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ORIGINAL ARTICLE

Burden of early hospitalization after simultaneous liver–kidney transplantation: Results from the US Multicenter SLKT Consortium

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Abstract

The burden of early hospitalization (within 6 months) following simultaneous liver–kidney transplant (SLKT) is not known. We examined risk factors associated with early hospitalization after SLKT and their impact on patient mortality conditional on 6-month survival. We used data from the US Multicenter SLKT Consortium cohort study of all adult SLKT recipients between 2002 and 2017 who were discharged alive following SLKT. We used Poisson regression to model rates of early hospitalizations after SLKT. Cox regression was used to identify risk factors associated with mortality conditional on survival at 6 months after SLKT. Median age (N = 549) was 57.7 years (interquartile range [IQR], 50.6–63.9) with 63% males and 76% Whites; 33% had hepatitis C virus, 20% had non–alcohol-associated fatty liver disease, 23% alcohol-associated liver disease, and 24% other etiologies. Median body mass index (BMI) and Model for End-Stage Liver Disease–sodium scores were 27.2 kg/m^2 (IQR, 23.6–32.2 kg/m^2) and 28 (IQR, 23–34), respectively. Two-thirds of the cohort had at least one hospitalization within the first 6 months of SLKT. Age, race, hospitalization at SLKT, diabetes mellitus, BMI, and discharge to subacute rehabilitation (SAR) facility after SLKT were independently associated with a high incidence rate ratio of early hospitalization. Number of hospitalizations within the first 6 months did not affect conditional survival. Early hospitalizations after SLKT were very common but did not affect conditional

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; DGF, delayed graft function; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; KDPI, Kidney Donor Profile Index; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease–sodium; NAFLD, non–alcohol-associated fatty liver disease; OPTN, Organ Procurement and Transplantation Network; PI, principal investigator; RRI, renal risk index; RRT, renal replacement therapy; SAR, subacute rehabilitation; SE, standard error; SLKT, simultaneous liver–kidney transplantation; WIT, warm ischemia time.

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survival. Although most of the risk factors for early hospitalization were nonmodifiable, discharge to SAR after initial SLKT was associated with a significantly higher incidence rate of early hospitalization. Efforts and resources should be focused on identifying SLKT recipients at high risk for early hospitalization to optimize their predischarge care, discharge planning, and long-term follow-up.

INTRODUCTION

Simultaneous liver–kidney transplantation (SLKT) incidence has risen significantly since the inception of Model for End-Stage Liver Disease (MELD)–based allocation.[1–3] As non–alcohol-associated fatty liver disease (NAFLD) has become one of the leading indications for liver transplantation (LT) with the rise of the obesity epidemic, this has further driven an increase in SLKT because of concomitant advanced chronic kidney disease (CKD) in these patients.[1,4] A recent study from the US Multicenter SLKT Consortium showed that compared with calendar year 2002, SLKT recipients in 2017 were older by 7 years and more likely to have CKD.[5] Although the 1-year post-SLKT survival rate has improved over time, 16% will have Stage 4–5 CKD by 5 years following SLKT.[5,6]

Early hospitalizations after solid organ transplant affect patient survival, increase morbidity and costs, and negatively impact quality of life and other patient-related outcomes.[7–10] Limiting readmissions from many medical conditions[11,12] and surgical procedures[12] is considered a benchmark of quality in health care. Although deceased donor organ transplantation is not included in this category, early hospitalization affects 1- and 3-year patient and graft survival rates and may indirectly affect the program-specific reports—a metric of transplant center performance.[13]

The 30-day readmission rate after kidney transplant is substantial and reported to be 32% in the United States.[8,14,15] One study that used linked data from the Scientific Registry of Transplant Recipients and Centers from Medicare and Medicaid Services found that 58% had at least one hospitalization in the first 6 months after discharge from the index LT hospitalization.[10] However, no studies to date have examined the incidence and risk factors of early hospitalization among SLKT recipients, creating a significant knowledge gap in the understanding of early hospitalizations after SLKT.

Therefore, we examined the incidence and risk factors associated with early hospitalization after SLKT. Furthermore, we evaluated the impact of early hospitalization on patient mortality conditional on 6-month survival.

PATIENTS AND METHODS

Patients and data collection

The US Multicenter SLKT Consortium (Figure 1)[5,6] includes candidate, donor, and recipient data on all adult (aged ≥18 years) recipients of SLKT performed at six centers (Columbia University Irving Medical Center; Duke University; Northwestern University; University of California, San Francisco; Michigan Medicine, University of Michigan; University of Washington) in six different United Network of Organ Sharing regions between February 2002 to June 2017 as described previously.[5,6] The current study included the SLKT recipients who were discharged alive after their index transplant hospitalization. Because the practices and SLKT policies changed during the span of 15 years, we divided the time period as Era 1 (2002–2008; first consensus conference in 2008[16]), Era 2 (2009–2012; Organ Procurement and Transplantation Network [OPTN] policy was instituted in 2009), and Era 3 (2012–2017; second consensus conference resulted in changes in sustained acute kidney injury [AKI] definitions[17]) as described previously.[5]

Each center provided the counts of hospitalization (between discharge from the index hospitalization and 6 months of SLKT, 6–12 months of SLKT, and >12 months of LT) and causes of hospitalization based on the discharge diagnosis. Because the aim of the study was to examine the burden of early hospitalization, we focused on hospitalization within the first 6 months of SLKT. Within the first 6 months, we further

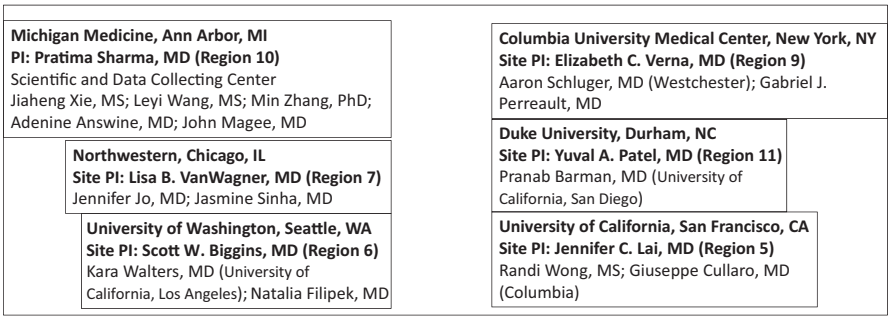

FIGURE 1 The US multicenter SLKT consortium

collected the counts of episodes of hospitalizations between discharge from index SLKT and 30, 31–90, and 91–180 days.

The reasons for early hospitalization were divided into broad categories a priori: infection (any positive blood culture, urine culture, or pneumonia), kidney related (kidney allograft related, such as AKI, electrolyte imbalance, renal replacement therapy [RRT]), liver related (liver allograft related, such as biliary or vascular complications), biopsy-proven rejection (liver and kidney), cardiovascular (acute coronary syndrome, arrhythmia, congestive heart failure, stroke, and peripheral vascular disease), and others (all other reasons that did not fit any of these categories).

The study was approved by each participating center's institutional review boards, and data use agreements were established. De-identified coded data were uploaded in the Research Electronic Data Capture at the University of Michigan, the data coordinating center for this consortium.

Immunosuppression

The immunosuppression protocols among all six centers were similar and used tacrolimus-based immunosuppression with mycophenolic acid and corticosteroids as described previously. Northwestern University revised their immunosuppression protocol in April 2015 and included induction with basiliximab on Days 0 and 2 in addition to solumedrol and a maintenance phase with tacrolimus, mycophenolic acid, with a corticosteroid taper to 5 mg indefinitely. In all other centers, immunosuppression protocols for SKLT were similar to the kidney transplant–alone immunosuppression protocol. Induction with thymoglobulin, basiliximab, and dacluzimab was based on the presence of panel reactive antibodies and sensitization. The therapeutic tacrolimus trough levels in all the centers were similar and based on days after SLKT. The levels were maintained between 8 and 12 ng/ml in the first 90 days among all the centers.[6]

Analytic approach

The primary outcome was number of hospitalizations within 6 months of SLKT. The secondary outcome was mortality conditional on survival at 6 months after SLKT. The continuous variables were expressed as median (interquartile range [IQR]), and the categorical variables were expressed as percentages. The MELD-sodium (MELD-Na) score was calculated using the OPTN calculator. The renal risk index (RRI) score[18] was calculated using the RRI calculator. Kidney Donor Profile Index (KDPI),[19] an important factor in deceased donor kidney allocation, went into effect on December 4, 2014, with the implementation of the new kidney allocation system. Hence, all the components of the KDPI were not available on patients who received transplants before 2012. Therefore, we used the kidney donor age as a covariate for donor quality in the main models as described previously.[6] In a subanalysis, we fitted two separate models to explore the association between (1) KDPI and hospitalization at 6 months (univariate logistic model) and (2) KDPI and overall mortality (univariate Cox model).

We chose Poisson regression to examine incidence rate ratios of various recipient and donor factors that would affect the incidence of early hospitalization because the data structure had only the counts of hospitalization in the first 6 months and dates of hospitalizations were not available. The Poisson regression coefficient is a difference between the logs of expected counts to incidence rate ratios. The incidence rate ratio was computed by exponentiating the Poisson regression coefficient. This model was a priori adjusted for age, race, sex, etiology of liver disease, location at time of SLKT (ambulatory, hospital floor, intensive care unit [ICU]), SLKT era, pre-LT dialysis, body mass index (BMI), hypertension, diabetes mellitus, MELD-Na score, RRI, induction, kidney delayed graft function (DGF), cold ischemia time (CIT), warm ischemia time (WIT), donor age, and center. We forced the center in the final adjusted Poisson model to examine the unmeasured center effect.

We examined the cumulative probability of survival at 6 months after SLKT using Kaplan–Meier analysis. Next, we performed the survival analysis conditional on being alive at 6 months after SLKT. The time of entry in the cohort is at 6 months after SLKT to the end of the follow-up period. We also presented a Kaplan–Meier survival curve to show the overall cumulative probability of survival. This was stratified by number of hospitalizations within 6 months of SLKT conditional on being alive at 6 months after SLKT. Cox regression stratified by centers was used to identify risk factors associated with mortality. The focus in this model was the impact of the early (i.e., first 6 months following SLKT) hospitalization on subsequent conditional survival (i.e., given survival of the patient through the "early" post-SLKT period). This model was adjusted for the baseline covariates that showed significance ($p < 0.05$) on univariate analysis. The results were presented as hazard ratio (HR) and 95% confidence interval (CI). All analyses were performed in SAS 9.4.

RESULTS

Patient characteristics

The baseline characteristics of the cohort ($N = 549$) are shown in Table 1. Briefly, the median age at the time of SLKT was 58.0 years (IQR, 50.7–64.6) with 63% males and 76% Whites. Hepatitis C was the leading diagnosis (33%) followed by alcohol-associated liver disease (23%) and NAFLD (20%). The median BMI

TABLE 1 Characteristics of SLKT recipients

		Number of early hospitalizations				
Covariates	**Total**	**None**	**One**	**Two**	**More than two**	
N	**549**	**175**	**151**	**100**	**123**	***p* value**
Age, years	57.7 (50.6–63.9)	58.0 (50.7–64.6)	58.1 (51.0–64.1)	56.5 (50.7–64.3)	57.2 (49.7–62.1)	0.57
Female	202 (37)	66 (38)	54 (36)	37 (37)	45 (37)	0.99
White	417 (76)	120 (68)	109 (72)	78 (78)	110 (90)	0.003
Black	68 (12)	26 (15)	21 (14)	12 (12)	9 (7)	
Others	64 (12)	29 (17)	21 (14)	10 (10)	4 (3)	
MELD score at SLKT	28.0 (23.0, 34.0)	28.0 (22.0, 35.0)	28.0 (23.0 34.0)	28.0 (24.0, 34.5)	29.0 (22.0, 35.0)	0.47
NAFLD	110 (20)	26 (15)	35 (23)	22 (22)	27 (22)	0.74
Alcohol-associated disease	128 (23)	48 (27)	33 (22)	21 (21)	26 (21)	
Hepatitis C virus	177 (33)	57 (33)	45 (30)	34 (34)	41 (33)	
Others	134 (24)	44 (25)	38 (25)	23 (23)	29 (24)	
Ambulatory	160 (29)	58 (33)	51 (34)	26 (26)	25 (20)	0.15
Floor	71 (13)	23 (13)	19 (13)	10 (10)	19 (15)	
ICU	318 (58)	94 (54)	81 (54)	64 (64)	79 (64)	
Dialysis at SLKT	164 (30)	56 (32)	50 (33)	25 (25)	33 (27)	0.42
Hypertension	295 (54)	87 (50)	79 (52)	66 (66)	63 (51)	0.055
Diabetes mellitus	229 (42)	62 (35)	66 (43)	44 (44)	57 (46)	0.22
BMI, kg/m^2	27.2 (23.6–32.2)	27.2 (23.7–32.2)	27.1 (24.7–31.3)	26.6 (22.5–33.4)	28.2 (23.2–32.5)	0.99
RRI score	7.6 (5.3–12.3)	7.6 (5.4–11.4)	7.6 (5.2–12.0)	7.6 (5.1–13.4)	7.8 (5.5–13.7)	0.89
Donor age, years	36.0 (23.0–48.0)	36.0 (23.0–48.0)	36.0 (25.0–34.0)	37.0 (25.0–47.0)	33.0 (21.0–49.0)	0.64
Induction	129 (24)	38 (22)	38 (25)	21 (21)	32 (26)	0.72
Tacrolimus	521 (95)	166 (95)	141 (94)	96 (96)	118 (96)	0.74
Discharge to SAR after SLKT	172 (31)	47 (27)	44 (29)	29 (29)	52 (42)	0.03
Length of stay for index SLKT admission, days	19.0 (10.0–33.0)	20.0 (10.0–33.0)	18.0 (9.0–34.0)	19.0 (9.0–36.5)	19.0 (10.0–39.0)	0.61
No kidney DGF	426 (78)	130 (75)	117 (78)	78 (78)	101 (82)	0.47

Note: Data are provided as *n* (%) or median (IQR).

Abbreviations: BMI, body mass index; DGF, delayed graft function; ICU, intensive care unit; IQR, interquartile range; NAFLD, non–alcohol-associated fatty liver disease; RRI, renal risk index; SAR, subacute rehabilitation; SLKT, simultaneous liver–kidney transplantation.

and MELD-Na were 27.2 kg/m^2 (IQR, 23.6–32.2 kg/m^2) and 28 (IQR, 23–34), respectively. Hypertension and diabetes mellitus were prevalent in 54% and 42%, respectively. Of the patients, 31% were discharged to subacute rehabilitation (SAR) following the SLKT index hospitalization.

The median donor age was 36.0 years (IQR, 23.0–48.0 years); 93% were donation after brain death, and cerebrovascular disease or head injury was the most common cause of death (68%) followed by anoxia or asphyxiation (20%). Donor biopsy data were not available at all centers.

Of SLKT recipients, 95% were on tacrolimus, 82% were on triple immunosuppression (calcineurin inhibitors, mycophenolate, and corticosteroids), and only 3% were on calcineurin inhibitor monotherapy at the time of index SLKT hospitalization discharge. One-fourth (24%) of the patients received induction therapy after SLKT, and of those who received induction therapy, 74% received basiliximab, 18% received thymoglobulin, and 7% received dacluzimab.

A total of 133 (23%) patients developed kidney DGF requiring RRT during transplant hospitalization. The median time spent on RRT for kidney DGF was 13 days (IQR, 4–40 days). Post-SLKT stage 4–5 CKD was higher in patients with DGF versus without (32% vs. 17%; $p < 0.001$).

Frequency, causes, and predictors of early hospitalization after SLKT

There were 803 episodes of hospitalizations within the first 6 months after SLKT. Table 2 shows the counts of hospitalization stratified by discharge alive to 30, 31–90, and 91–180 days after SLKT. Approximately 41% of early hospitalizations occurred within the first 30 days of SLKT. Of SLKT recipients, 68% had at least one hospitalization within 6 months of SLKT (Figure 2). Among those who had one hospitalization, two-thirds were within 30 days, and the rest were between 31 and 180 days from SLKT. A majority of the recipient and

TABLE 2 Counts of hospitalization episodes within the first 6 months

	Number of early hospitalizations		
	One	Two	More than two
Days from SLKT (episodes of hospitalization = 803[a])	***N* = 151[b]**	***N* = 100**	***N* = 123**
Discharge alive from index SLKT—30 days (episodes of hospitalization = 331)	92	87	152
31–90 days (episodes of hospitalization = 227)	28	61	138
91–180 days (episodes of hospitalization = 229)	27	38	164

Abbreviation: SLKT, simultaneous liver–kidney transplantation.

[a]Data were not available in 16 episodes of hospitalization to classify into time frames.

[b]Four of them were in the one-hospitalization group.

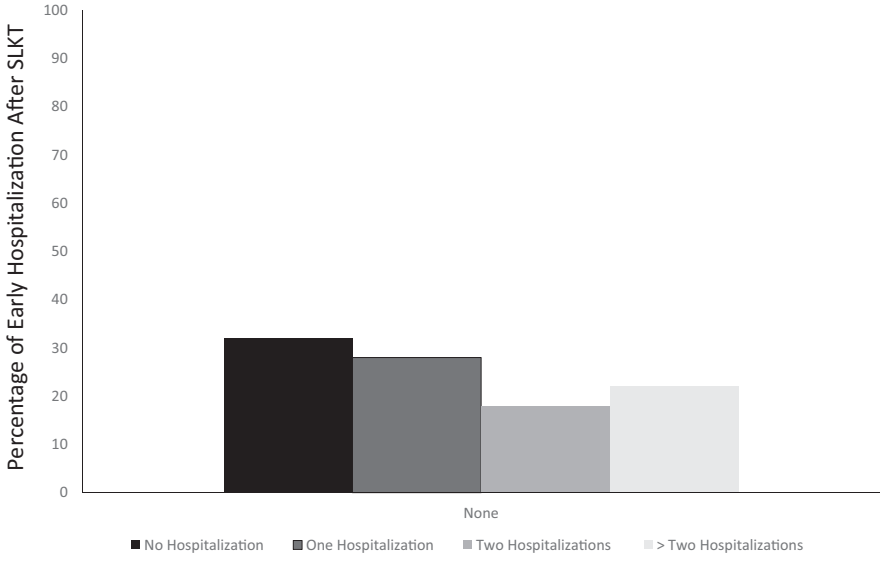

FIGURE 2 Percentage of early hospitalization after SLKT

donor factors were similar among those with no, one, two, or more than two hospitalizations except for recipient race and proportion of discharge to SAR after index SLKT (Table 1).

The main causes of hospitalization within the first 6 months of SLKT were infections (25%), kidney related (21%), liver related (17%), rejection (10%), cardiovascular (7%), and others (14%). Within the first 6 months of SLKT, there were 80 rejection episodes among 71 SLKT recipients; 36 were kidney rejection and 44 were liver rejection episodes. Of note, 12 patients had both liver and kidney rejection episodes within the first 6 months of SLKT. Of those SLKT recipients who had two or more hospitalizations, 28% were for similar reasons, which included infections, kidney related (AKI, dehydration), liver related (biliary cause), and rejection (liver and kidney).

Table 3 shows the independent associations affecting early hospitalization incidence rate ratios following SLKT. Younger age, admitted to hospital in a non-ICU setting (vs. ambulatory status), diabetes mellitus, discharge to SAR after SLKT index admission, White race, and BMI <18.5 kg/m^2 (compared with 25–29 kg/m^2) were associated with an increased incidence rate ratio for early hospitalization. SLKT era, sex, etiology of liver disease, RRI, donor age, WIT and CIT, MELD at SLKT, and kidney DGF did not affect early hospitalization incident rate ratios. Diabetes mellitus increased the incidence rate ratio for early hospitalization by 23% by keeping all other variables constant in the model (Table 3). Similarly, discharge to SAR after index SLKT was associated with a 24% increase in incidence rate ratio independent of all other variables in the model (Table 3).

Figure 3 shows the cumulative probability of survival at 6 months in these patients. The 6-month cumulative survival was >95%.

Conditional survival 6 months after SLKT

Figures 4 and 5 show the overall cumulative survival rates stratified by numbers of hospitalization conditional on being alive at 6 months after SLKT. The 1-year overall conditional survival was >95% (Figure 4). The cumulative survival stratified by number of hospitalizations was not significantly different (p = 0.6) (Figure 5).

Race, etiology of liver disease, era of SLKT, hypertension, diabetes mellitus, discharge location from the index hospitalization, and WIT were significant ($p < 0.5$) on univariate analysis. On multivariable analysis, all other causes of liver disease except alcohol and hepatitis C (HR, 1.81; 95% CI, 1.09–3.02; p = 0.02), receipt of SLKT after 2012 compared with between 2002 and 2008 (HR, 1.87; 95% CI, 1.02–3.43; p = 0.04), and WIT of liver (HR, 1.01; 95% CI, 1.00–1.01; $p < 0.001$). Number of hospitalizations within the first 6 months did not affect survival after 6 months of SLKT (p = 0.35).

KDPI subanalysis

The KDPI information was available in 176 SLKT recipients who were discharged alive after the index SLT hospitalization. The median KDPI was 32 (IQR, 15–57). There was no association between (1) KDPI and

TABLE 3 Independent associations with number of early hospitalizations after SLKT

Covariates	Estimate (SE)	Incident rate ratio (95% CI)	p value
Age, 10 years	−0.073 (0.0036)	0.93 (0.90–0.96)	<0.001
Black, reference = White	−0.38 (0.13)	0.68 (0.60–0.78)	0.004
Other, reference = White	−0.49 (0.15)	0.61 (0.53–0.71)	0.001
Status at SLKT surgery, reference = ambulatory			
Floor	0.35 (0.14)	1.42 (1.09–1.85)	0.009
ICU	0.18 (0.15)	1.21 (0.89–1.62)	0.23
BMI, reference = <18.5 kg/m^2			
18.5–24 kg/m^2	−0.38 (0.24)	0.69 (0.43–1.11)	0.12
25–29 kg/m^2	−0.55 (0.25)	0.58 (0.36–0.94)	0.03
≥30 kg/m^2	−0.36 (0.25)	0.70 (0.43–1.13)	0.15
Diabetes mellitus, reference = no	0.20 (0.086)	1.23 (1.03–1.45)	0.02
Discharge to SAR from index SLKT, reference = home	0.22 (0.082)	1.24 (1.06–1.46)	0.008

Abbreviations: BMI, body mass index; CI, confidence interval; ICU, intensive care unit; SAR, subacute rehabilitation; SE, standard error; SLKT, simultaneous liver–kidney transplantation.

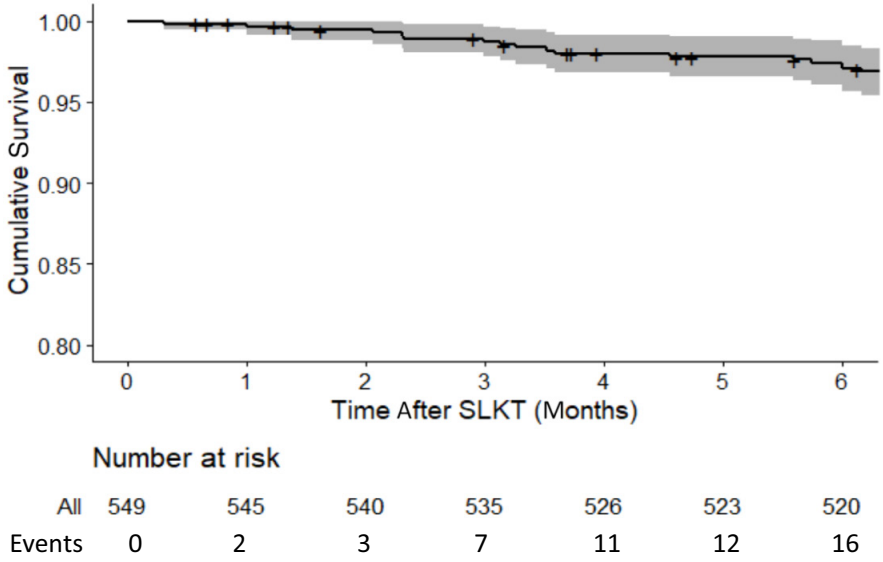

FIGURE 3 Cumulative probability of survival within 6 months of SLKT

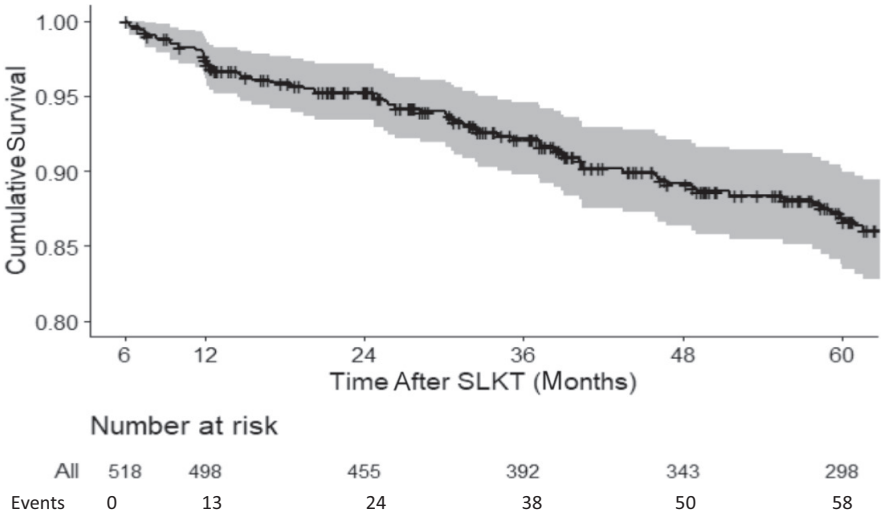

FIGURE 4 Overall cumulative probability of survival conditional on being alive 6 months after SLKT

odds of hospitalization at 6 months (odds ratio, 1.00; p = 0.95) and (2) KDPI and overall mortality (HR, 1; p = 0.9).

DISCUSSION

With the increased incidence of SLKT over time, it is essential to rigorously evaluate what factors influence health care use and outcomes with dual-organ transplantation, particularly given the known high costs of SLKT and donor organ scarcity.[7] There is a significant knowledge gap in the understanding of the epidemiology of early hospitalizations after SLKT because of the lack of data. This is the first study to investigate the contribution of recipient and donor factors on the incidence rate ratio of early hospitalizations following SLKT and whether the magnitude of early hospitalization impacts mortality.

Various studies suggest that 30-day hospitalizations among kidney transplants alone are 30%–32%,[8,14,15] and the 30- and 90-day hospitalizations in LT-alone recipients is approximately 31%–45%.[20–23] We found that the early hospitalizations after SLKT are more frequent than the early hospitalizations among LT-alone patients[10] and kidney transplant recipients. Despite frequent early hospitalizations, the 6-month survival as well as overall survival conditional on being alive at 6 months after SLKT was excellent.

In 2020, the average total cost associated with LT procedures was $878,400. These costs were distributed across 30-day pretransplant procedures, procurement,

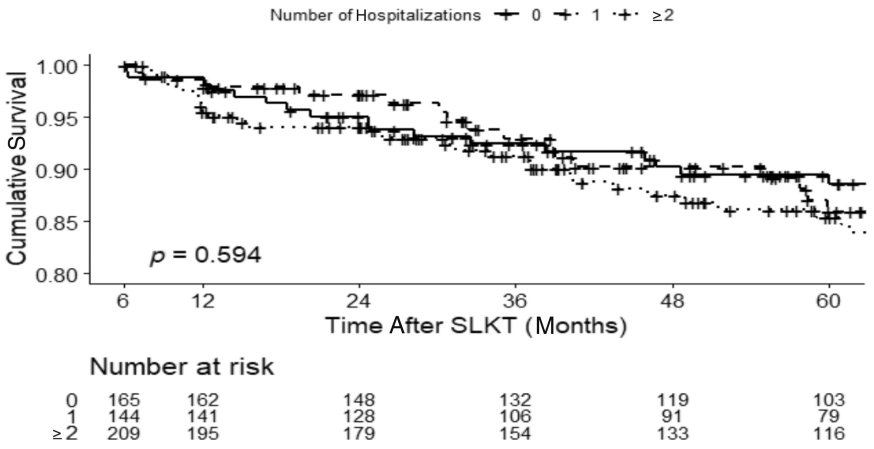

FIGURE 5 Overall cumulative probability of survival conditional on being alive 6 months after SLKT stratified by number of early hospitalizations

hospital transplant admission, physician, procedure, 180-day posttransplant admission, and immunosuppressant charges.[7] The parallel cost for SLKT was steeper (>$1.3 million).[7] Notably, the 180-day posttransplant discharge cost for SLKT is about $100,000 higher than for LT alone and $150,000 higher than for kidney transplant alone.[7] The difference in the 180-day posttransplant discharge cost for SLKT is likely related to the increased resource use following SLKT.

In our multicenter analysis, we did not have the more robust frailty measures such as the liver frailty index given the retrospective nature of our data. However, our study identified two key risk factors for early hospitalization and included low BMI (<18.5 kg/m^2) and need for SAR after index SLKT hospitalization. Hence medical optimization with regard to malnutrition, sarcopenia, and frailty are likely important to limit early hospitalizations. Prior studies have shown that muscle wasting and malnutrition are poor prognosticators for patients with cirrhosis that impact outcomes independent of MELD score.[24,25] Frailty is also associated with increased post-SLKT mortality, liver and kidney graft losses, and hospital length of stay at index admission.[26] As such, methods to boost pre-SLKT nutritional status, including using tube feeds and prehabilitation measures, may have important impacts for improving post-SLKT early hospitalization risk.

Our study found that diabetes mellitus impacted the rate ratio of early hospitalization after SLKT as seen in LT-alone patients.[10] Although we did not capture the degree of diabetes mellitus control with our study, it is plausible that a lack of glycemic control can increase the risk of early hospitalization given its impact on wound healing and infection risk.

Because Black patients are at higher risk for early hospitalization after kidney transplant alone, we were expecting similar results in our SLKT cohort. Instead, our study demonstrated a lower incidence rate ratio for Black patients and patients of other races compared with White patients. The phenotypic and functional characteristics of the circulating blood cells of the SLKT recipients resembled those of solitary LT recipients and appear to be associated with donor-specific hypo-alloresponsiveness.[27] This association needs to be investigated further to examine out the protective role of race in donor-specific hypo-alloresponsiveness among SLKT recipients. We did not find any sex-based differences in early hospitalization rates. Similar to LT recipients,[10] younger age was associated with an increased incidence rate ratio. We could not find any inflection point for the age. This association needs to be further examined in subsequent studies.

We previously reported a 1-year overall survival rate of 92% in our SLKT cohort.[5] The 6-month survival rate as well as the overall and 1-year survival rates conditional on being alive at 6 months after SLKT were excellent in our cohort despite a significant burden of early hospitalizations. These findings were contrary to the LT-alone recipients in whom early hospitalizations significantly affected the overall survival conditional on being alive at 6 months after transplant.[10] This may be related to the nature of hospitalizations after SLKT compared with LT, as a significant portion (21%) were kidney related and in part related to the use of renal replacement therapies among SLKT recipients.

Our study also found that SLKT recipients with NAFLD had a significantly higher risk of death compared with other etiologies of liver disease. This effect was independent of the number of early hospitalizations. A plausible reason could be that patients with NAFLD may have higher rates of comorbidities such as CKD and cardiovascular diseases that may lead to increased mortality.[28,29] Moreover, those who received SLKT in Era 2 had a higher risk of death compared with Era 1. This era effect was likely attributed to increasing age, more comorbidities, and NAFLD among SLKT recipients in the later years.[5]

The limitations of our study include the retrospective design, heterogeneity, and variability in practices during the long study period across the six centers, resulting in potential bias attributed to unmeasured characteristics and patient selection. However, we adjusted for center to overcome the center-level variability. Another shortcoming was that our data had counts for hospitalization instead of dates of hospitalization. Hence, we could not report the incidence rates or cumulative probability of hospitalization. To overcome this limitation, we used Poisson regression, which is ideal for counts data and provided us with the incidence rate ratios during a defined interval. We did not have all the components to calculate KDPI before the year 2011. We therefore used donor age, an important component of the KDPI. It is possible that our study may not have fully captured the hospitalizations that occurred in the community following SLKT. However, this is typically very rare in the first 6 months after SLKT because of the common policy to direct admissions to the transplant center and transfer patients to the transplant center if admitted elsewhere. Finally, our study lacked more robust frailty measures such as the liver frailty index because of the retrospective nature of our study. However, we used BMI and discharge to SAR as a surrogate for functional status.

In conclusion, early hospitalizations after SLKT were very common but did not affect conditional survival. Efforts and resources should be focused on identifying SLKT recipients at high risk for early hospitalization to optimize their predischarge care, discharge planning, and long-term follow-up. Furthermore, modification of actionable risk factors such as diabetes mellitus and BMI may further reduce the resource use associated with early hospitalizations.

AUTHOR CONTRIBUTIONS

Pratima Sharma contributed to the research design, provide oversight for data collection, data quality and integrity, data collection and interpretation, and manuscript writing and editing. Leyi Wang and Jiaheng Xie contributed to the data analysis and interpretation and manuscript writing. Min Zhang contributed to the provide oversight for data collection, data quality and integrity, data collection and interpretation, and manuscript editing. John Magee and Adeline Answine contributed to the data interpretation and manuscript editing. Pranab Barman, Aaron Schluger, and Kara Walter contributed to the data collection and interpretation and manuscript editing. Natalia Filipek and Scott W. Biggins contributed to the data collection and manuscript editing. Giuseppe Cullaro contributed to the research design, data interpretation, and manuscript editing. Randi Wong, Jennifer C. Lai, and Yuval A. Patel contributed to the research design, data collection and interpretation, and manuscript editing. Jennifer Jo, Jasmine Sinha, and Lisa B. VanWagner contributed to the research design, data collection and interpretation, and manuscript editing. Gabriel J. Perreault and Elizabeth C. Verna contributed to the research design, provide oversight for data collection, data quality and integrity, data collection and interpretation, and manuscript editing.

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CONFLICT OF INTEREST

Lisa B. VanWagner consults for Gerson Lehrman Group and Noble Insights. She received grants from W. L. Gore & Associates.

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REFERENCES

1. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Castro S, et al. OPTN/SRTR 2018 annual data report: kidney. Am J Transplant. 2020;20(Suppl 1):20–130.
2. Sharma P. Liver-kidney: indications, patient selection, and allocation policy. Clin Liver Dis (Hoboken). 2019;13:165–9.
3. Bari K, Sharma P. Optimizing the selection of patients for simultaneous liver-kidney transplant. Clin Liver Dis. 2021;25:89–102.
4. Likhitsup A, Hassan A, Mellinger J, Askari F, Winder GS, Saeed N, et al. Impact of a prohibitive versus restrictive tobacco policy on liver transplant candidate outcomes. Liver Transpl. 2019;25:1165–76.
5. Cullaro G, Sharma P, Jo J, Rassiwala J, VanWagner LB, Wong R, et al. Temporal trends and evolving outcomes after simultaneous liver-kidney transplantation (SLKT): results from the US SLKT Consortium. Liver Transpl. 2021;27:1613–22.
6. Sharma P, Sui Z, Zhang M, Magee JC, Barman P, Patel Y, et al. Renal outcomes after simultaneous liver-kidney transplantation: results from the US multicenter simultaneous liver-kidney transplantation consortium. Liver Transpl. 2021;27:1144–53.
7. Bentley ST, Ortner NJ. 2020 U.S. organ and tissue transplants: cost estimates, discussion, and emerging issues. Milliman Res Rep. 2020. [cited 2021 Oct 10]. Available from: https://member.aanlcp.org/wp-content/uploads/2021/03/2020-US-organ-tissue-transplants.pdf
8. McAdams-Demarco MA, Grams ME, King E, Desai NM, Segev DL. Sequelae of early hospital readmission after kidney transplantation. Am J Transplant. 2014;14:397–403.

9. Burra P, De Bona M. Quality of life following organ transplantation. Transpl Int. 2007;20:397–409.
10. Sharma P, Goodrich NP, Schaubel DE, Smith AR, Merion RM. National assessment of early hospitalization after liver transplantation: risk factors and association with patient survival. Liver Transpl. 2017;23:1143–52.
11. Axon RN, Williams MV. Hospital readmission as an accountability measure. JAMA. 2011;305:504–5.
12. CMS. Hospital readmissions reduction program; 2021. [cited 2022 Mar 31]. Available from: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/Value-Based-Programs/HRRP/Hospital-Readmission-Reduction-Program
13. VanWagner LB, Skaro AI. Program-specific reports: implications and impact on program behavior. Curr Opin Organ Transplant. 2013;18:210–5.
14. Lubetzky M, Yaffe H, Chen C, Ali H, Kayler LK. Early readmission after kidney transplantation: examination of discharge-level factors. Transplantation. 2016;100:1079–85.
15. McAdams-Demarco MA, Grams ME, Hall EC, Coresh J, Segev DL. Early hospital readmission after kidney transplantation: patient and center-level associations. Am J Transplant. 2012;12:3283–8.
16. 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;8:2243–51.
17. Nadim MK, Sung RS, Davis CL, Andreoni KA, Biggins SW, Danovitch GM, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. Am J Transplant. 2012;12:2901–8.
18. Sharma P, Goodrich NP, Schaubel DE, Guidinger MK, Merion RM. Patient-specific prediction of ESRD after liver transplantation. J Am Soc Nephrol. 2013;24:2045–52.
19. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A comprehensive risk quantification score for deceased donor kidneys: the kidney donor risk index. Transplantation. 2009;88:231–6.
20. Buchanan P, Dzebisashvili N, Lentine KL, Axelrod DA, Schnitzler MA, Salvalaggio PR. Liver transplantation cost in the model for end-stage liver disease era: looking beyond the transplant admission. Liver Transpl. 2009;15:1270–7.
21. Pereira AA, Bhattacharya R, Carithers R, Reyes J, Perkins J. Clinical factors predicting readmission after orthotopic liver transplantation. Liver Transpl. 2012;18:1037–45.
22. Shankar N, Marotta P, Wall W, Albasheer M, Hernandez-Alejandro R, Chandok N. Defining readmission risk factors for liver transplantation recipients. Gastroenterol Hepatol (N Y). 2011;7:585–90.
23. Yu J, Hosmer A, Parks T, Sonnenday CJ, Sharma P. Predictors of early hospitalization after deceased donor liver transplantation. Dig Dis Sci. 2015;60:3242–7.
24. Gunsar F, Raimondo ML, Jones S, Terreni N, Wong C, Patch D, et al. Nutritional status and prognosis in cirrhotic patients. Aliment Pharmacol Ther. 2006;24:563–72.
25. Kalafateli M, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the model for end-stage liver disease score. J Cachexia Sarcopenia Muscle. 2017;8:113–21.
26. Shamseddeen H, Pike F, Ghabril M, Patidar KR, Desai AP, Nephew L, et al. Karnofsky performance status predicts outcomes in candidates for simultaneous liver-kidney transplant. Clin Transplant. 2021;35:e14190.
27. Taner T, Park WD, Stegall MD. Unique molecular changes in kidney allografts after simultaneous liver-kidney compared with solitary kidney transplantation. Kidney Int. 2017;91:1193–202.
28. Sharma P, Sun Y, Neal J, Erley J, Shen J, Tischer S, et al. Renal outcomes of liver transplantation recipients receiving standard immunosuppression and early renal sparing immunosuppression: a retrospective single center study. Transplant Direct. 2019;5:e480.
29. VanWagner LB, Lapin B, Skaro AI, Lloyd-Jones DM, Rinella ME. Impact of renal impairment on cardiovascular disease mortality after liver transplantation for nonalcoholic steatohepatitis cirrhosis. Liver Int. 2015;35:2575–83.

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