To determine which models were used, the marginal log likelihood was compared between models treating BMI as spline, categorical, and continuous [10].

## Results

### Outcomes of obese patients following SLK

A total of 7,205 patients identified in the UNOS database from Oct 10, 1987 to June 30, 2016 and were included in this study. Patients were divided into 3 cohorts for analysis: normal weight recipients, (NW) BMI <30; overweight/obese recipients (OW), BMI 30–39; and morbidly obese recipients (MO), BMI ≥40. Demographic data for the three groups is provided (Table 1). The 3 cohorts were relatively similar except the prevalence of MO was lower in the African-American group. Higher rates of diabetes were noted in the OW and MO groups and not surprisingly progressively more patients had NASH as their primary liver diagnosis as the BMIs of the groups increased. The mean MELD at the time of transplant was higher in the OW and MO groups versus the NW group (28.4, 30.4, and 32.4 for NW, OW, and MO, respectively). Donor

characteristics including cold ischemia time were comparable across all three cohorts.

Not surprisingly, the overall length of stay was slightly longer for the morbidly obese group versus the OW and NW groups (Table 2). However, overall short and long-term survival was comparable between the NW, OW, and MO groups ($P = 0.74$) (Fig. 1). Similarly, kidney and liver graft short and long-term survival were not statistically significant ($P = 0.29$ and $P = 0.26$, respectively, Fig. 2a and b).

There was a trend toward a higher mean creatinine at 1 and 3 years post transplant although there was a significant amount of missing data which limits the interpretation of these findings. However, the number of failed grafts and patients returning to dialysis were equivalent across the three groups. Overall, rejection rates of the kidney were statistically similar at the end of 1 year post-transplant across all groups, but there was a slightly higher rate of treatment of kidney rejection in the first 6 months (6.01% vs. 9.2% for the NW versus MO, respectively).

### Risk factors for Graft Loss following SLK

A frailty model incorporating a cubic B-spline function for BMI effect into the baseline hazard function was used to estimate the covariate effects in association with patient and graft survival [11]. After working with different number of knots, we found a natural cubic spline with five internal knots converged well. In that model, the spline effect was found to be not significant ($P = 0.2703$, 0.2792, 0.2612 for patient, liver graft and kidney graft respectively) (Table 3). Thus, a frailty model treating BMI as either continuous or categorical (three-level categorization) was used to measure the association between all the covariates and the time to failure. Comparing the two models, the model with categorical BMI had a slightly larger likelihood value than that of the model treating BMI as continuous. Thus, adjusted HR and their inference results are presented for the full model treating BMI as three-level categorical variable along with interactions between BMI with albumin, MELD and NASH being reported.

Univariate and multivariate analysis was performed to determine factors associated with patient survival as well as kidney and liver graft survivals (Tables 4–6). BMI when used as a categorical or linear variable was not found to be a significant risk factor. In multivariate analysis, several recipient factors were found to be associated with poor overall survival (Table 4, Fig. 3) including: presence of HCV (HR 1.41, CI 1.23–1.59), delayed kidney graft function (HR 1.62, CI 1.41–1.85), donor's age (10 year increments, HR 1.07, CI 1.01–1.13), presence of diabetes (HR 1.22, CI 1.07–1.40), and KDRI <1.13 (HR 0.80, CI 0.68–0.94). Interestingly, hepatorenal syndrome (HR 0.60, CI 0.48–0.73) was associated with a lower risk of mortality post SLK. Risk factors for liver graft loss (Table 5, Fig. 4) were similar with the presence of diabetes mellitus (HR 1.23, CI 1.08–1.41), donor age (10 year increments, HR 1.084, CI 1.03–1.15), HCV (HR 1.40, CI 1.23–1.57), and delayed kidney graft function (HR 1.59, CI 1.39–1.81) being associated with worse outcomes. Hepatorenal syndrome (HR 0.58, CI 0.48–0.72) was associated with a lower risk of graft loss. Factors associated with kidney graft survival (Table 6, Fig. 5) were similar to the liver multivariate analysis with donor age (10 year increments, 1.10, CI 1.04–1.16), HCV (HR 1.33, CI 1.20–1.50), diabetes mellitus (HR 1.26, CI 1.10–1.43), and delayed kidney graft function (HR 1.78, CI 1.57–2.03) associated with graft loss. Hepatorenal syndrome (HR 0.64, CI 0.53–0.78) was associated with improved kidney graft survival. Interestingly, NASH was not a predictor of kidney graft, liver graft, or overall patient survival. Additionally, the transplant region random effect was found to be significant for all three outcomes of overall patient ($P = 0.001$), liver graft ($P = 0.009$), and kidney graft ($P = 0.0008$) survival with variability of the regions to be 0.017, 0.013, and 0.016 respectively. This indicates overall survival and graft survival were indeed correlated at the regional level.

Interactions between BMI and known risk factors were also performed to determine if in certain subgroups, morbid obesity was a factor in poor outcomes (Tables 4 and 5 and Tables S1–S3). Categorical BMI was used to examine interactions with higher MELDs (≥29), albumin <3, and in recipients with NASH. In all subset analyses, morbid obesity failed to show any significant interactions and results in poor outcomes both in overall patient and in liver and kidney graft survival. It can be seen however that albumin <3 and MELD ≥29 had more significant effect when BMI are normal for patient mortality and graft failure generally.

## Discussion

The prevalence of obesity continues to increase around the world resulting in higher rates of diabetes mellitus, hypertension, hyperlipidemia, fatty liver disease and cardiovascular disease [5]. This constellation of symptoms, often referred to as the metabolic syndrome, has resulted in rising rates of nonalcoholic fatty liver disease

**Table 1.** Patient demographics.

| | Normal weight $n = 5345$ | Obese $n = 1,677$ | Morbidly obese $n = 183$ | *P*-value |
|---|---|---|---|---|
| *Recipient characteristics* | | | | |
| Age, mean (SD) | 50.48 ± 15.16 | 55.04 ± 9.67 | 53.35 ± 8.99 | <0.001 |
| Gender, male/female | 3523/1821 | 1035/642 | 88/95 | <0.001 |
| Ethnicity | | | | |
| Caucasian | 3403 (64.00%) | 1172 (70.05%) | 128 (70.33%) | <0.001 |
| African American | 808 (15.20%) | 205 (12.25%) | 19 (10.44%) | 0.003 |
| Other | 1106 (20.80%) | 296 (17.69%) | 35 (19.23%) | 0.021 |
| Diagnosis | | | | |
| Hepatitis C | 1804 (37.99%) | 549 (35.28%) | 60 (34.48%) | 0.118 |
| Hepatitis B | 154 (2.88%) | 27 (1.61%) | 1 (0.55%) | 0.003 |
| NASH | 252 (4.72%) | 275 (16.40%) | 53 (28.96%) | <0.001 |
| Hepatocellular Cancer | 340 (6.36%) | 123 (7.33%) | 15 (8.20%) | 0.261 |
| Alcohol | 851 (15.92%) | 231 (13.77%) | 22 (12.02%) | 0.047 |
| Re-transplants (Liver) | 822 (15.38%) | 136 (8.11%) | 15 (8.20%) | <0.001 |
| Re-transplants (Kidney) | 394 (7.37%) | 50 (2.98%) | 2 (1.09%) | <0.001 |
| Comorbidities | | | | |
| Diabetes Mellitus | 737 (13.98%) | 360 (21.65%) | 38 (20.88%) | <0.001 |
| Dialysis at Txp | 3303 (61.81%) | 1037 (61.84%) | 117 (63.93%) | 0.844 |
| HRS at Txp | 736 (13.96%) | 254 (15.27%) | 38 (20.88%) | 0.018 |
| PVD | 99 (1.85%) | 42 (2.50%) | 6 (3.28%) | 0.125 |
| MELD at Txp | 28.38 ± 9.49 | 30.39 ± 8.59 | 32.41 ± 8.17 | <0.001 |
| GFR at Txp | 4.07 ± 2.51 | 3.98 ± 2.23 | 3.53 ± 1.77 | 0.116 |
| Ascites | 3544 (81.06%) | 1253 (85.06%) | 139 (83.23%) | 0.002 |
| Albumin | 3.05 ± 0.79 | 2.96 ± 0.76 | 2.88 ± 0.86 | <0.001 |
| Immunosuppression | | | | |
| Anti –T cell Induction | 1089 (21.14%) | 343 (20.83%) | 32 (17.68%) | 0.524 |
| IL-2 receptor Inhibitor | 1648 (33.09%) | 490 (30.43%) | 64 (36.16%) | 0.082 |
| CNI maintenance | 4123 (77.15%) | 1392 (83.01%) | 151 (82.51%) | <0.001 |
| MMF/Aza | 5124 (95.88%) | 1610 (96.00%) | 174 (95.08%) | 0.835 |
| Regions* | | | | |
| Region 1 | 230 (4.30%) | 66 (3.94%) | 8 (4.37%) | 0.803 |
| Region 2 | 601 (11.25%) | 170 (10.14%) | 17 (9.29%) | 0.344 |
| Region 3 | 838 (15.68%) | 229 (13.66%) | 27 (14.75%) | 0.129 |
| Region 4 | 532 (9.96%) | 167 (9.96%) | 22 (12.02%) | 0.655 |
| Region 5 | 990 (18.53%) | 260 (15.50%) | 34 (18.58%) | 0.018 |
| Region 6 | 92 (1.72%) | 38 (2.27%) | 3 (1.64%) | 0.344 |
| Region 7 | 777 (14.54%) | 284 (16.94%) | 42 (22.95%) | 0.001 |
| Region 8 | 318 (5.95%) | 103 (6.14%) | 7 (3.83%) | 0.452 |
| Region 9 | 234 (4.38%) | 59 (3.52%) | 4 (2.19%) | 0.124 |
| Region 10 | 414 (7.75%) | 170 (10.14%) | 10 (5.46%) | 0.003 |
| Region 11 | 318 (5.95%) | 131 (7.81%) | 9 (4.92%) | 0.018 |
| *Donor factors* | | | | |
| Age | 33.56 ± 15.46 | 35.90 ± 14.22 | 35.72 ± 14.56 | <0.001 |
| African American | 815 (15.35%) | 251 (15.05%) | 26 (14.21%) | 0.885 |
| Gender, male/female | 3214/2130 | 1304/1032 | 119/64 | 0.274 |
| Terminal Creatinine | 1.04 ± 0.79 | 1.11 ± 1.03 | 1.18 ± 1.31 | <0.001 |
| KDRI | 1.13 ± 0.36 | 1.14 ± 0.36 | 1.14 ± 0.42 | 0.841 |
| Cold Ischemia (Liver) | 7.30 ± 3.83 | 7.27 ± 3.94 | 7.06 ± 3.58 | 0.489 |
| Cold Ischemia (Kidney) | 12.57 ± 8.29 | 12.78 ± 9.04 | 12.56 ± 6.69 | 0.632 |

SD, standard deviation; NASH, non-alcoholic steatohepatitis; Txp, transplant; HRS, hepatorenal syndrome; PVD, peripheral vascular disease; MELD, model for end-stage liver disease; GFR, glomerular filtration rate; IL-2, interleukin-2; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; Aza, azathioprine; KDRI, kidney donor risk index; UNOS, United Network for Organ Sharing.

*Geographic regions as designated by UNOS.

**Table 2.** Recipient outcomes.

| | Normal weight $n = 5589$ | Obese $n = 1669$ | Morbidly obese $n = 180$ | *P*-value |
|---|---|---|---|---|
| Length of Stay | 25.87 ± 91.01 | 23.03 ± 25.23 | 27.80 ± 30.70 | 0.004 |
| Delayed Graft Function (Kidney) | 1001 (18.85%) | 385 (23.04%) | 58 (31.87%) | <0.001 |
| Creatinine (@ 1 years) – 68%* | 1.40 ± 0.92 | 1.48 ± 0.82 | 1.58 ± 1.19 | <0.001 |
| Creatinine (@ 3 years) – 47%* | 1.46 ± 1.03 | 1.54 ± 0.98 | 1.78 ± 1.51 | <0.001 |
| Creatinine (@ 5 years) – 33%* | 1.49 ± 1.07 | 1.54 ± 1.05 | 1.72 ± 1.21 | 0.004 |
| Rejection | | | | |
| Liver (1 year) | 352 (12.01%) | 102 (10.38%) | 14 (12.84%) | 0.355 |
| Kidney (1 year) | 317 (10.05%) | 87 (8.59%) | 14 (12.73%) | 0.226 |
| Cause of death | | | | |
| Cardiovascular | 208 (11.87%) | 65 (12.38%) | 8 (13.33%) | 0.904 |
| Infection | 391 (22.30%) | 108 (20.57%) | 12 (20.00%) | 0.659 |
| Cancer | 138 (7.87%) | 43 (8.19%) | 3 (5.00%) | 0.685 |

*Data available on % of patients.

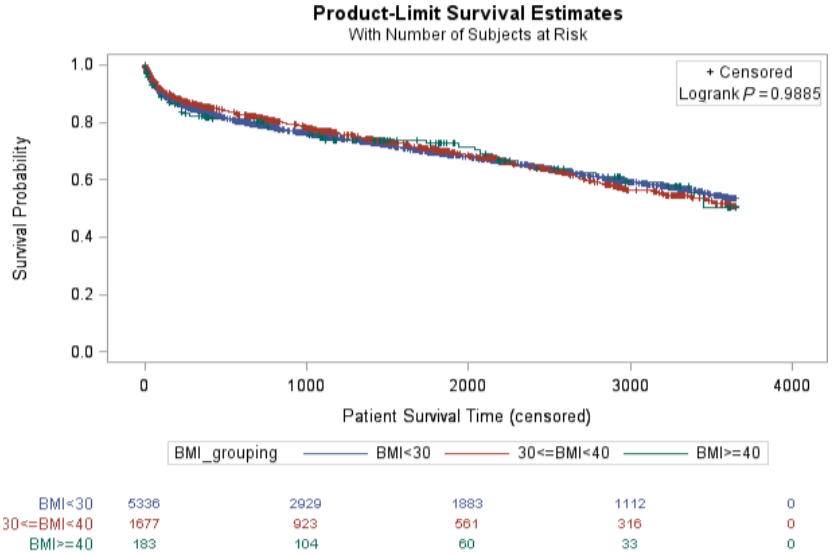


**Figure 1** Patient Survival. Kaplan–Meier curve depicting overall survival in patients that underwent SLK with BMI <30 (solid line), 30–39 (dashed line), >40 (dotted line).

(NAFLD) and NASH [12]. NASH is also now becoming one of the leading indications for liver transplantation [2]. In addition to being a burden to a person's well-being and health, obesity is also thought to have a global effect on health care increasing health care costs [13]. In the perioperative setting, morbidly obese patients in many cases have higher rates of perioperative complications [14,15]. In light of this, it is imperative that the results of organ transplantation in obese patients be comparable to those of non-obese patients in order to ensure that transplanted organs are not wasted.

Very limited data is presently available for SLK in morbidly obese patients. This is likely reflective of the fact that morbid obesity is generally viewed as contraindication to both isolated kidney and/or liver transplantation at many centers. A recent publication by Singhal *et al.* examined the outcomes of SLK in NASH patients and found poorer long term kidney graft survival in patients with NASH and BMI >30 compared to patients with primary biliary cirrhosis, primary sclerosing cholangitis, and alcohol-related liver disease [3]. These findings were irrespective of the presence of diabetes mellitus. In this study using the UNOS database, we found no difference in the long-term patient and graft survival (liver and kidney) outcomes of SLK in obese and morbidly obese individuals as compared to non-obese individuals. Although, higher GFRs were



Transplant International 2019; 32: 206–217

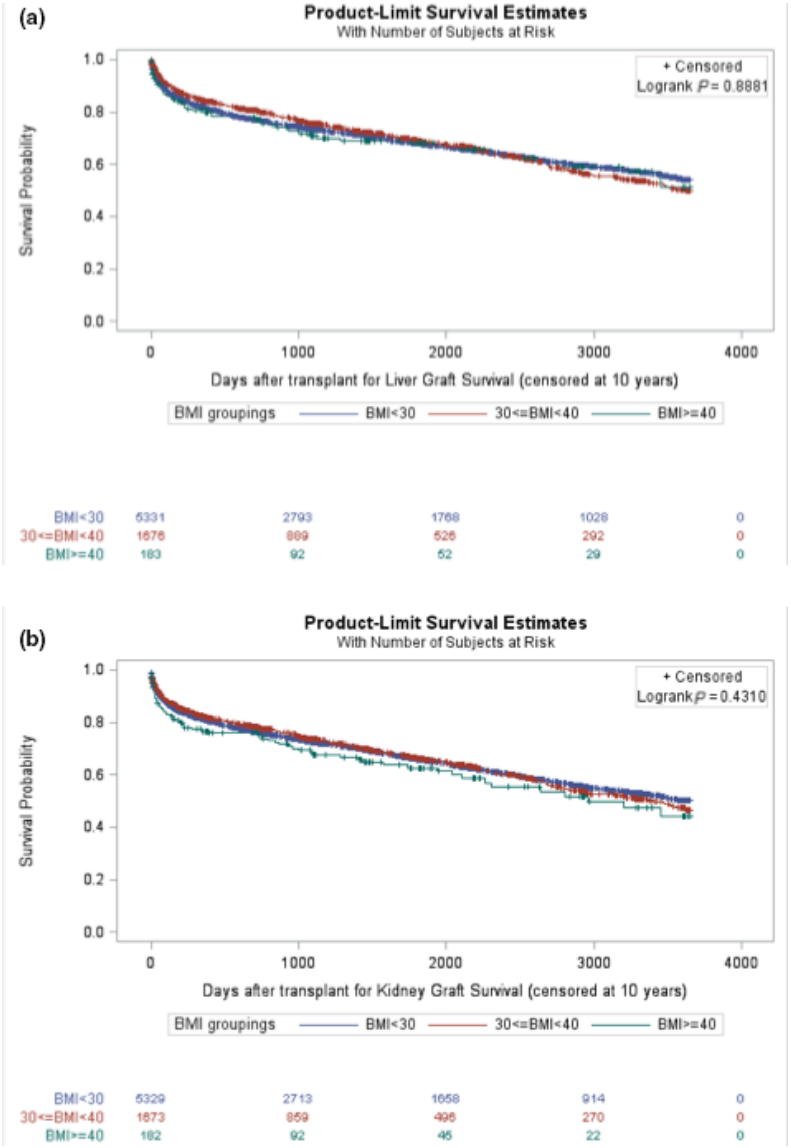


**Figure 2** Graft Survival with Kaplan–Meier curve depicting individual graft survival for liver (a) and Kidney (b) in patients that underwent SLK with BMI <30 (solid line), 30–39 (dashed line), >40 (dotted line).

reported at 1 and 3 years for patients with higher BMIs, there was a large amount of missing data that limits the interpretation of these findings. Reassuringly though, there was no appreciable difference in graft loss over time between the NW, OW, and MO cohorts.

In 2005 in the AASLD guidelines for liver transplantation, morbid obesity was listed as a contraindication to transplantation [16]. This recommendation was largely based on old UNOS data that suggested higher incidences of primary non-function, cardiovascular events and mortality in morbidly obese patients [17]. These recommendations have led to many centers using morbid obesity as a relative or absolute contraindication to liver transplantation. More recent reviews of the SRTR database have contradicted these results and have demonstrated no difference in short and long-term graft and patient survival [18,19]. Several single center studies have also supported these findings suggesting that improvements in liver transplantation techniques and

**Table 3.** Model comparisons.

| | Marginal LogLikelihood |
|---|---|
| Patient survival | |
| BMI Spline cubic spline | −9876.4 |
| BMI continuous | −9891.5 |
| BMI categorical | −9890.3 |
| Liver graft | |
| BMI Spline cubic spline | −9949.3 |
| BMI continuous | −9960.9 |
| BMI categorical | −9957.5 |
| Kidney graft | |
| BMI Spline cubic spline | −10600.1 |
| BMI continuous | −10609.9 |
| BMI categorical | −10606.6 |

**Table 4.** Univariate and multivariate analysis for patient survival following SLK.

| Parameter | UV *P*-value | MV *P*-value | HR (95% CI)* |
|---|---|---|---|
| BMI Grouping (as compared to Normal) | | | |
| Obese | 0.93 | 0.7974 | 1.028 (0.834, 1.267) |
| Morbidly Obese | 0.88 | 0.4208 | 0.833 (0.533, 1.300) |
| Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.0059 | 0.4945 | 1.056 (0.903, 1.235) |
| Others | 0.0005 | 0.0013 | 0.771 (0.659, 0.903) |
| Diabetes Mellitus | <0.0001 | 0.0032 | 1.222 (1.069, 1.396) |
| NASH | *0.4829* | 0.5245 | 0.906 (0.667, 1.229) |
| HRS | <0.0001 | <0.0001 | 0.595 (0.482, 0.734) |
| HCV | <0.0001 | <0.0001 | 1.410 (1.250, 1.590) |
| MELD < 29 | 0.0010 | 0.2903 | 0.872 (0.677, 1.124) |
| KDRI < 1.13 | <0.0001 | 0.0070 | 0.796 (0.675, 0.940) |
| PVD | 0.1293 | 0.8947 | 1.026 (0.698, 1.508) |
| DGF | <0.0001 | <0.0001 | 1.615 (1.411, 1.847) |
| Dialysis at TX | 0.6676 | 0.0200 | 1.168 (1.025, 1.331) |
| CIT (Liver) <7.3 | <0.0001 | 0.1646 | 0.913 (0.803, 1.038) |
| CIT (Kidney) <12.6 | 0.0018 | 0.5232 | 0.957 (0.835, 1.096) |
| Males vs. Females | 0.2221 | 0.9352 | 0.995 (0.881, 1.123) |
| Albumin < 3 | <0.0001 | 0.5159 | 1.082 (0.853, 1.372) |
| Ascites | 0.4361 | 0.4417 | 1.067 (0.905, 1.258) |
| Age (for 10 years increase) | <0.0001 | 0.2147 | 1.035 (0.980, 1.093) |
| Creatinine at TX (for 1-unit increase) | 0.0012 | 0.0004 | 0.952 (0.926, 0.978) |
| Donor Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.9775 | 0.5267 | 1.052 (0.899, 1.232) |
| Others | 0.0085 | 0.0973 | 1.139 (0.977, 1.329) |
| Donor Males vs. Females | 0.1020 | 0.5236 | 1.040 (0.923, 1.171) |
| Donor Age (for 10 years increase) | <0.0001 | 0.0185 | 1.070 (1.011, 1.132) |
| Donor Creatinine (for 1-unit increase) | 0.0343 | 0.9254 | 1.004 (0.928, 1.085) |
| Interactions (BMI group by MELD) | | | |
| Obese by MELD <29 | – | 0.1015 | Details Below |
| Morbidly Obese by MELD <29 | – | 0.8220 | Details Below |
| Interactions (BMI group by Albumin) | | | |
| Obese for Albumin <3 | – | 0.7449 | Details Below |
| Morbidly Obese for Albumin <3 | – | 0.4137 | Details Below |
| Interactions (BMI group by NASH) | | | |
| Obese by NASH | – | 0.0976 | Details Below |
| Morbidly Obese by NASH | – | 0.4605 | Details Below |

UV, univariate; MV, multivariate; BMI, body mass index; NASH, non-alcoholic steatohepatitis; HRS, hepatorenal syndrome; HCV, hepatitis C virus; MELD, model for end stage liver disease; KDRI, kidney donor risk index; PVD, peripheral vascular disease; DGF, delayed graft function; TX, transplant; CIT, cold ischemia time.

*Hazard Ratio from PH multivariate model.

patient selection can result in similar outcomes for morbidly obese patients. However, some studies have suggested an increase in length of hospital stay post liver transplant and an increase in perioperative complications. These, however, do not appear to effect long-term outcomes. The accuracy and utility of BMI in patients with ESLD has also been called into question and the use of a modified BMI that also takes into account serum albumin has been shown by one group to more accurately predict long-term outcomes [20].

Similarly, a BMI of 40 is considered a contraindication to kidney transplantation at many centers across the United States including our own center. In addition, in 2007, insurance companies began to deny transplantation for patients with BMIs >40. These recommendations are based on studies that demonstrated initial poor kidney function with higher rates of DGF and decreased long-term graft survival in obese patients [21,22]. Morbidly obese patients were also found to have increased rates of rejection and higher



Transplant International 2019; 32: 206–217

**Table 5.** Univariate and multivariate analysis for liver graft survival following SLK.

| Parameter | UV *P*-value | MV *P*-value | HR (95% CI)* |
|---|---|---|---|
| BMI Grouping (as compared to Normal) | | | |
| Obese | 0.80 | 0.6908 | 1.044 (0.846, 1.287) |
| Morbidly Obese | 0.68 | 0.3789 | 0.807 (0.501, 1.300) |
| Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.0049 | 0.3075 | 1.084 (0.929, 1.265) |
| Others | 0.0015 | 0.0024 | 0.783 (0.669, 0.917) |
| Diabetes Mellitus | <0.0001 | 0.0023 | 1.231 (1.077, 1.407) |
| NASH | 0.2149 | 0.1687 | 0.792 (0.569, 1.104) |
| HRS | <0.0001 | <0.0001 | 0.584 (0.475, 0.718) |
| HCV | <0.0001 | <0.0001 | 1.392 (1.234, 1.570) |
| MELD < 29 | 0.0109 | 0.8357 | 0.974 (0.761, 1.247) |
| KDRI < 1.13 | <0.0001 | 0.0156 | 0.816 (0.692, 0.962) |
| PVD | 0.0815 | 0.7351 | 1.066 (0.735, 1.547) |
| DGF | <0.0001 | <0.0001 | 1.589 (1.389, 1.817) |
| Dialysis at TX | 0.8179 | 0.0365 | 1.150 (1.009, 1.310) |
| CIT (Liver) < 7.3 | <0.0001 | 0.0888 | 0.895 (0.787, 1.017) |
| CIT (Kidney) < 12.6 | <0.0001 | 0.3090 | 0.933 (0.815, 1.067) |
| Males vs. Females | 0.4676 | 0.8091 | 0.985 (0.873, 1.112) |
| Albumin < 3 | <0.0001 | 0.4630 | 1.093 (0.862, 1.387) |
| Ascites | 0.0996 | 0.7268 | 1.029 (0.875, 1.210) |
| Age (for 10 years increase) | 0.0188 | 0.8568 | 1.005 (0.953, 1.060) |
| Creatinine at TX (for 1-unit increase) | 0.0018 | 0.0007 | 0.955 (0.929, 0.981) |
| Donor Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.4534 | 0.1734 | 1.114 (0.954, 1.302) |
| Others | 0.9127 | 0.0877 | 1.144 (0.980, 1.335) |
| Donor Males vs. Females | 0.0063 | 0.7272 | 1.021 (0.907, 1.150) |
| Donor Age (for 10 years increase) | <0.0001 | 0.0047 | 1.084 (1.025, 1.147) |
| Donor Creatinine (for 1-unit increase) | 0.0673 | 0.8430 | 1.007 (0.934, 1.088) |
| Interactions (BMI group by MELD) | | | |
| Obese by MELD < 29 | – | 0.0936 | Details Below |
| Morbidly Obese by MELD < 29 | – | 0.5582 | Details Below |
| Interactions (BMI group by Albumin) | | | |
| Obese for Albumin < 3 | – | 0.5058 | Details Below |
| Morbidly Obese for Albumin < 3 | – | 0.4182 | Details Below |
| Interactions (BMI group by NASH) | | | |
| Obese by NASH | – | 0.0635 | Details Below |
| Morbidly Obese by NASH | – | 0.1357 | Details Below |

UV, univariate; MV, multivariate; BMI, body mass index; NASH, non-alcoholic steatohepatitis; HRS, hepatorenal syndrome; HCV, hepatitis C virus; MELD, model for end stage liver disease; KDRI, kidney donor risk index; PVD, peripheral vascular disease; DGF, delayed graft function; TX, transplant; CIT, cold ischemia time.

*Hazard Ratio from PH multivariate model.

rates of DGF similar to the findings in this study [22]. However, several more recent studies have suggested that the long-term outcomes of kidney transplantation are acceptable and BMI should not be used to determine candidacy for kidney transplant [23,24]. The increase in rejection could be accounted for due to possible under dosing of immunosuppression due to a cap on the upper dosage limit. It is possible that a more aggressive host immune system exists in the higher chronic inflammatory state known to be associated with obesity [25,26]. Factors that could explain this finding include a sampling bias in that patients with acute rejection received closer follow-up, timelier diagnosis and more optimal immunosuppression compared with those without rejection. Given the inherent limitations of a registry study, there could also be 'non-response bias' resulting in an under-reporting of acute rejection episodes.

**Table 6.** Univariate and multivariate analysis for kidney graft survival following SLK.

| Parameter | UV *P*-value | MV *P*-value | HR (95% CI)* |
|---|---|---|---|
| BMI Grouping (as compared to Normal) | | | |
| Obese | 0.896 | 0.5003 | 1.070 (0.879, 1.303) |
| Morbidly Obese | 0.195 | 0.3831 | 0.823 (0.531, 1.275) |
| Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.0031 | 0.2592 | 1.091 (0.938, 1.268) |
| Others | 0.0027 | 0.0008 | 0.771 (0.662, 0.898) |
| Diabetes Mellitus | <0.0001 | 0.0005 | 1.256 (1.104, 1.430) |
| NASH | 0.4107 | 0.3351 | 0.864 (0.641, 1.163) |
| HRS | <0.0001 | <0.0001 | 0.639 (0.526, 0.777) |
| HCV | <0.0001 | <0.0001 | 1.326 (1.179, 1.491) |
| MELD < 29 | 0.0059 | 0.2602 | 0.869 (0.681, 1.110) |
| KDRI < 1.13 | <0.0001 | 0.0042 | 0.793 (0.677, 0.929) |
| PVD | 0.2389 | 0.9938 | 1.001 (0.691, 1.453) |
| DGF | <0.0001 | <0.0001 | 1.782 (1.569, 2.025) |
| Dialysis at TX | 0.5549 | 0.0192 | 1.164 (1.025, 1.322) |
| CIT (Liver) < 7.3 | <0.0001 | 0.0549 | 0.886 (0.783, 1.003) |
| CIT (Kidney) < 12.6 | <0.0001 | 0.3901 | 0.945 (0.829, 1.076) |
| Males vs. Females | 0.0661 | 0.5021 | 0.961 (0.855, 1.079) |
| Albumin < 3 | <0.0001 | 0.6018 | 1.062 (0.848, 1.330) |
| Ascites | 0.0311 | 0.9600 | 0.996 (0.853, 1.163) |
| Age (for 10 years increase) | 0.3695 | 0.8417 | 0.995 (0.945, 1.047) |
| Creatinine at TX (for 1-unit increase) | 0.0289 | 0.0069 | 0.965 (0.940, 0.990) |
| Donor Ethnicity (vs. Caucasians) | | | |
| African Americans | 0.4911 | 0.1839 | 1.107 (0.953, 1.287) |
| Others | 0.8224 | 0.0931 | 1.137 (0.979, 1.321) |
| Donor Males vs. Females | 0.0019 | 0.6481 | 1.027 (0.916, 1.152) |
| Donor Age (for 10 years increase) | <0.0001 | 0.0007 | 1.098 (1.040, 1.159) |
| Donor Creatinine (for 1-unit increase) | 0.0148 | 0.6546 | 1.017 (0.946, 1.093) |
| Interactions (BMI group by MELD) | | | |
| Obese by MELD < 29 | – | 0.2541 | Details Below |
| Morbidly Obese by MELD < 29 | – | 0.6216 | Details Below |
| Interactions (BMI group by Albumin) | | | |
| Obese for Albumin < 3 | – | 0.6445 | Details Below |
| Morbidly Obese for Albumin < 3 | – | 0.3530 | Details Below |
| Interactions (BMI group by NASH) | | | |
| Obese by NASH | – | 0.0951 | Details Below |
| Morbidly Obese by NASH | – | 0.0958 | Details Below |

UV, univariate; MV, multivariate; BMI, body mass index; NASH, non-alcoholic steatohepatitis; HRS, hepatorenal syndrome; HCV, hepatitis C virus; MELD, model for end stage liver disease; KDRI, kidney donor risk index; PVD, peripheral vascular disease; DGF, delayed graft function; TX, transplant; CIT, cold ischemia time.

*Hazard Ratio from PH multivariate model.

The link between fatty liver disease and kidney dysfunction is just coming to light [27]. In addition to known risk factor associated with the metabolic syndrome (i.e. hypertension and diabetes), NALFD also results in chronic inflammatory state that induces injury to the kidneys [27,28]. It is possible that in addition to providing some immunologic protection to the kidney, SLK also gets rid of the necroinflammatory response associated with NAFLD/NASH. This could potentially be one explanation why we see better long-term outcomes in SLK in the MO group as compared to morbidly obese patients that undergo kidney transplant alone.

Obesity and the recurrence of NASH in the post-transplant setting is not insignificant [29]. Although meaningful weight loss in the pre-transplant setting is likely unrealistic, weight loss post transplant might help to obtain optimal long-term results following transplantation. Bariatric



Transplant International 2019; 32: 206–217

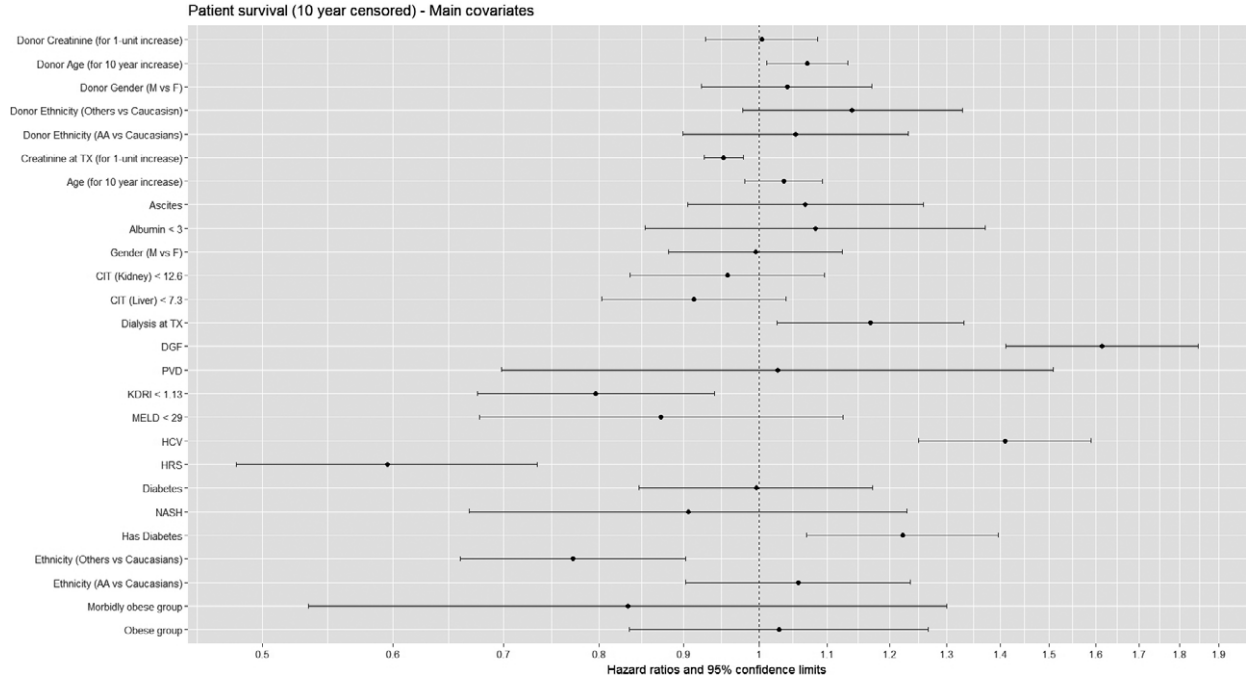


**Figure 3** Forest plot indicating hazard ratios and 95% confidence limit from multivariate analysis for Patient Survival.

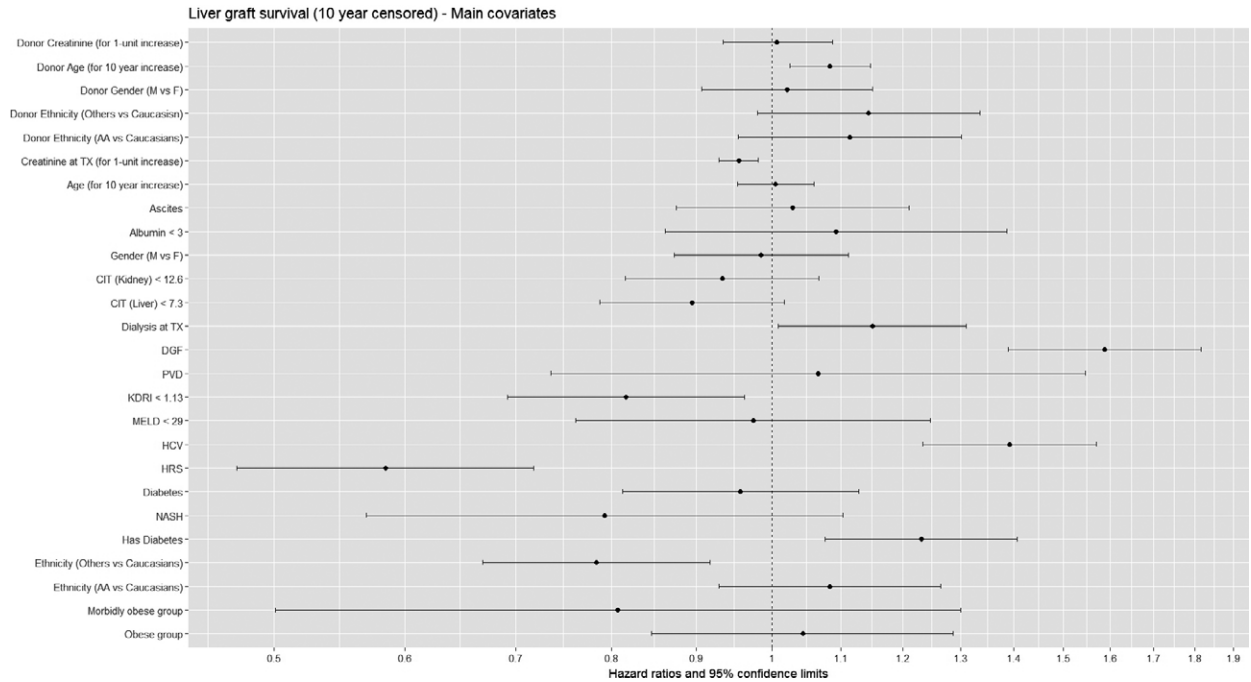


**Figure 4** Forest plot indicating hazard ratios and 95% confidence limit from multivariate analysis for liver graft loss.

surgery either at the time of transplant or post transplantation has been performed successfully and reported [30–33]. The Mayo Clinic has performed the largest series of liver transplantation immediately followed by sleeve gastrectomy and have obtained excellent long-term results [32]. A recent series from Israel confirmed the feasibility of performing a combined liver transplant and sleeve gastrectomy [34]. Many of these patients had a significant

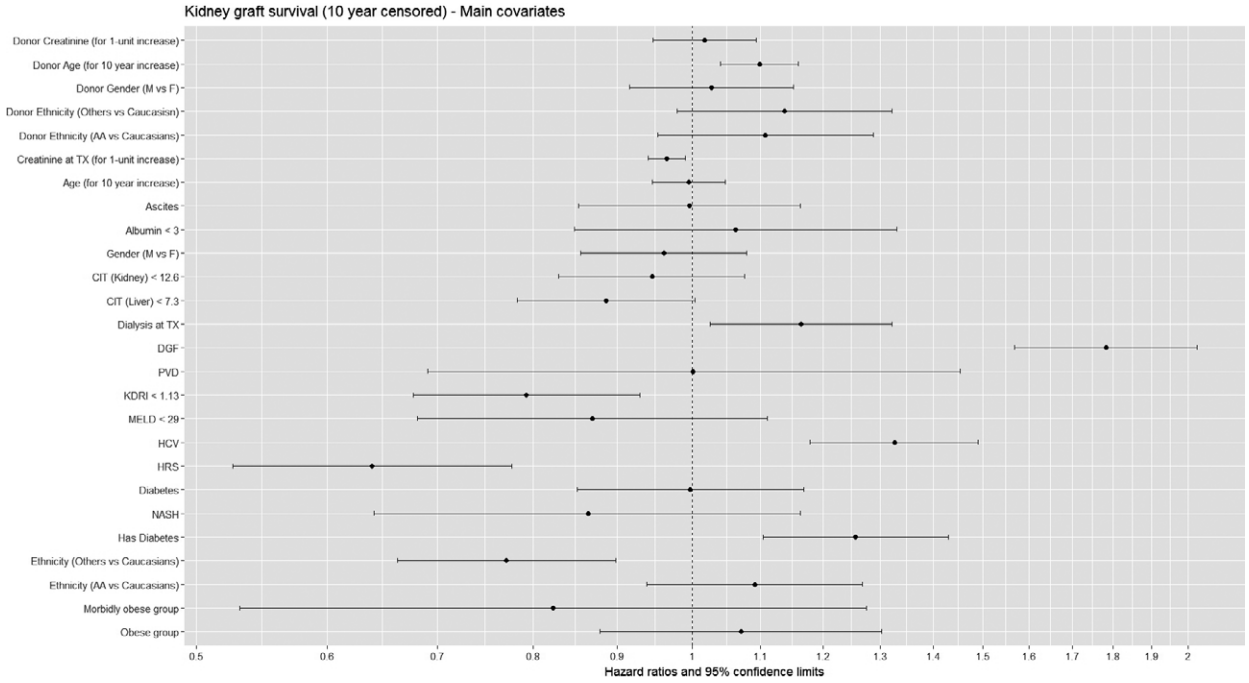


**Figure 5** Forest plot indicating hazard ratios and 95% confidence limit from multivariate analysis for kidney graft loss.

amount of weight loss that was largely maintained in the long-term.

While this is one of the largest database reviews of SLK in obesity, this study has some limitations. Like all large studies, the data sets are not complete and are compiled from multiple centers that have differing practices, experience, and outcomes. Limited information is also collected in these databases limiting the breadth of examination of the different cohorts. The number of patients in the MO group is also small in comparison to the other two groups. In addition, there might be confounding variables that are not captured by the SRTR (e.g. cardiovascular risk factors), and thus the MO patients might have been much healthier (i.e. less heart disease or other comorbidities) than the other groups. A large, prospective trial would be needed to address many more in depth questions regarding SLK in obese patients.

In conclusion, outcomes from SLK are comparative regardless of BMI. Patients with BMIs >40 should be carefully assessed for candidacy for SLK and should not be automatically denied a lifesaving combined organ transplant solely based on BMI. Larger studies are warranted to examine SLK in obese patients to generate more conclusive guidelines. However, a trial should be done in the setting of post-transplant obesity treatment to try to mitigate the presumed detrimental effect of recurrent NASH on long-term liver and kidney allograft survival.

## Authorship

JWY: performed data collection/analysis and wrote manuscript. GG: designed research study and performed analyzed data. LK and DB: performed data analysis and critical revision of manuscript. MSS, CSB, RTS, and ML: performed critical revision of the manuscript. TWR: designed research study, performed analyzed data, and wrote the manuscript.

## Conflicts of interest

The authors have declared no conflicts of interest.

## Funding

The authors have declared no funding.

## SUPPORTING INFORMATION

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

**Table S1.** Interaction terms for patient survival following SLK.

**Table S2.** Interaction terms for liver graft survival following SLK.

**Table S3.** Interaction terms for kidney graft survival following SLK.

## REFERENCES


1. Eason JD, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of consensus conference on simultaneous liver kidney transplantation (SLK). *Am J Transplant* 2008; **8**: 2243.
2. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; **141**: 1249.
3. Singal AK, Hasanin M, Kaif M, Wiesner R, Kuo YF. Nonalcoholic steatohepatitis is the most rapidly growing indication for simultaneous liver kidney transplantation in the United States. *Transplantation* 2016; **100**: 607.
4. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA* 2002; **287**: 356.
5. Ng M, Fleming T, Robinson M, *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766.
6. Busk TM, Bendtsen F, Moller S. Hepatorenal syndrome in cirrhosis: diagnostic, pathophysiological, and therapeutic aspects. *Expert Rev Gastroenterol Hepatol* 2016; 10.1080/17474124.2016.1196132 [Epub ahead of print]
7. Fussner LA, Charlton MR, Heimbach JK, *et al.* The impact of gender and NASH on chronic kidney disease before and after liver transplantation. *Liver Int* 2014; **34**: 1259.
8. Feng S, Goodrich NP, Bragg-Gresham JL, *et al.* Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
9. Hougaard P. Frailty models for survival data. *Lifetime Data Anal* 1995; **1**: 255.
10. Lam KF, Kuk AY. A marginal likelihood approach to estimation in frailty models. *J Am Stat Assoc* 1997; **92**: 985.
11. Ruppert D, Wand MP, Carroll RJ. *Semiparametric Regression. Cambridge Series in Statistical and Probablistic Mathematics*. Cambridge, UK: Cambridge University Press, 2003.
12. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73.
13. Hammond RA, Levine R. The economic impact of obesity in the United States. *Diabetes Metab Syndr Obes* 2010; **3**: 285.
14. Doyle SL, Lysaght J, Reynolds JV. Obesity and post-operative complications in patients undergoing non-bariatric surgery. *Obes Rev* 2010; **11**: 875.
15. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009; **250**: 166.
16. Murray KF, Carithers RL Jr, AASLD. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology* 2005; **41**: 1407.
17. Nair S, Cohen DB, Cohen MP, Tan H, Maley W, Thuluvath PJ. Postoperative morbidity, mortality, costs, and long-term survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 2001; **96**: 842.
18. Orci LA, Majno PE, Berney T, Morel P, Mentha G, Toso C. The impact of wait list body mass index changes on the outcome after liver transplantation. *Transplant Int* 2013; **26**: 170.
19. Singhal A, Wilson GC, Wima K, *et al.* Impact of recipient morbid obesity on outcomes after liver transplantation. *Transplant Int* 2015; **28**: 148.
20. Tanaka T, Renner EL, Selzner N, Therapondos G, Lilly LB. The impact of obesity as determined by modified body mass index on long-term outcome after liver transplantation: Canadian single-center experience. *Transpl Proc* 2013; **45**: 2288.
21. Armstrong KA, Campbell SB, Hawley CM, Johnson DW, Isbel NM. Impact of obesity on renal transplant outcomes. *Nephrology* 2005; **10**: 405.
22. Gore JL, Pham PT, Danovitch GM, *et al.* Obesity and outcome following renal transplantation. *Am J Transplant* 2006; **6**: 357.
23. Bennett WM, McEvoy KM, Henell KR, Pidikiti S, Douzdjian V, Batiuk T. Kidney transplantation in the morbidly obese: complicated but still better than dialysis. *Clin Transplant* 2011; **25**: 401.
24. Cannon RM, Jones CM, Hughes MG, Eng M, Marvin MR. The impact of recipient obesity on outcomes after renal transplantation. *Ann Surg* 2013; **257**: 978.
25. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol* 2011; **29**: 415.
26. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. *Nature* 2017; **542**: 177.
27. Musso G, Gambino R, Tabibian JH, *et al.* Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; **11**: e1001680.
28. Machado MV, Goncalves S, Carepa F, Coutinho J, Costa A, Cortez-Pinto H. Impaired renal function in morbid obese patients with nonalcoholic fatty liver disease. *Liver Int* 2012; **32**: 241.
29. Molloy RM, Komorowski R, Varma RR. Recurrent nonalcoholic steatohepatitis and cirrhosis after liver transplantation. *Liver Transpl Surg* 1997; **3**: 177.
30. Al-Nowaylati AR, Al-Haddad BJ, Dorman RB, *et al.* Gastric bypass after liver transplantation. *Liver Transpl* 2013; **19**: 1324.
31. Duchini A, Brunson ME. Roux-en-Y gastric bypass for recurrent nonalcoholic steatohepatitis in liver transplant recipients with morbid obesity. *Transplantation* 2001; **72**: 156.
32. Heimbach JK, Watt KD, Poterucha JJ, *et al.* Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. *Am J Transplant* 2013; **13**: 363.
33. Tichansky DS, Madan AK. Laparoscopic Roux-en-Y gastric bypass is safe and feasible after orthotopic liver transplantation. *Obes Surg* 2005; **15**: 1481.
34. Nesher E, Mor E, Shlomai A, *et al.* Simultaneous liver transplantation and sleeve gastrectomy: prohibitive combination or a necessity? *Obes Surg* 2017; **27**: 1387.