

Impact of Sarcopenia on Clinical Outcomes of Patients Undergoing Simultaneous Liver and Kidney Transplantation: A Cohort Study

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TITLE PAGE:

TITLE: Impact of sarcopenia on clinical outcomes of patients undergoing simultaneous liver and kidney transplantation: a cohort study.

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Highlights:

- Sarcopenia is associated with an increased risk of infections and mortality post-LT
- No data are available on the impact of sarcopenia in SLKT recipients.
- Sarcopenia threshold was defined as TPA<1460mm² (women) and <1560mm² (men)
- Prospective and multi-centre studies are needed to evaluate frailty in this population

Keywords:

Liver transplantation, Kidney transplantation, sarcopenia, infection, postoperative complication, long-term outcomes.

Abbreviations:

Simultaneous liver and kidney transplantation (SLKT);

Disclosure:

The authors declare no conflicts of interest.

Funding:

NA

ABSTRACT:

Background : The impact of sarcopenia in patients undergoing simultaneous liver and kidney transplantation (SLKT) has not been fully delineated. The aim of this single-centre-cohort-study was to evaluate the impact of sarcopenia on the clinical outcomes.

Methods: Between 2003 and 2018, 79 patients underwent SLKT. Sarcopenia was assessed via the total psoas muscle area (TPA) at the level of the 3rd. lumbar vertebra. Sarcopenia threshold was TPA<1460mm² (women) and <1560mm² (men). We identified post-operative biliary, vascular and digestive complications. Survival analysis was performed by the Kaplan Meier method (log-rank test).

Results: We included 43/79 SLKT recipients (56%male, median age of 58 [53-63] years). The prevalence of cirrhosis was 74% (n=32) with median MELD-score of 21 (20-22) and that of polycystic-liver-disease was 26% (n=11). End-stage-renal-disease of unknown origin was 36.2% (n=12). Dialysis before transplantation was performed in 54,8% (n=23) of patients. The median TPA was 1138 (926-1510) mm², and sarcopenia was detected in 72% of patients (n=31). No difference in patient or death-censored graft-survival between sarcopenic and non-sarcopenic groups at 1 year was reported. Also, no differences at 6-months' post-transplant-complication-free and infection-free-survival rates were found.

Conclusion: In this cohort of patients, no differences were observed in patients, grafts, complications or infection-free survival between sarcopenic or no sarcopenic SLKT patients. Future multi-centre studies are needed to validate and extend the generalisability of these findings.

Introduction:

The role of sarcopenia in affecting outcomes of patients undergoing transplantation has not been fully delineated. This is particularly important in the case of liver transplantation (LT) as 40-70% of pre-transplant cirrhotic patients have already been identified as sarcopenic. ¹⁻⁴ This condition, which is defined by the progressive loss of skeletal muscle mass, strength, and function, is associated with a 2-fold increased risk in mortality whilst on the waiting list. In addition, even after LT, these patients are more likely to require mechanical ventilation and have a longer stay in Intensive Care Unit (ICU). ^{4,5,6-12}. Sarcopenia is also associated with an increased risk of infections and mortality post-LT ⁹

Furthermore, studies in kidney transplantation (KT) have found frailty to be associated with an increased risk of delirium, early hospital readmission, and longer length of stay (LOS) in hospital post-transplant. ¹³⁻¹⁶ In this regard, sarcopenia has been used as an indicator of potential patient performance when predicting outcomes in populations undergoing general surgery or KT¹⁴⁻¹⁶. However, no studies have explored the impact of sarcopenia in patients undergoing simultaneous liver and kidney transplantation (SLKT). This is important to elucidate as SLKT patients are rarer and much more heterogenous as a cohort. They are also more clinically challenging to manage pre-, intra- and postoperatively. Hence, the aims of this study were to evaluate the impact of sarcopenia on the clinical outcomes of patients undergoing SLKT.

PATIENTS AND METHODS:

This was a single-centre, nested-cohort study of patients undergoing SLKT in a high-volume, French Transplant Centre.

Study outcomes

- The primary outcome of the study was to assess the impact of sarcopenia on the complication-free survival in patients undergoing SLKT.
- Secondary outcomes were the impact of sarcopenia on the infection rate, infection-free survival, and on patient and graft (liver and kidney) survival.

Patient identification

All medical records of patients listed for LT alone or combined (liver-kidney, liver-heart) in the Liver Transplant program of Pitié-Salpêtrière University Hospital, Paris, France, were prospectively collected in an institutional digital database since 2003. The whole cohort of 1704 patients was regularly followed-up as per our local protocols.

We identified the nested cohort of adult patients who had undergone simultaneous SLKT from 1st January 2003 to 31st December 2018. Patients who underwent sequential liver or kidney transplantation (in other words, during two different surgical interventions with an inbetween interval longer than 24h) were excluded. In addition, any SLKT patients who lacked cross-sectional imaging two months before, or one week after SLKT were also excluded.

Clinical management of patients

The preoperative workup included cross-sectional imaging for the evaluation of vascular and biliary anatomy as well as to identify hepatocellular carcinoma (HCC) in patients with cirrhosis.

The actual SLKT procedures were performed sequentially: orthotropic LT was done first, followed by heterotopic KT, by two different surgical teams (liver and urology). Liver and kidney Doppler ultrasounds were performed daily for the first 7 days post-op. All patients were subject to our routine immunosuppression protocol of steroids, tacrolimus, mycophenolate (MMF) and induction therapy via basiliximab or thymoglobulin.

The follow-up of SLKT patients was organized by the transplant coordination team (4 trained nurses) with an LT hepatologist, LT surgeon or transplant nephrologist. Patients were seen weekly during the first postoperative month, twice a month during the second month and then once every month for the first 6 months. The outpatient clinic consultation included blood and urinary testing as well as any imaging (Doppler ultrasound, CT or MRI) if clinically indicated. All data involving the patient's post-operative course such as complications, rehospitalisation, primary disease recurrence or deaths were also collected. The follow-up duration was life-long.

Definitions of study variables

- Sarcopenia. The working definition of sarcopenia was based on the total psoas area (TPA), measured on cross-sectional imaging (CT scan or MRI, with or without contrast enhancement) at the third lumbar vertebra during the pre-transplant workup^{11, 17}. All such imaging was performed 4 months before SLKT or within the first 7 days following SLKT. The reason for including the imaging even performed during the first-week post-op was based on the assumption that psoas and paravertebral muscles would not be grossly affected by major variations in size and mass. Moreover, a previously published study from Golse *et al* had utilised a similar strategy¹¹. The TPA thresholds considered in men and women were 1561 mm² and 1464 mm² respectively. Hence, any patient with TPA values below these limits was considered as sarcopenic¹¹. The TPA measurements of the left and right psoas regions were performed using the in-house radiology visualisation software (Carestream Pacs version 12.1.6, Carestream Health, Inc). The final TPA measurement utilised was an addition of both the left and right values.
- Patient survival: Measured as the time from SLKT to death or last follow-up time-point.
- <u>Liver graft survival</u>: Measured as the time from SLKT to either requiring liver retransplantation (regardless of cause) or if not re-transplanted, time of death or last followup time-point.

- <u>Death-censored kidney graft survival</u>: Measured as the time from SLKT to graft failure requiring renal replacement therapy (hemodialysis, or second KT, regardless of the cause of graft failure).
- Complications: Considered as the occurrence of any complication during the initial post-operative period or recognised during outpatient follow-up. The complications were categorised as biliary (eg. leak, stenosis), vascular (eg. haemorrhage, stenosis or thrombosis of hepatic artery or portal vein) and digestive. The complication-free survival time was considered as the time from SLKT until the occurrence of the most severe complication or if not, their last follow-up time-point.
- Infections: Considered as any infection occurring in the follow-up period. All infections
 were classified under the following categories; pneumonia, urinary tract, biliary tract,
 cutaneous and bacteraemia. The infection-free survival time was considered as the time
 from SLKT until the time-point of the occurrence of the infections or the last follow-up.

Data sources and management

All data in our patient database was compiled using inpatient/outpatient records, radiology reports, operative reports, and laboratory or pathology reports. Further data was also available from the CRISTAL database of the French National Biomedical Agency¹⁸. All data was processed in compliance with local institutional protocols.

Study size

The study size consisted of all patients who met the relevant inclusion and exclusion criteria as detailed above in **Patient identification**.

Statistical methods

Baseline characteristics: SLKT patients affected by sarcopenia were compared to those without sarcopenia. Categorical (qualitative) variables were reported as percentages, while quantitative continuous variables were summarized as means and standard deviation (SD) or median and range for discrete variables, as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney U test.

Primary outcome: We compared sarcopenic and non-sarcopenic patients in terms of their complication-free survival. Cumulative complication free-survival curves were estimated through the Kaplan-Meier method and compared using the log-rank test.

Secondary outcomes: We compared sarcopenic and non-sarcopenic patients in terms of the impact on patient and graft (liver and kidney) survival, on the infection rate and infection-free survival. Curves for each outcome were plotted by the same Kaplan-Meier method and compared by using the log-rank test. Given the small sample size, no imputation method was used. All variables with p<0.05 were considered statistically significant.

We performed two-tailed analyses of all data. Analyses were performed with R software (3.6.1; www.cran.r-project.org, Vienna, Austria). The study was designed in March 2019. Data collection was done from March-June 2019. From July-August 2019, we performed all data analyses.

The reporting of this study is based on the STROBE Statement and guidelines ¹⁹.

RESULTS

Patient demographics

We identified 79 SLKT (4.6%) patients out of a cohort of 1704 liver transplantations having been performed at our unit over the study period. After the exclusion of 36 incomplete records, 43 SLKT recipients were included in the study cohort (**Figure 1**). Demographic and clinical characteristics are shown in **Table 1**.

The median age of recipients was 58 (53-63) and 55.8% (n=24) were male. Amongst them, 74.4% (n=32) had cirrhosis, with a median MELD score of 21 (20-22). Patients whilst awaiting a transplant already had cirrhosis-related complications such as hepatic encephalopathy (70.7%, n=29), hepato-renal-syndrome (HRS; 7.9%, n=3) and HCC (21.4%, n=9). Polycystic liver disease was identified in 26.8% (n=11) of patients. End-stage renal disease of unknown origin was observed in 36.2% (n=12). Dialysis before transplantation was performed in 54.8% (n=23). The median length of ICU and hospital stay after SLKT was 10 (5-18) and 17 (13-32) days, respectively. The immunosuppressive regimen after SLKT consisted of prednisolone and MMF for all, with tacrolimus for 97.6% (n=41) of them and cyclosporin for the remainder. In addition, 25.5% (n=11) of patients received induction therapy via basiliximab or thymoglobulin.

Sarcopenia data and outcomes

In our study, 9.3% (n=4) of patients were defined as underweight (body mass index; BMI <18.5 kg/m²). The median TPA of all patients was 1138 (926-1510) ± mm². Sarcopenia was observed in 72% of patients (n=31). Besides BMI and TPA, no other clinical or biological differences were observed between the sarcopenic and non-sarcopenic groups (**Table 1**). After SLKT, the overall rate of postoperative complications was 65.6%. However, there was no difference in post-operative complication-free survival at 6 months: 50% (95%CI: 0.284-0.880) vs. 53%, (95%CI: 0.3791-0.745) in the sarcopenia vs. non-sarcopenia groups, respectively (p=0.61) (**Figure 2**). The most common complications are summarized in **Table 2**.

The overall rate of infections post-transplantation was 63%. However, we identified no difference in infection-free survival between both groups at 6 months: 52% (95%CI: 0.213-0.787) vs. 65% (95%CI: 0.4643-0.536), respectively (p= 0.088) (**Figure 3**).

Survival data

The median time of follow up was 34 (12-64) months. We also identified clinically comparable graft and patient survival (**Figure 4**). Patient survival at 6 months was 93% (95%CI: 0.850-1) vs. 91% (95%CI: 0.772-1) in the sarcopenic and non-sarcopenic groups (**Figure 5**). Additionally, survival at 12 months was 93% (95%CI: 0.850-1) vs. 91% (95%CI: 0.772-1) (p=0.76) in the two groups, respectively (**Figure 5**).

With regards to liver graft survival at 6 months, the rates were similar in the two groups: 95% (95%CI: 0.859-1) vs. 90% (95%CI: 0.754-1). Similarly, graft survival at 12 months was 95% (95%CI: 0.859-1) vs. 90% (95%CI: 0.754-1) (p= 0.8), respectively (**Figure 6**).

We found similar data for the kidney graft survival. Death-censored kidney graft survival at 6 months was 86% (95%CI: 0.745-1) vs. 83% (95%CI: 0.647-1) in the sarcopenic and non-sarcopenic groups, respectively. At 12 months, it was 86% (95%CI: 0.745-1) vs. 83% (95%CI: 0.647-1) (p= 0.83), respectively (**Figure 7**). The most common causes of death are reported in **Table 2**.

DISCUSSION

In this study, we observed a 72% rate of sarcopenia within SLKT recipients as per the TPA thresholds reported by Golse *et al* ¹¹. In our cohort, 98% of sarcopenic patients initially presented with normal BMI and only 1 non-sarcopenic patient had a BMI <18 Kg/m². We would hypothesise that BMI may be overestimated due to the presence of local oedema and ascites.

Despite the heterogeneity in the literature with regards to the definition of sarcopenia and methods for diagnosis (with CT or MRI), the L3 skeletal muscle index (L3SMI) is the most commonly reported method. Some studies have used paravertebral or TPA measurements, by identifying the outlined and total surface area of psoas muscle at the level of L3-L4 ²⁰. Other studies have used the transversal psoas muscle thickness at the level of the umbilicus and recently the L3 SMI was recommended as the method of choice instead ²¹. This method seemed to best correlate with whole-body muscle mass and is considered superior to psoas muscle measurements or TPA in predicting survival. The authors of that study suggested L3 SMI cut-offs in patients with cirrhosis of <50 cm²/m² in men and <39 cm²/m² in women ²¹.

The key contribution of this study to the literature is the thorough assessment of the role of sarcopenia in the very rare and heterogenous SLKT patient cohort. We have importantly reported on a comprehensive set of pre-transplant and post-transplant clinical factors. This study builds upon previously published work involving patients undergoing single organ transplants only^{6, 14,16, 21-26}. Nevertheless, we recognise the small size of our cohort (albeit rare) and are presently undertaking a multicentre review of SLKT patients in France.

Interestingly, our study neither identified a difference in the rate of complications (50% vs 53% p=0.61) nor infections (52% vs 65% p= 0.088) between the non-sarcopenic and sarcopenic groups. Infection-free survival was also not significantly different between the two groups.

In this study, we observed an excellent rate of overall survival. A previous French study, performed on a cohort of SLKT, described a one and two-year overall survival of 85% and 82%, respectively. Mortality occurred during the first month and was mainly related to infectious complications. Infections are favoured by undernutrition (BMI <18 kg/m2), by the severity of liver disease and by a previous liver or kidney transplantation ²⁷.

Moreover, despite the high rate of sarcopenia in our cohort, we reported clinically comparable graft and patient survival. First, a possible explanation for this could be due to the high percentage of patients affected by polycystic liver-kidney disease in both groups (9% vs 33% in the non-sarcopenic vs sarcopenic groups, respectively): the benign nature of polycystic disease, and the usually positive outcomes after transplantation ²⁸, may explain our good results. Second, in our study, we have looked at the effects of sarcopenia in post-LT outcomes, however no data was analyze regarding the nutritional status. Gunsar F et all., in a large cohort of cirrhotic patients, introduced a composite score that takes into account nutritional status with dietary intake, sarcopenia and links nutrition with functional muscle mass for a given individual (The Royal Free Hospital-Global Assessment - RFH-GA). RFH-GA was independently associated with mortality with a relative hazard ratio of 5.26 for severely malnourished patients²⁹.

Lastly, in our cohort, in the non-sarcopenic and sarcopenic groups, both the median MELD and MELD-Na scores were low. This could partially explain the results of our study, nonetheless according to Kalafateli et all., in a study performed on large cohort of cirrhotic patients, the RFH-GA was not associated with the MELD score. In this study, the malnutrition and the MELD scores were the predictors of post-transplant outcomes (hospital-infection, mechanical ventilation duration >24h, ICU stay >5 days, hospital stay >20days). Despite this, the single 12 months mortality predictor was the L3-PMI, malnourishment, assessed with RFH-GA score, and MELD score were not found significant³⁰.

Indeed, our data is comparable with already published data that reported a comparable survival among SLKT and LT recipients. Interestingly, in that study, survival seemed to be affected by dialysis at LT and by donor quality (Liver-donor risk index >1,5) ^{31,32}. In our study,

no difference was found between SLKT patients who were on dialysis or not according to sarcopenia.

There are several limitations of our work: (1) its retrospective design, (2) its small sample size - only 43/79 patients were included as per our identification criteria outlined above, (3) the definition of sarcopenia with the TPA threshold, based on a study with similar LT population but without SLKT, (4) the absence of dynamic variations of psoas muscle before and after SLKT, (5) the absence of evaluation of the nutritional support therapy. Hence, the TPA sarcopenia threshold could be different in their subset population. In addition, it was neither possible to perform a multivariate analysis in our cohort nor a propensity-score match.

In conclusion, our study demonstrated a high rate of sarcopenia in this cohort of SLKT patients. However, they all had clinically comparable 1-year graft and patient survival. We also identified no difference in post-transplant complications or infections between sarcopenic or non-sarcopenic patients. Going forward, we consider that larger-scale studies are needed to validate our findings and improve our ability to predict clinical outcomes in this rare patient cohort.

TABLE LEGENDS:

TABLE 1: Comparison of clinical and biological characteristics of Sarcopenic and Non-Sarcopenic simultaneous liver and kidney transplanted patients.

Table 2. Outcomes on Sarcopenic and Non-Sarcopenic simultaneous liver and kidney transplanted patients.

Table 1. Comparison of baseline characteristics of sarcopenic and non-sarcopenic patients prior to simultaneous liver-kidney transplantation.

	Overall N=43	Non-sarcopenia N=12	Sarcopenia N=31	р
Age (median)	58 (53-63)	58 (52-63)	58 (53.0-63)	0.723
Sex (%)	24 (55.8)	10 (23.3)	14 (32.6)	0.055
BMI (median)	24 (21-26)	27 (24-29)	23 (20.8-24)	0.013
Psoas right (median)	599 (458-772)	904 (783-1050)	510 (411.5-636)	<0.001
Psoas left (median)	562 (425-713)	1006 (803-1122)	439 (375.5-570)	<0.001
TPA (median)	1138 (926-1510)	1792(1594-2125)	956 (831.5-1162)	<0.001
Aetiology of liver disease (%):				0.315
Alcoholic	9 (22.0)	4 (33.3)	5 (16.1)	
Viral	9 (22.0)	5 (41.6)	7 (22.5)	
HCC	12 (29.3)	4 (33.3)	8 (25.8)	
Polycystic disease	11 (26.8)	1 (8.3)	10 (32.2)	
MELD (median)	21 (20-22)	21 (20-24)	21 (19.8-22)	0.467
MELD-NA (median)	22 (20-23)	22 (20-24)	22 (19.5-23)	0.913
Bilirubin (μmol/L)	9 (7-20)	7 (5-25)	10 (8.0-20)	0.692
Creatinine (µmol/L)	365 (274-520)	365 (239-605)	368 (277.8-510)	0.716
INR	,	1 (1-1)	1 (1.0-1)	0.174
Sodium (mmol/L)	139 (136-140)	139 (137-140)	138 (135.0-140)	0.537
Albumin (g/L)	34 (29-41)	32 (29-38)	36 (29.4-43)	0.250
Child-Pugh score (%)	,	,	,	0.294
A	8 (38.0)	4 (33.3)	4 (13)	
В	7 (33.3)	1 (14.3)	6 (19.3)	
С	6 (28.5)	2 (16.6)	4 (13)	
Complications of cirrhosis (%)	, ,	, ,	, ,	
HRS	3 (7.9)	0 (0.0)	3 (11.5)	0.563
SBP	6 (15.4)	1 (8.3)	5 (18.5)	0.739
HE	29 (70.7)	7 (58.3)	21 (68)	0.380
HCC	9 (21.4)	4 (33.3)	5 (16.7)	0.440
Bleeding	3 (7.7)	, ,	,	
Aetiology of kidney disease (%)	,			0.734
Diabetes	8 (24.2)	0 (0)	8 (67.5)	
Anti-calcineurin toxicity	4 (12.1)	0 (0)	4 (15.3)	
Unknown	12 (36.2)	5 (71.4)	7 (26.9)	
Dialysis (%)	23 (54.8)	7 (58.3)	16 (53.3)	1.000
SH* before LT (%)	9 (22.5)	4 (36.4)	5 (17.2)	0.202
IS treatment (%)	,	,	` '	
Cyclosporine	1 (2.4)	0 (0.0)	1 (3.3)	1.000
Tacrolimus	41 (97.6)	12 (100.0)	29 (96.7)	1.000
Prednisone	43 (100.0)	12 (100.0)	30 (100.0)	NA
MMF*	43 (100.0)	12 (100.0)	30 (100.0)	NA
Antibody therapies	11 (26.2)	5 (41.7)	6 (20.0)	0.292
Days of ICU after LT (median)	10 (5-18)	10 (4-13)	10 (6.0-26)	0.490
Days of SH after LT (median)	17 (13-32)	14 (11-48)	21 (15.2-31)	0.872
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HSR: hepato-renal syndrome; SBP: Spontaneous bacterial peritonitis; HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; SH: standard hospitalisation; ICU: Intensive Care Unit; MMF: Mycophenolate-mofetil.

Table 2. Comparing primary and secondary outcomes between sarcopenic and non-sarcopenic patients after simultaneous liver-kidney transplantation.

	Overall	T		
	population N=43	Non-sarcopenia N=12	Sarcopenia N=31	p
Median follow-up time (months)	34 (12-64)	26 (10-55)	37 (14.5-66)	0.515
Primary outcomes:	,	,	,	
Complications (%)	28 (67)	7 (58)	21 (70)	0.717
Type of complication :	, ,	, ,	, ,	0.722
Others	6 (77)	1 (8)	5 (17)	
Biliary	5 (12)	2 (17)	3 (10)	
Digestive	2 (5)	1 (8.3)	1 (3.3)	
Vascular	15 (36)	3 (25.0)	12 (40)	
Median time of complications, months (min-max)	42 (1-43)	5 (1-22)	6 (0.2-43)	0.895
Complications free survival at 6-months	-	50%	53%	0.61
(%)		95%CI:	95%CI:	
		0.284-0.880	0.3791-0.745	
Infections (%)	28 (68.2)	5 (41.7)	21 (72)	0.133
Infection-free survival at 6-months, %	-	52%	65%	0.088
(95%CI)		(0.213-0.787)	(0.4643-0.536)	
Secondary outcomes:				
Death (%)	5 (12)	1 (8)	4 (13)	1.000
Cause of death (%):				0.599
Infections	2 (40)	1 (100)	1 (25)	
Cardiovascular	1 (20)	0 (0)	1 (25)	
MOF*	1 (20)	0 (0)	1 (25)	
Other	1 (20)	0 (0)	1 (25)	
Death-censured patient survival at 1-year	-	91%	93%	0.76
(%)		95%CI: 0.772-1	95%CI: 0.850-1	
Liver graft dysfunction (%)	29 (15)	1 (8)	2 (7)	1.000
Median time of liver graft dysfunction, months (min-max)	34 (16-56)	32 (16-56)	34 (17.0-60)	0.934
Liver graft survival at 1-year, % (95% CI)	-	90%	95%	0.8
		(0.754-1)	(0.859-1)	
Kidney graft dysfunction (%)	6 (15)	2 (17)	4 (14)	1.000
Median time of kidney graft dysfunction, months (min-max)	22 (8-55)	25 (6-44)	34 (12.5-57)	0.661
Kidney graft survival at 1-year, % (95% CI)	-	83%	86%	0.83
		(0.647-1)	(0.745-1)	

*MOF: Multi-organ failure.

FIGURES LEGENDS:

- FIGURE 1. Patients' inclusion Flow Diagram.
- FIGURE 2. The Kaplan-Meier survival estimation of the SKLT study cohort
- FIGURE 3. The Kaplan-Meier complication free survival estimation of the SKLT study cohort
- FIGURE 4. The Kaplan-Meier infection-free survival estimation of the SKLT study cohort
- FIGURE 5. The Kaplan-Meier patient survival estimation of the SKLT study cohort
- FIGURE 6. The Kaplan-Meier liver graft survival estimation of the SKLT study cohort
- FIGURE 7. The Kaplan-Meier kidney graft survival estimation of the SKLT study cohort

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Figure 1. Patient Identification Schematic Diagram













