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## OPEN

# Need for Pretransplant Midodrine Does Not Negatively Impact Simultaneous Liver-kidney Transplant Outcomes

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**Background.** Midodrine is often needed pretransplant to improve hemodynamics in simultaneous liver-kidney transplant candidates. Previous research has shown that patients requiring midodrine before kidney transplant alone have increased posttransplant risk for delayed allograft function, graft failure, and death. However, the impact of pretransplant midodrine use on outcomes after simultaneous liver-kidney transplant is unknown. **Methods.** We performed a retrospective study of all adult (age  $\geq 18$  y) simultaneous liver-kidney transplant recipients from a single academic transplant center from February 1, 2002, to June 30, 2019. **Results.** Sixty-four simultaneous liver-kidney transplants were performed in our institution during this time period, of which, 43 were not on midodrine before transplant, 17 were on midodrine alone, and 4 were on intravenous (IV) vasopressor therapy. Despite the midodrine group having a higher MELD-Na at listing, higher MELD-Na at transplant, and being older, there were no significant differences in key outcomes including delayed renal allograft function, estimated glomerular filtration rate at transplant discharge, and estimated glomerular filtration rate at 1 y after transplant compared with the nonmidodrine group. There was no significant difference in graft failure or survival at last follow-up. **Conclusions.** Our study suggests that need for pretransplant midodrine should not be a barrier to simultaneous liver-kidney transplant.

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## INTRODUCTION

Renal dysfunction after liver transplantation is associated with increased mortality and is at least partially mediated by pretransplant renal dysfunction.<sup>1</sup> Pretransplant renal dysfunction is a common finding in patients with cirrhosis,

with estimates as high as 50% in outpatients with decompensated cirrhosis.<sup>1</sup> As a result of the vasodilatory physiology and impaired cardiac function of end-stage liver disease, patients commonly develop symptomatic hypotension. This can be exacerbated with prolonged hemodialysis requirement,<sup>2</sup> which may be needed in cases of both intrinsic glomerular injury or hepatorenal syndrome (HRS) type 2. Midodrine is an alpha-1 adrenergic receptor agonist that induces arterial and venous vasoconstriction and is often used to manage symptomatic hypotension and help facilitate hemodialysis in these patients.<sup>3,4</sup> It is also used as part of a combination therapy for HRS, along with albumin infusions and octreotide. The need for midodrine before kidney transplantation (KT) alone has been shown to increase the risk for poor posttransplant outcomes including delayed graft function, graft failure, and death.<sup>5,6</sup> As a result, in the kidney transplant program at our institution, the need for midodrine is a contraindication to listing for kidney transplant. However, specifically in cases of liver transplantation alone for HRS, pretransplant use of midodrine has not been associated with differences in renal function or mortality.<sup>7</sup>

Simultaneous liver-kidney transplantation (SLKT) has been used as a means to mitigate the risk of postliver transplant renal dysfunction. Current eligibility for SLKT is determined by the length and nature of kidney injury: acute kidney injury (requiring hemodialysis or glomerular filtration rate  $\leq 25$  mL/min) sustained for at least 6 consecutive weeks or chronic

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kidney disease (glomerular filtration rate  $\leq 60$  mL/min) for at least 90 consecutive days. The number of SLKTs in the United States has increased almost 2-fold from 2007 to 2017 (from 431 patients to 720 patients), encompassing 9.6% of all liver transplants in 2017.<sup>8</sup> With the ongoing organ shortage and increased frequency of SLKTs, it is imperative to optimize outcomes to allow for responsible allocation of these scarce resources. Given the poor outcomes in KT alone, there is concern that the need for midodrine for hypotension in SLKT candidates represents a poor prognostic factor and may cause transplant surgeons to consider these patients as increased risk. Although midodrine is commonly used in patients on hemodialysis and in the management of HRS, the outcomes of SLKT recipients that required pretransplant midodrine are unknown. We sought to evaluate whether the need for pretransplant midodrine resulted in worse outcomes after SLKT, as is seen in KT alone recipients. Because of the physiologic differences leading to renal dysfunction in patients who require KT alone versus those who require SLKT, we hypothesize that need for midodrine before SLKT should not have a negative impact on outcomes.

## MATERIALS AND METHODS

We conducted a retrospective study of all adult (age  $\geq 18$  y) SLKT recipients from a single academic transplant center from February 1, 2002 to June 30, 2019. Patient, donor, and procedural characteristics were captured. Data regarding posttransplant course including hospitalizations, episodes of rejection, and infection, and development of cardiovascular disease were captured until the day of last recorded follow-up or death. Patients that received pretransplant midodrine and those that did not receive pretransplant midodrine were compared. Patients on IV vasopressor before SLKT were too few and therefore not compared.

Descriptive statistics of donor, recipient, and operative characteristics, and outcomes are presented by midodrine use and summarized using mean, SD, median, quartiles frequency, or percent, as appropriate. Characteristics were tested using a Wilcoxon rank sum, Fisher exact test, or equal variance *t* test. Analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC). This study was approved by the Duke University Institutional Review Board.

## RESULTS

Sixty-four SLKTs that met inclusion criteria were performed in our transplant institution during the time period specified. Of these, 43 were not on midodrine before transplant, 17 were on midodrine alone, and 4 were on IV vasopressor therapy with or without midodrine. These 4 patients on IV vasopressor therapy were not included in our analyses. Recipient characteristics are noted in Table 1. Patients on midodrine were significantly older but without significant differences in gender, race, body mass index, or medical comorbidities such as hypertension, diabetes, or coronary artery disease. The incidence of chronic kidney disease was also similar between the 2 groups.

Patients on midodrine were more likely to have HRS and lower systolic and diastolic blood pressures at time of transplant, but there was no significant difference in hemodialysis need at listing. Midodrine patients also had higher prevalence

**TABLE 1.**  
Recipient patient characteristics by recipient midodrine use

Recipient characteristics by midodrine groups				
	None (N = 43)	Midodrine (N = 17)	Total (N = 60)	P
<b>Age at transplant</b>				0.001 <sup>a</sup>
Mean (SD)	52.6 (10.3)	61.5 (5.5)	55.2 (10.0)	
Median	54.0	62.0	58.0	
Q1, Q3	44.0, 61.0	59.0, 66.0	49.5, 63.0	
<b>Gender</b>				0.346 <sup>b</sup>
Female	14 (32.6%)	3 (17.6%)	17 (28.3%)	
Male	29 (67.4%)	14 (82.4%)	43 (71.7%)	
<b>Race</b>				0.024 <sup>b</sup>
White	26 (60.5%)	15 (88.2%)	41 (68.3%)	
Black	16 (37.2%)	1 (5.9%)	17 (28.3%)	
Other	1 (2.3%)	1 (5.9%)	2 (3.3%)	
<b>BMI</b>				0.358 <sup>a</sup>
Mean (SD)	28.1 (5.5)	29.6 (6.3)	28.6 (5.8)	
Median	27.4	27.9	27.5	
Q1, Q3	24.8, 32.9	26.3, 33.5	25.1, 32.9	
<b>Etiology of liver disease</b>				—
AIH	0 (0.0%)	1 (5.9%)	1 (1.7%)	
ALD	3 (7.0%)	8 (47.1%)	11 (18.3%)	
HBV	0 (0.0%)	1 (5.9%)	1 (1.7%)	
HCV	14 (32.6%)	0 (0.0%)	14 (23.3%)	
HCV/ALD	4 (9.3%)	0 (0.0%)	4 (6.7%)	
NASH	6 (14.0%)	7 (41.2%)	13 (21.7%)	
PBC	2 (4.7%)	0 (0.0%)	2 (3.3%)	
PSC	2 (4.7%)	0 (0.0%)	2 (3.3%)	
Other	12 (27.9%)	0 (0.0%)	12 (20.0%)	
<b>Native kidney Dx</b>				—
DM (type 1 and 2)	10 (23.3%)	3 (17.6%)	13 (21.7%)	
CNI toxicity	3 (7.0%)	0 (0.0%)	3 (5.0%)	
HRS	9 (20.9%)	11 (64.7%)	20 (33.3%)	
HTN	7 (16.3%)	0 (0.0%)	7 (11.7%)	
Other/missing	14 (32.6%)	3 (17.6%)	17 (28.3%)	
<b>Comorbidities</b>				
HTN	29 (67.4%)	7 (41.2%)	36 (60.0%)	0.082 <sup>b</sup>
DM	21 (48.8%)	8 (47.1%)	29 (48.3%)	1.000 <sup>b</sup>
CAD	4 (9.3%)	2 (11.8%)	6 (10.0%)	1.000 <sup>b</sup>
CKD	39 (90.7%)	14 (82.4%)	53 (88.3%)	0.393 <sup>b</sup>
HRS	15 (34.9%)	11 (64.7%)	26 (43.3%)	0.046 <sup>b</sup>
Hemodialysis at listing	24 (55.8%)	11 (64.7%)	35 (58.3%)	0.575 <sup>b</sup>
<b>SBP</b>				0.007 <sup>a</sup>
N	34	17	51	
Mean (SD)	133.1 (28.4)	109.6 (19.8)	125.3 (28.0)	
Median	127.5	105.0	125.0	
Q1, Q3	113.0, 151.0	100.0, 127.0	104.0, 144.0	
<b>DBP</b>				0.027 <sup>a</sup>
N	34	17	51	
Mean (SD)	70.4 (14.7)	60.6 (11.1)	67.2 (14.3)	
Median	71.0	63.0	67.0	
Q1, Q3	59.0, 81.0	54.0, 68.0	56.0, 76.0	
<b>Ascites</b>				0.168 <sup>b</sup>
None	8 (19.0%)	1 (5.9%)	9 (15.3%)	
Mild	12 (28.6%)	2 (11.8%)	14 (23.7%)	
Moderate	11 (26.2%)	5 (29.4%)	16 (27.1%)	
Severe	11 (26.2%)	9 (52.9%)	20 (33.9%)	
Missing	1	0	1	
<b>Hepatic encephalopathy</b>	24 (55.8%)	15 (88.2%)	39 (65.0%)	0.019 <sup>b</sup>

(Continued)

**TABLE 1. (Continued)**

Recipient characteristics by midodrine groups				
	None (N = 43)	Midodrine (N = 17)	Total (N = 60)	P
<b>Esophageal varices</b>	16 (37.2%)	8 (47.1%)	24 (40.0%)	0.564 <sup>b</sup>
<b>MELD-Na at listing</b>				0.002 <sup>a</sup>
Mean (SD)	25.1 (6.9)	30.1 (5.2)	26.5 (6.8)	
Median	23.0	29.0	25.0	
Q1, Q3	20.0, 30.0	27.0, 33.0	21.0, 30.5	
<b>MELD-Na at transplant</b>				0.003 <sup>a</sup>
Mean (SD)	25.8 (6.7)	31.3 (6.2)	27.3 (7.0)	
Median	23.0	31.0	26.0	
Q1, Q3	21.0, 30.0	28.0, 34.0	22.0, 31.5	
<b>Status at listing</b>				0.073 <sup>b</sup>
Ambulatory	36 (83.7%)	9 (56.3%)	45 (76.3%)	
Hospitalized—floor	4 (9.3%)	4 (25.0%)	8 (13.6%)	
Hospitalized—ICU	3 (7.0%)	3 (18.8%)	6 (10.2%)	
Missing	0	1	1	
<b>PRA</b>				0.816 <sup>a</sup>
N	28	15	43	
Mean (SD)	3.4 (7.0)	1.6 (3.0)	2.8 (6.0)	
Median	0.0	0.0	0.0	
Q1, Q3	0.0, 3.5	0.0, 3.0	0.0, 3.0	
<b>Immunosuppression</b>				0.639 <sup>b</sup>
Cyclosporine	1 (2.3%)	1 (5.9%)	2 (3.3%)	
Rapamune	1 (2.3%)	0 (0.0%)	1 (1.7%)	
Tacrolimus	41 (95.3%)	16 (94.1%)	57 (95.0%)	
<b>Induction</b>				0.006 <sup>b</sup>
Basiliximab	11 (26.2%)	1 (5.9%)	12 (20.3%)	
Dacluzimab	8 (19.0%)	0 (0.0%)	8 (13.6%)	
Thymoglobulin	4 (9.5%)	0 (0.0%)	4 (6.8%)	
None	19 (45.2%)	16 (94.1%)	35 (59.3%)	
Missing	1	0	1	

<sup>a</sup>Wilcoxon test.

<sup>b</sup>Fisher Exact test.

AIH, autoimmune hepatitis; ALD, alcohol liver disease; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CNI, calcineurin inhibitor; DBP, diastolic blood pressure; DM, diabetes mellitus; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HRS, hepatorenal syndrome; HTN, hypertension; ICU, intensive care unit; MELD-Na, model for end-stage liver disease-sodium; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; PRA, panel-reactive antibody; PSC, primary sclerosing cholangitis; SBP, spontaneous bacterial peritonitis.

**TABLE 2.**

**Description of midodrine use**

Midodrine use	Total (N = 17)
<b>Midodrine duration (d)</b>	
Mean (SD)	111.4 (95.0)
Median	91.0
Q1, Q3	22.0, 181.0
<1 mo	5 (29.4%)
1–3 mo	3 (17.6%)
>3 mo	9 (52.9%)
<b>Midodrine daily dose (mg)</b>	
Mean (SD)	32.4 (17.1)
Median	30.0
Q1, Q3	15.0, 45.0
<10 mg/d	1 (5.9%)
10–30 mg/d	9 (52.9%)
>30 mg/d	7 (41.2%)

of hepatic encephalopathy, and higher model for end-stage liver disease-sodium (MELD-Na) at listing and at transplant compared with those not on midodrine. There was no difference in presence of ascites or esophageal varices.

Pretransplant midodrine use was typically >3 mo, and the majority took between 10 and 30 mg total daily dose (Table 2). Donor characteristics were similar between the groups (Table 3), including no significant differences between demographics, cold, and warm ischemia times, panel-reactive antibody, and kidney donor profile index.

Regarding short-term outcomes, there were no significant differences in transplant hospitalization length of stay, incidence of delayed renal allograft function, need for post-transplant hemodialysis, need for midodrine at discharge, or estimated glomerular filtration rate (eGFR) at discharge of transplant hospitalization. After transplant, there were no differences in eGFR at 1 y, number of hospitalizations in the first

**TABLE 3.**

**Donor and operative characteristics by recipient midodrine use**

Donor and operative characteristics by midodrine groups				
	None (N = 43)	Midodrine (N = 17)	Total (N = 60)	P
<b>Donor age</b>				0.989 <sup>a</sup>
N	27	17	44	
Mean (SD)	33.6 (13.6)	33.6 (11.6)	33.6 (12.7)	
Median	35.0	28.0	33.5	
Q1, Q3	22.0, 44.0	24.0, 45.0	23.0, 44.5	
<b>Donor sex</b>				0.521 <sup>b</sup>
Female	7 (25.9%)	6 (35.3%)	13 (29.5%)	
Male	20 (74.1%)	11 (64.7%)	31 (70.5%)	
Missing	16	0	16	
<b>Donor type</b>				1.000 <sup>b</sup>
DBD	42 (97.7%)	17 (100.0%)	59 (98.3%)	
DCD	1 (2.3%)	0 (0.0%)	1 (1.7%)	
<b>COD</b>				0.954 <sup>b</sup>
Anoxia	11 (40.7%)	8 (47.1%)	19 (43.2%)	
Cerebrovascular/stroke	8 (29.6%)	4 (23.5%)	12 (27.3%)	
Head trauma	7 (25.9%)	5 (29.4%)	12 (27.3%)	
Other	1 (3.7%)	0 (0.0%)	1 (2.3%)	
Missing	16	0	16	
<b>CIT (min)</b>				0.097 <sup>c</sup>
N	29	16	45	
Mean (SD)	485 (240)	406 (264)	457 (249)	
Median	480	329	379	
Q1, Q3	307, 623	265, 463	287, 588	
<b>WIT (min)</b>				0.694 <sup>a</sup>
N	29	17	46	
Mean (SD)	33.4 (7.6)	34.4 (9.3)	33.8 (8.2)	
Median	33.0	35.0	34.0	
Q1, Q3	27.0, 40.0	27.0, 41.0	27.0, 40.0	
<b>KDPI</b>				0.764 <sup>a</sup>
N	26	17	43	
Mean (SD)	36.5 (22.6)	38.5 (18.5)	37.3 (20.9)	
Median	36.5	41.0	38.0	
Q1, Q3	21.0, 47.0	23.0, 49.0	21.0, 47.0	

<sup>a</sup>Equal variance t test.

<sup>b</sup>Fisher Exact test.

<sup>c</sup>Wilcoxon test.

CIT, cold ischemia time; COD, cause of death; DBD, donation after brain death; DCD, donation after circulatory death; KDPI, kidney donor profile index; WIT, warm ischemia time.

**TABLE 4.****Outcomes by midodrine use****Outcomes by midodrine groups**

	None (N = 43)	Midodrine (N = 17)	Total (N = 60)	P
<b>eGFR</b>				
N				
Median (Q1, Q3)				
At discharge	36 51.7 (44.2, 83.3)	14 76.5 (49.1, 105.8)	50 57.1 (46.2, 85.5)	0.115 <sup>a</sup>
Year 1	34 60.5 (57.0, 74.0)	9 57.0 (46.0, 61.0)	43 60.0 (54.0, 74.0)	0.193 <sup>a</sup>
Year 2	31 60.0 (52.0, 75.0)	5 56.0 (54.0, 60.0)	36 60.0 (53.0, 73.5)	–
Year 3	26 60.0 (51.0, 75.0)	3 54.0 (38.1, 56.0)	29 59.0 (51.0, 75.0)	–
Year 5	17 55.0 (47.0, 71.0)	1 61.0	18 56.5 (47.0, 71.0)	–
<b>Hospital LOS</b>				
Mean (SD)	20.2 (24.4)	26.7 (28.0)	22.0 (25.4)	0.305 <sup>a</sup>
Median	13.0	14.0	13.0	
Q1, Q3	9.0, 20.0	10.0, 34.0	9.0, 24.0	
Renal failure	8 (18.6%)	4 (23.5%)	12 (20.0%)	0.726 <sup>b</sup>
Post-Txp hemodialysis	7 (16.3%)	3 (17.6%)	10 (16.7%)	1.000 <sup>b</sup>
Midodrine use at discharge	0 (0.0%)	2 (11.8%)	2 (3.3%)	0.077 <sup>b</sup>
Status at last follow-up				
Alive	35 (81.4%)	14 (82.4%)	49 (81.7%)	1.000 <sup>b</sup>
Dead	8 (18.6%)	3 (17.6%)	11 (18.3%)	
<b>Number of hospitalizations</b>				
N				
Median (Q1, Q3)				
0–6 mo	30 2.0 (1.0, 3.0)	8 1.5 (1.0, 3.0)	38 2.0 (1.0, 3.0)	0.651 <sup>a</sup>
6–12 mo	15 1.0 (1.0, 2.0)	1 1.0	16 1.0 (1.0, 2.0)	–
>12 mo	20 3.0 (1.5, 4.0)	2 1.0 (1.0, 1.0)	22 3.0 (1.0, 4.0)	–

<sup>a</sup>Wilcoxon test.<sup>b</sup>Fisher Exact test.

BMI, body mass index; eGFR, estimated glomerular filtration rate; LOS, length of stay.

6 mo posttransplant, or survival at last follow-up between the groups (Table 4). Data beyond 1 y were collected and suggest that there were no significant differences in these outcomes out to 5 y, but follow-up numbers were too few to test for statistical significance.

## DISCUSSION

Our study is the first to evaluate whether the use of pretransplant midodrine resulted in worse outcomes after SLKT. Despite the midodrine group having a higher MELD-Na at listing, higher MELD-Na at transplant, and older age, there were no significant differences in key outcomes including delayed graft function, eGFR at transplant discharge, and eGFR at 1 y after transplant compared with the nonmidodrine group. There was no difference in graft failure or survival at last follow-up. The majority of patients on pretransplant midodrine were not on midodrine at posttransplantation discharge (88.2%). Our study supports that requirement for pretransplant midodrine should not be a barrier to simultaneous liver-kidney transplant.

Our findings contrast with studies in KT alone recipients that have shown worse outcomes for patients that require midodrine pretransplant. There are significant pathophysiologic differences between patients requiring SLKT versus those requiring KT alone. The underlying mechanism resulting in hypotension may be more liver-related in SLKT candidates and is therefore typically ameliorated with a successful liver transplant. In KT alone patients, end-stage renal disease largely develops from hypertension and diabetes, which lead to calcification and remodeling of large vessels and arterial stiffening resulting in decreased vascular compliance, myocardial fibrosis resulting in diastolic dysfunction, and autonomic dysfunction.<sup>5</sup> These physiologic changes tend to worsen with hemodialysis use and with more time awaiting organ transplantation. A patient with this underlying pathophysiology, who then develops hypotension with or without hemodialysis, represents a higher risk patient, as their hypotension is likely related to concomitant cardiovascular compromise. These changes leading to pretransplant hypotension are unlikely to improve after KT alone and can contribute to reduced perfusion of the renal allograft. In contrast, in



patients with end-stage liver disease, renal hypoperfusion is influenced by splanchnic vasodilation, as opposed to the vessel-mediated changes in end-stage renal disease. Midodrine is used in patients with cirrhosis to reverse this effect and augment systemic blood pressure. Because of transplant dynamics, patients with end-stage liver disease typically do not wait as long for organ transplantation. Thus, the changes that are associated with renal dysfunction may not permanently impact the vessels or heart in SLKT patients and splanchnic vasodilation starts to improve immediately after implantation and reperfusion of the liver.

Much of the prior literature focuses on patients specifically with HRS, and it is well known that liver transplant ameliorates HRS. Initial studies demonstrated that patients with HRS have diminished renal function after liver transplantation,<sup>9,10</sup> but it was clear from these studies that the majority of these patients recovered enough renal function to avoid hemodialysis altogether after liver transplantation. However, it is not known if patients who require blood pressure augmentation have different outcomes than patients who do not. An initial small study found no difference in 3-y survival or in incidence of posttransplant renal dysfunction in patients with HRS treated with vasoconstrictors compared with LT recipients who did not have HRS.<sup>11</sup> Rice et al<sup>7</sup> expanded upon this and additionally found that there were no differences in renal function after liver transplant between patients treated with triple therapy (albumin, octreotide, midodrine) for HRS and those that were not. In addition, they found that most patients did not require hemodialysis after liver transplant. These findings suggest that the physiologic mechanism behind renal dysfunction may be reversed with improvement in portal hemodynamics. Notably, this study only included patients with HRS undergoing liver transplantation, whereas patients undergoing SLKT may have renal failure from a variety of causes, representing a more real-world cohort that may also not be adversely affected by pretransplant midodrine use.

Although it has been demonstrated that transplantation for and with HRS is beneficial to the patient and largely results in good outcomes, the data behind outcomes for SLKTs are less well known. The uniqueness of our study lies with the population of patients undergoing SLKT, which includes patients with HRS and those with persistent hypotension because of end-stage liver disease, a reflection of real-world practice. Our study demonstrates that although patients receiving midodrine undergoing SLKT were older and sicker, short-term outcomes are better than KT alone recipients receiving midodrine. Hypotension associated with the latter is likely driven by long-lasting effects from years of end-stage renal disease mediated vascular damage. We show that the need for pretransplant midodrine does not negatively impact eGFR at discharge and at 1 y hospital length of stay, posttransplant need for hemodialysis, midodrine use at discharge, or mortality. This suggests that midodrine use should not be a barrier to transplanting a patient who needs both liver and kidney and

should allay fears that midodrine will be required after SLKT, as only 2 patients required the medication at discharge.

Although our study is novel, it is limited by small numbers of overall patients and retrospective nature. Additionally, nearly half of the SLKTs in our cohort were performed within the past 4 y, and a third were performed within the past 2 y, representative of a shift in national trends. Therefore, long-term follow-up (beyond 1 y) for a majority of our cohort is not known, limiting our ability to draw conclusions on renal allograft function over time.

In summary, our study examined whether outcomes for SLKT recipients were negatively impacted by the need for midodrine pretransplant. Our findings did not find a difference in key outcomes after SLKT including rate of delayed renal allograft function, eGFR at transplant discharge and at 1 y, and need for posttransplant hemodialysis. These results suggest need for pretransplant midodrine should not on its own be a barrier to SLKT. Further study is needed with a larger patient cohort and longer follow-up duration to validate these findings.

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