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Sex-based Differences and Comparative Predictive Value of MELD 3.0 in Simultaneous Liver-Kidney Transplantation Waitlist Outcomes After Standardization of Listing Criteria in the United States

Emily A. Leven, MD,[1] Ditian Li, MPH,[2] Emilia Bagiella, PhD,[2] Thomas D. Schiano, MD,[3] and Lauren Tal Grinspan, MD, PhD[3]

Background. Sex disparities in solid organ transplantation are well documented. Relative changes in sex-based outcome disparities after the 2017 standardization of simultaneous liver-kidney (SLK) listing criteria in the United States have not been reported. We hypothesized that this policy's objective measures of kidney dysfunction may differentially affect SLK patients by sex and that the use of MELD 3.0 in the SLK population might provide unique benefit to female transplant candidates. **Methods.** Organ Procurement and Transplantation Network data were retrospectively analyzed comparing 2013–2016 with 2018–2021 SLK listings. Waitlist outcomes and Model for End-stage Liver Disease (MELD) 3.0 reclassifications were compared by sex and listing period. **Results.** There were 2626 and 2609 male patients and 1670 and 1919 female patients pre- and post-policy changes, respectively. The proportion of female SLK listings post-policy change (42.4%) was higher than both female SLK listings pre-policy change (38.9%) and female single-organ liver listings post-policy change (36.8%; $P < 0.01$). A statistically significant interaction between sex and listing group (pre- versus post-policy change) was present in multivariable analysis ($P = 0.02$). Female patients were more likely to have a higher MELD 3.0 score than the listing MELD/MELD-Na score when the listing MELD score was <30 ($P < 0.01$). Among all patients who died on the waitlist, female patients were nearly twice as likely to be underrepresented by listing MELD compared with MELD 3.0 (23% female and 13% male patients; $P < 0.01$). **Conclusions.** Waitlist outcomes were changed differentially between male and female patients after the 2017 SLK policy change. The application of MELD 3.0 to SLK patients is likely to benefit female patients.

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In single-organ liver transplantation (LT) in the United States, female patients experience longer waitlist times and higher waitlist mortality than male patients.[1-6] Female patients experience higher rates of mismatched recipient-donor organ size,[7-10] increased frailty,[11,12] lower likelihood of exception points for hepatocellular carcinoma (HCC),[4]

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[1] *Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY.*

[2] *Department of Population Health, Center for Biostatistics, Icahn School of Medicine at Mount Sinai, New York, NY.*

[3] *Recanati/Miller Transplantation Institute, Icahn School of Medicine at Mount Sinai, New York, NY.*

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Correspondence: Emily A. Leven, MD, Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Place Box 1069, New York, NY 10029. (emily.leven@mountsinai.org).

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and underestimation of renal dysfunction in the creatinine-based organ allocation scores—the Model for End-stage Liver Disease (MELD) and Model for End-stage Liver Disease-Sodium (MELD-Na). All of these factors contribute to female patients experiencing longer waitlist times and increased rates of waitlist mortality and delisting for clinical deterioration (reported to United Network for Organ Sharing [UNOS] as "condition deteriorated, too sick for transplantation.")[2,3,6,13-15] Sex-based differences in renal function estimation are important not only in dictating waitlist times but also prognostically, as pretransplant renal complications are closely linked to waitlist[16] and posttransplant outcomes.[17] A measure misrepresenting acute kidney injury (AKI) or chronic kidney disease (CKD) may alter clinician behavior in the period leading up to transplantation regarding diagnosis and management of CKD, initiation of renal replacement therapy (RRT), and listing for simultaneous liver-kidney (SLK) transplantation.[18,19]

Before 2017, no standardized criteria for SLK listing eligibility existed. In 2017, the UNOS implemented a new policy requiring one of the following criteria to be met for SLK listing: (1) CKD (glomerular filtration rate [GFR] ≤60 mL/min for 90 consecutive days) with new RRT requirement or decrease in GFR to ≤30 mL/min, (2) sustained AKI for 6 wk (RRT at least once every 7 d or GFR ≤25 mL/min measured once every 7 d), and (3) metabolic disease affecting both liver and kidneys.[20]

Little has been reported on the impact of the SLK policy change on waitlist outcomes in male and female patients. Standardization of listing criteria using GFR might increase the number of female patients eligible for SLK; however, organ allocation and waitlist time for SLK candidates remain tied to the creatinine-based MELD-Na (and now MELD 3.0) and is further complicated by additional constraints leading to longer waitlist times in kidney organ matching related to HLA sensitization and potential histocompatibility mismatch from fetal exposure in female patients.[19,21] A retrospective analysis of UNOS data capturing the first 2 y of patients listed under the new SLK policy showed that all patients were listed for SLK at lower GFRs and that regional variability in median GFR at listing decreased after the policy's implementation, suggesting successful standardization in listing practices. Sex-based listing patterns and outcomes were not specifically examined, but a larger proportion of female patients underwent SLK after 2017 compared with before.[22] Another retrospective analysis of the first 2 y of SLK outcomes after policy standardization compared SLK patients listed from January 2015 to July 2017 and those listed from September 2017 to March 2019, and similarly found a decrease in average GFR at the time of listing and an increased proportion of female patients listed for SLK after the policy change.[23] No difference in overall 90-d waitlist mortality was observed between the pre- and post-policy change groups when accounting for sex; the specific impact of sex as a covariate was not reported.[23] Finally, a retrospective analysis of patients listed for SLK in the 3 y pre- and post-policy change found a 3% increase in female listings and a 3% increase in listings for alcohol-related liver disease (ALD) regardless of sex, demonstrating changing demographics in the SLK population.[24]

Given the observed shifts in demographics in both single-organ LT listings over time[25] and SLK listings after the 2017 policy change, we hypothesized that the SLK policy may have a differential impact on male and female candidates. The primary aim of this study was to compare waitlist outcomes (death, transplantation, delisting for clinical deterioration, and delisting for clinical improvement) by sex before and after SLK listing criteria standardization. Secondary outcomes included waitlist patterns and outcomes by sex, ethnicity, and transplant indication pre- and post-policy change.

Another significant change recently affecting SLK patients is the adoption of MELD 3.0 for liver and SLK allocation in the United States. Although SLK patients were included in the cohort used to develop the MELD 3.0 algorithm, it has not been modeled independently in the SLK population.[26] It is expected that the increased coefficient for female sex and decreased creatinine cap would be especially relevant in equalizing assigned MELD 3.0 scores to male and female patients with significant kidney dysfunction. We therefore hypothesized that the SLK population, who are uniformly experiencing significant renal dysfunction, represents a unique subset of LT patients experiencing a different magnitude of MELD 3.0 effects on waitlist outcomes compared with the previously studied cohort of combined LT and SLK patients. Given the recent adoption of MELD 3.0, it will be some time before enough data are available to study this rigorously among patients who have been listed and allocated organs using MELD 3.0. Therefore, we sought to evaluate the predictive value of the difference in reported MELD versus calculated MELD 3.0 at SLK listing on waitlist outcomes in our large SLK population as a proxy measure for how the current MELD 3.0 system might perform.

MATERIALS AND METHODS

Study Population

This study used data from UNOS Standard Transplant and Research files for liver and kidney transplants between January 1, 2010, and June 30, 2022. Adult patients were included if they were listed for SLK within the study period. Listing groups included adult SLK listings from January 1, 2013, to December 31, 2016, in the pre-policy change group and from January 1, 2018, to December 31, 2021, in the post-policy change group. Retransplantation, status 1, multiorgan (aside from SLK), and 2017 listings (SLK policy change year) were excluded. Patients with a diagnosis of autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis were combined into a single "autoimmune" group, given small numbers. Patients with concomitant hepatitis C virus (HCV) and ALD were considered in the HCV group because it was felt that concomitant HCV-associated kidney dysfunction made these patients more similar to patients with HCV-associated liver disease than to those with ALD.[27,28] Sex, race, and ethnicity were categorized as reported to UNOS. Follow-up was censored at 3 y. MELD scores were those reported by UNOS at the time of listing for organ allocation (natural MELD without exception points). The term "MELD" is used hereafter to refer to both the reported listing MELD (before 2016) and the reported listing MELD-Na (after its adoption in 2016). Organ Procurement and Transplantation Network data during this time used the terminology nonalcoholic fatty liver disease; new nomenclature is used in this report for metabolic dysfunction–associated steatotic liver disease (MASLD).[29] The project was exempt from Institutional Review Board review due to the use of publicly available deidentified data.

Statistics

All variables are reported as means and SDs or counts and percentages, as appropriate. Univariable and multivariable competing risk models using the Fine-Gray approach were used to compare pre- and post-policy change waitlist outcomes (death, transplantation, delisting due to deterioration, delisting due to improvement) between sexes in each listing period; outcomes for each listing period are presented separately. Covariates were selected for use in the multivariable models (including the primary outcome model with an interaction term for sex and pre-/post-policy change listing group) based on statistical significance in univariable models ($P < 0.05$) and on clinical importance. Age, sex, and MELD were included in the models regardless of statistical significance. Secondary outcomes were evaluated by comparing pre- and post-policy groups separately, as described below.

MELD 3.0 scores were calculated using raw data values reported by UNOS at the time of listing, applying methods described by Kim et al.[3] Relative differences in the likelihood of reclassification from listing MELD to MELD 3.0 by sex were measured using chi-square tests. All analyses were conducted using SAS version 9.4 (SAS Institute Inc). All tests were conducted at the 0.05 significance level.

RESULTS

There were 157 495 listings for LT (single-organ LT alone, not including SLK listings) during the study period; details of inclusion and exclusion are displayed in Figure 1. Some patients met multiple exclusion criteria. A total of 8824 patients listed for SLK were included: 2626 male patients (61.1%) and 1670 female patients (38.9%) listed for pre-policy change and 2609 male patients (57.6%) and 1919 female patients (42.4%) listed for post-policy change (Table 1). During the same period, 24 969 (65.4%) male and 13 199 (34.6%) female LT listings were included pre-policy change and 27 096 (63.2%) male and 15 774 (36.8%) female listings were included post-policy change (Table 2). This represented a significantly higher proportion of female SLK listings compared with that seen in the LT group during the same time period for both pre- and post-policy change groups ($P < 0.01$ pre-policy change, $P < 0.01$ post-policy change; **Figure S1, SDC,** http://links.lww.com/TXD/A746). The top indications for female SLK listing differed from those for LT listing (Tables 1 and 2). Female patients listed post-policy change were on average older and had higher MELD and creatinine than pre-policy change; there was also a relative increase in listing for ALD seen in female patients (but not male patients) post-policy change (Table 1). The mean MELD at SLK listing was 24 for female and 25 for male patients in the pre-policy change group and 25 for both male and female patients in the post-policy change group. Mean SLK listing creatinine was lower for female patients in both the pre- and post-policy change groups compared with male patients in each respective listing group; the mean creatinine at SLK listing for each sex increased post-policy change (3.15 pre-policy change versus 3.25 post-policy change in female patients; 3.89 pre-policy change versus 4.15 post-policy change in male patients; Table 1).

Competing risk time to event models were used to evaluate the likelihood of each outcome of interest for male and female patients in the pre- versus post-period. Compared with pre-policy change, fewer patients overall were delisted for clinical deterioration and more patients underwent transplantation post-policy change. Female patients were more likely to die on the waitlist or be removed from the waitlist due to clinical deterioration compared with male patients pre-policy change and compared with both male and female patients post-policy change. Similarly, female patients pre-policy change were the least likely to undergo transplantation compared with male patients pre-policy change and compared with all patients post-policy change (Figure 2).

Multivariable analyses (Table 3) were performed on the basis of the results of univariable testing as described in Materials and Methods. Multivariable models showed that in both the pre- and post-policy change groups, age and MELD were independently associated with an increased risk of waitlist death. Female patients were significantly less likely than male patients to undergo transplantation in the pre-policy change group (hazard ratio [HR], 0.85; 95% confidence interval [CI], 0.75-0.96; $P = 0.01$), although this sex-associated difference was no longer present in the post-policy change group (HR, 1.11; 95% CI, 0.99-1.24; $P = 0.09$). Furthermore, no differences were observed in the likelihood of transplantation for any ethnicity or transplant indication. A relatively small number of patients were delisted because of clinical improvement (n = 187), and this was more commonly

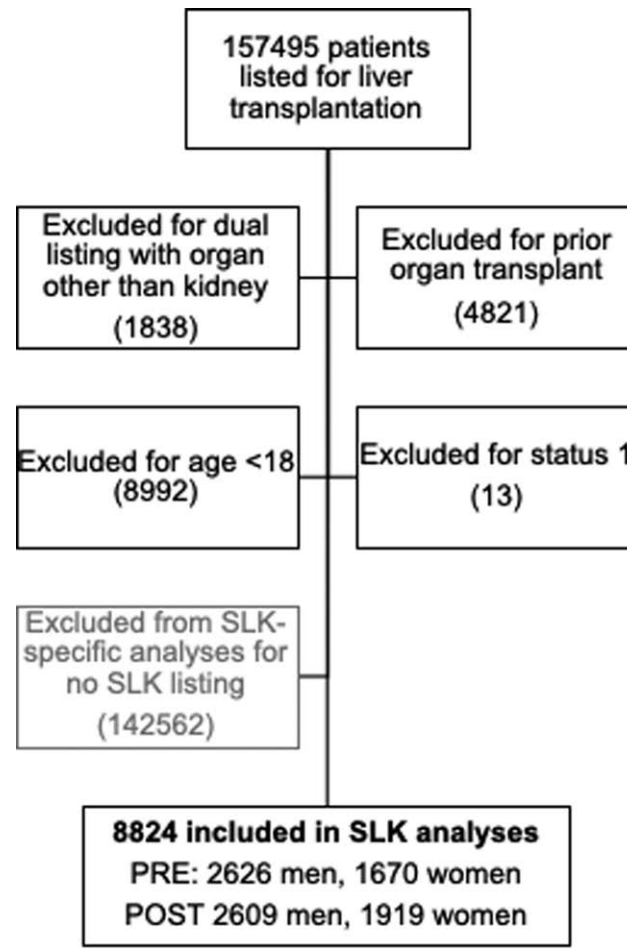

FIGURE 1. Patient inclusion and exclusion. SLK, simultaneous liver-kidney transplantation.

TABLE 1.

SLK patient characteristics

SLK patients	Pre-policy change			Post-policy change		
	Female	Male	*P*	Female	Male	*P*
Count, n (%)	1670 (38.9%)	2626 (61.1%)		1919 (42.4%)	2609 (57.6%)	
Age at listing, y, mean (SD)	57 (9.4)	57 (9.2)	0.08	58 (10.3)	57 (10.4)	**<0.01**
MELD at listing, mean (SD)	24 (8.5)	25 (8.1)	**0.04**	25 (7.8)	25 (7.3)	0.46
Creatinine at listing, mean (SD)	3.15 (2.1)	3.89 (2.7)	**<0.01**	3.25 (2.1)	4.15 (2.6)	**<0.01**
Height, cm, mean (SD)	162 (7.5)	176 (8.4)	**<0.01**	162 (7.6)	176 (8.3)	**<0.01**
Ethnicity			0.16			0.21
White	1010 (23.5%)	1637 (38.1%)		1160 (25.6%)	1652 (36.5%)	
Black	249 (5.8%)	339 (7.9%)		208 (4.6%)	265 (5.9%)	
Hispanic	308 (7.2%)	513 (11.9%)		432 (9.5%)	526 (11.6%)	
Asian	74 (1.7%)	105 (2.4%)		82 (1.8%)	132 (2.9%)	
Other	29 (0.7%)	32 (0.7%)		37 (0.8%)	43 (0.9%)	
Transplant indication			**<0.01**			**<0.01**
MASLD	478 (11.1%)	1010 (23.5%)		759 (16.8%)	609 (13.4%)	
Autoimmune	133 (3.1%)	1011 (23.5%)		121 (2.7%)	62 (1.4%)	
ALD	257 (6.0%)	1012 (23.5%)		437 (9.7%)	1020 (22.5%)	
HCV	375 (8.7%)	1013 (23.5%)		152 (3.4%)	351 (7.8%)	
Other	427 (9.9%)	1014 (23.5%)		450 (9.9%)	567 (12.5%)	
Waitlist days, mean (SD)	320 (362)	309 (353)	0.29	228 (215)	245 (233)	0.05

Statistically significant *P* values are denoted in bold.ALD, alcohol-related liver disease; HCV, hepatitis C virus; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-stage Liver Disease; SLK, simultaneous liver-kidney.

TABLE 2.

LT patient characteristics

LT patients	Pre-policy change			Post-policy change		
	Female	Male	*P*	Female	Male	*P*
Count (%)	13199 (34.6%)	24969 (65.4%)		15774 (36.8%)	27096 (63.2%)	
Age at listing, y, mean (SD)	55 (11.1)	56 (9.6)	**<0.01**	55 (11.8)	56 (11.0)	**<0.01**
MELD at listing, mean (SD)	18 (9.3)	17 (9.1)	**<0.01**	20 (10.0)	19 (10.0)	**<0.01**
Creatinine at listing, mean (SD)	1.07 (0.82)	1.18 (0.81)	**<0.01**	1.11 (0.84)	1.27 (0.97)	**<0.01**
Height, cm, mean (SD)	162 (7.2)	176 (7.9)	**<0.01**	162 (7.8)	177(8.6)	**<0.01**
Ethnicity			**<0.01**			**<0.01**
White	9094 (23.8%)	18110 (47.4%)		10868 (25.4%)	19635 (45.8%)	
Black	1225 (3.2%)	1833 (4.8%)		1174 (2.7%)	1412 (3.3%)	
Hispanic	2111 (5.5%)	3576 (9.4%)		2869 (6.7%)	4479 (10.4%)	
Asian	538 (1.4%)	1142 (3.0%)		560 (1.3%)	1173 (2.7%)	
Other	231 (0.6%)	308 (0.8%)		303 (0.7%)	397 (0.9%)	
Transplant indication			**<0.01**			**<0.01**
MASLD	2491 (6.5%)	2757 (7.2%)		4004 (9.3%)	4416 (10.3%)	
Autoimmune	2316 (6.1%)	1502 (3.9%)		2371 (5.5%)	1673 (3.9%)	
ALD	2058 (5.4%)	5810 (15.2%)		4201 (9.8%)	9762 (22.8%)	
HCV	2853 (7.5%)	7774 (20.4%)		1230 (2.9%)	3192 (7.4%)	
Other	3480 (9.1%)	7126 (18.7%)		3967 (9.3%)	8048 (18.8%)	
Waitlist days, mean (SD)	351 (374)	327 (348)	**<0.01**	248 (292)	238 (277)	**<0.01**

Statistically significant *P* values are denoted in bold.ALD, alcohol-related liver disease; HCV, hepatitis C virus; LT, liver transplant; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-stage Liver Disease.

observed in female than male patients in the pre- but not post-policy change listing group (HR, 2.34; 95% CI, 1.32-4.14; $P < 0.01$; HR, 1.6; 95% CI, 0.91-2.79; $P = 0.10$, respectively).

Multivariable analyses of the same covariates were performed in the LT population during the study period to compare the changes in the overall population eligible for LT to those observed in the SLK group before and after the policy change (**Table S1, SDC,** http://links.lww.com/TXD/A746). The patterns of waitlist outcomes for male and female patients in the pre- and post-policy change eras differed from those seen in patients listed for SLK.

Given the observed waitlist outcome differences between sexes in the pre- and post-policy change groups on multivariable analysis, a formal test of the interaction between sex and listing group was performed to evaluate the primary research question of sex-based differences in waitlist outcomes pre- and post-policy change. Testing for interaction terms established a statistically significant interaction

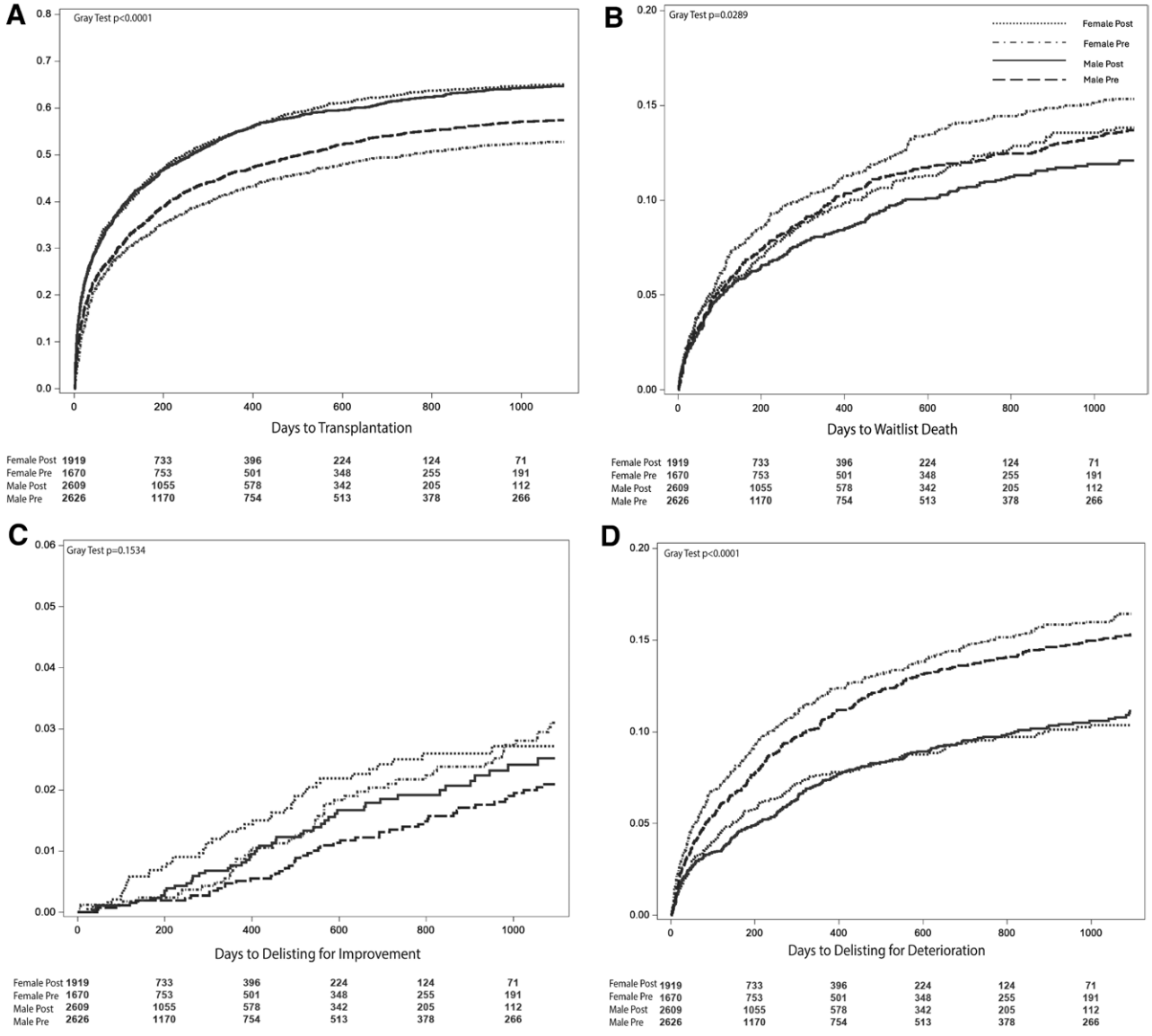

FIGURE 2. Competing risk of waitlist outcomes pre- and post-policy change by sex (using sex/listing period interaction term). Four clinical groups: female patients pre-policy change, male patients pre-policy change, female patients post-policy change, and male patients post-policy change. Cumulative incidence functions using Fine-Gray adjustment. A, Transplantation: the likelihood of transplantation between the 4 groups is significantly different ($P < 0.01$). Female patients pre-policy change are the least likely of all 4 groups to undergo transplantation. The likelihood of transplantation increases and equalizes between male and female patients after policy change. B, Waitlist death: the likelihood of waitlist mortality is significantly different between the 4 groups ($P = 0.029$). Female patients pre-policy change are the most likely of the 4 groups to experience waitlist mortality. The likelihood of waitlist mortality for female patients post-policy change decreases compared with pre-policy change and is similar to waitlist mortality for male patients in the same time period. C, Delisting for improvement: there is no significant difference in the likelihood of delisting for clinical improvement between the 4 groups. D, Delisting for deterioration: there is a significant difference in the likelihood of delisting for clinical deterioration between the 4 groups. Male and female patients pre-policy change have a higher likelihood of delisting pre-policy change than post-policy change.

between sex and listing group for the likelihood of transplantation ($P = 0.02$) but not waitlist death ($P = 0.89$), delisting for deterioration ($P = 0.27$), or delisting for improvement ($P = 0.65$; Table 4; **Table S2, SDC,** http://links.lww.com/TXD/A746).

Finally, patterns in listing MELD and calculated MELD 3.0 discordance were examined with chi-square tests according to the MELD groupings used in the development of MELD 3.0[3] (Tables 5–7). It was assumed that patients who were delisted for clinical deterioration died on the waitlist for the purposes of this analysis. If a patient's listing MELD was in a lower group than that of their calculated MELD 3.0, the patient was considered to be "upclassified" by the MELD 3.0. Similar to reports by Kim et al,[3] significantly more female than male patients were underrepresented by their listing MELD compared with their calculated MELD 3.0 scores (ie, MELD 3.0 score higher than MELD in 19.25% of female and 11.19% of male patients, chi-square $P < 0.01$; Table 6). This difference was statistically significant for listing MELD of <30. Similarly, female patients who died on the waitlist were more likely to be upclassified from MELD to MELD 3.0 score than male patients (22.98% of female versus 12.74% of male patients, chi-square $P < 0.01$; Table 6), particularly for MELD <30. Female patients were also more likely to be downclassified

TABLE 3.

Multivariable statistics, SLK patients

	Pre-policy change, multivariable							
	Death		Transplant		Deteriorated		Improved	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Pre-policy change, multivariable								
Female	1.1 (0.86-1.4)	0.46	0.85 (0.75-0.96)	**0.01**	1.01 (0.8-1.26)	0.95	2.34 (1.32-4.14)	**<0.01**
Age	1.02 (1.01-1.03)	**<0.01**	0.99 (0.99-1)	**<0.01**	1.04 (1.03-1.05)	**<0.01**	0.96 (0.95-0.98)	**<0.01**
MELD	1.01 (1-1.02)	**0.02**	1.05 (1.05-1.06)	**<0.01**	1.01 (1-1.02)	**<0.01**	0.93 (0.91-0.96)	**<0.01**
Height, cm	1 (0.99-1.01)	0.66	1 (0.99-1.01)	0.86	1 (0.98-1.01)	0.33	1.03 (1-1.06)	**0.04**
Ethnicity	Reference = White							
Black	0.76 (0.58-1)	0.05	1.02 (0.89-1.16)	0.80	0.89 (0.69-1.14)	0.35	2.01 (1.2-3.37)	**0.01**
Hispanic	1.07 (0.86-1.34)	0.52	0.72 (0.63-0.82)	**<0.01**	1.19 (0.97-1.46)	0.10	1.06 (0.57-1.96)	0.86
Asian	0.88 (0.57-1.38)	0.58	0.7 (0.55-0.89)	**<0.01**	1.05 (0.71-1.55)	0.80	0.28 (0.04-2.02)	0.21
Other	1.29 (0.71-2.36)	0.41	0.57 (0.36 - 0.88)	**0.01**	1.25 (0.69 - 2.26)	0.47	0.8 (0.11-5.79)	0.83
Transplant indication	Reference = HCV							
Autoimmune	1.15 (0.78-1.69)	0.48	0.87 (0.69-1.11)	0.27	1.15 (0.77-1.69)	0.50	0.65 (0.23-1.89)	0.43
ETOH	1.04 (0.82-1.31)	0.78	0.8 (0.7-0.91)	**<0.01**	1.19 (0.94-1.5)	0.15	1.24 (0.71-2.15)	0.46
MASLD	1.05 (0.83-1.33)	0.70	0.99 (0.87-1.13)	0.92	1.04 (0.82-1.31)	0.77	0.52 (0.25-1.08)	0.08
Other	0.81 (0.63-1.04)	0.09	0.95 (0.84-1.07)	0.38	1.25 (1-1.56)	0.05	0.92 (0.52-1.6)	0.76
Post-policy change, multivariable								
Female	0.92 (0.72-1.18)	0.51	1.11 (0.99-1.24)	0.09	0.91 (0.69-1.19)	0.49	1.6 (0.91-2.79)	0.10
Age	1.02 (1.01-1.03)	**<0.01**	1 (1-1.01)	0.26	1.02 (1.01-1.04)	**<0.01**	0.95 (0.94-0.97)	**<0.01**
MELD	1.02 (1-1.03)	**0.01**	1.06 (1.06-1.07)	**<0.01**	1.01 (1-1.03)	0.06	0.91 (0.89-0.94)	**<0.01**
Height, cm	0.99 (0.98-1)	0.08	1.01 (1-1.01)	**0.02**	1 (0.99-1.02)	0.68	1.01 (0.99-1.04)	0.33
Ethnicity	Reference = White)							
Black	0.95 (0.69-1.31)	0.76	0.87 (0.75-1.01)	0.07	0.96 (0.69-1.35)	0.83	1.34 (0.72-2.48)	0.35
Hispanic	1.04 (0.83-1.3)	0.77	0.91 (0.81-1.01)	0.08	1.19 (0.93-1.53)	0.17	0.55 (0.28-1.1)	0.09
Asian	0.75 (0.46-1.23)	0.26	0.96 (0.79-1.17)	0.69	0.92 (0.56-1.5)	0.73	1.68 (0.74-3.82)	0.22
Other	0.92 (0.46-1.85)	0.81	1 (0.74-1.35)	0.99	1.02 (0.49-2.14)	0.95	1.21 (0.29-5.07)	0.79
Transplant indication	Reference = HCV							
Autoimmune	1.14 (0.69-1.87)	0.61	1 (0.79-1.28)	0.99	1.39 (0.81-2.38)	0.23	0.96 (0.34-2.71)	0.93
ALD	0.9 (0.64-1.26)	0.54	1.07 (0.93-1.24)	0.33	0.85 (0.59-1.23)	0.39	1 (0.49-2.05)	0.10
MASLD	1.21 (0.88-1.65)	0.25	1.03 (0.9-1.19)	0.65	1.31 (0.92-1.86)	0.13	0.49 (0.23-1.05)	0.07
Other	0.89 (0.63-1.26)	0.52	1.07 (0.92-1.23)	0.37	1.36 (0.95-1.94)	0.09	0.63 (0.3-1.31)	0.21

Statistically significant *P* values are denoted in bold.ALD, alcohol-associated liver disease; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; MASLD, metabolic dysfunction–associated steatotic liver disease; MELD, Model for End-stage Liver Disease; SLK, simultaneous liver-kidney.

TABLE 4.

Interaction of waitlist outcomes by sex and listing group (pre-policy change vs post-policy change)

	Sex x listing group interaction							
	Death		Transplant		Deteriorated		Improved	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sex	–	0.89	–	0.09	–	0.92	–	**<0.01**
Listing group	–	**<0.01**	–	**<0.01**	–	**<0.01**	–	0.34
Sex × listing group	–	0.89	–	**0.02**	–	0.29	–	0.65
Female at pre-group	1.01 (0.82-1.25)	–	0.91 (0.82-1.02)	–	1.01 (0.83-1.23)	–	2.03 (1.24-3.33)	–
Female at post-group	1.00 (0.80-1.24)	–	1.05 (0.95-1.17)	–	0.88 (0.70-1.11)	–	1.78 (1.09-2.92)	–

Multivariable model evaluating the interaction between sex and listing group (pre- vs post-policy change) when adjusted for all clinical covariates reported in Table 3 (age, height, MELD, ethnicity, and transplant indication). *P* values for variables (sex and listing group) report the statistical significance of a variable with respect to the likelihood of respective outcome (eg, no statistically significant relationship between sex and likelihood of transplantation, as evidenced by a *P* value of 0.09 and CIs crossing 1 for both female patients listed in the pre-group and female patients listed in the post-group). Only hazard ratios and CIs for each outcome are reported for population groups: "female at pre-group" and "female at post-group."
Statistically significant *P* values are denoted in bold.CI, confidence interval; HR, hazard ratio; MELD, Model for End-stage Liver Disease.

by MELD 3.0 overall (7.72% female versus 6.57% male patients, chi-square $P = 0.04$); the only listing MELD subgroup in which this difference was statistically significant was listing MELD score of 30 to 39. No significant difference in the likelihood of waitlist death was seen between male and female patients who were downclassified by MELD 3.0 (Table 6). A 1-point deficit in reported UNOS MELD versus calculated MELD 3.0 at SLK listing (ie, delta MELD versus MELD 3.0) was associated with a 2% decreased likelihood of transplantation during the study period (HR, 0.98; 95% CI, 0.97-0.99; $P < 0.01$).

TABLE 5.

Reclassification from MELD-Na to MELD 3.0 by sex (total counts and among only patients who died on waitlist)

	Calculated MELD 3.0 at listing				
	6–9	10–19	20–29	30–39	≥40
Female patients, n					
Listing MELD-Na					
6–9	14	43	–	–	–
10–19	–	560	278	–	–
20–29	1	73	1363	273	0
30–39	0	4	128	573	97
≥40	0	0	8	63	110
Female deaths, n					
Listing MELD-Na					
6–9	2	9	–	–	–
10–19	–	128	90	–	–
20–29	–	19	322	95	–
30–39	–	2	35	138	17
≥40	–	–	3	30	28
Male patients, n					
Listing MELD-Na					
6–9	14	8	–	–	–
10–19	1	811	199	–	–
20–29	1	106	2522	271	–
30–39	–	7	124	759	108
≥40	–	–	13	92	196
Male deaths, n					
Listing MELD-Na					
6–9	3	2	–	–	–
10–19	-	190	63	–	–
20–29	-	20	598	66	–
30–39	0	4	34	161	28
≥40	–	–	6	29	44

Counts of patients with concordant/discordant reported MELD-Na at listing vs calculated MELD 3.0 at listing presented by sex. Pink cells represent patients whose MELD-Na was downclassified when recalculated as MELD 3.0. Blue cells represent patients whose MELD-Na was upclassified when recalculated as MELD 3.0 (ie, underrepresented by MELD). Counts of deaths in patients with concordant/discordant reports MELD-Na at listing vs calculated MELD 3.0 at listing presented by sex.
MELD-Na, Model for End-stage Liver Disease-Sodium.

DISCUSSION

Sex, socioeconomic, and racial/ethnic disparities in solid organ transplantation listing and outcomes have been well described.[1,13,30,31] Standardization of listing criteria in a national system impacts many patients and has the potential to codify barriers or equity in access to this limited life-saving resource. Therefore, it is important to measure patient outcomes after significant policy changes to understand their downstream effects. The findings of this article offer supporting evidence for current practice (standardized SLK listing and MELD 3.0 in SLK organ allocation) that has not been objectively measured and described previously.

Multiple disparities are observed in this report, including several affecting female patients—a greater proportion of female patients were listed for SLK post-policy change both compared with female SLK listings pre-policy change and female LT listings post-policy change. The post-policy change era included more female patients in the candidate pool who were overall sicker than before, as reflected by older age and higher listing MELD. However, female outcomes improved in many domains post-policy change. Female patients were significantly less likely than male patients to undergo transplantation before the SLK policy change but had higher rates of transplantation after, which may reflect changes in patient selection under the new policy. Overall, waitlist mortality decreased post-policy change compared with pre-policy change, with no significant differences observed between sexes. Female patients were more likely than male patients to be delisted for clinical improvement in both listing groups, although rates of delisting for female versus male patients were similar post-policy change. Although delisting for clinical improvement was relatively uncommon, this pattern may speak to clinicians' judgment that female patients are sicker than suggested by MELD and may benefit from the earlier listing. Transplant indications for patients delisted because of clinical improvement were

TABLE 6.

Chi-square tests for the likelihood of upclassification to higher MELD 3.0 category for male vs female patients (total counts and among only patients who died on waitlist)

Listing MELD	No. of female patients upclassified by MELD 3.0 (N = 3589), n (%)	No. of male patients upclassified by MELD 3.0 (N = 5235) , n (%)	*P*	No. of female deaths (N = 918), n (%)	No. of male deaths (N = 1248), n (%)	*P*
6–9	43 (1.20%)	8 (0.15%)	**<0.01**	9 (0.98%)	2 (0.16%)	**0.01**
10–19	278 (7.75%)	199 (3.80%)	**<0.01**	90 (9.80%)	63 (5.05%)	**<0.01**
20–29	273 (7.61%)	271 (5.18%)	**<0.01**	95 (10.35%)	66 (5.29%)	**<0.01**
30–39	97 (2.70%)	108 (2.06%)	0.0501	17 (1.85%)	28 (2.24%)	0.52
Total	691 (19.25%)	586 (11.19%)	**<0.01**	211 (22.98%)	159 (12.74%)	**<0.01**

Statistically significant *P* values are denoted in bold.MELD-Na, Model for End-stage Liver Disease-Sodium.

TABLE 7.

Chi-square tests for the likelihood of classification of listing MELD to lower MELD 3.0 category for male vs female patients (total counts and among only patients who died on waitlist)

Listing MELD	No. of female patients down-classified (N = 3589), n (%)	No. of male patients down-classified (N = 5235), n (%)	*P*	No. of female deaths (N = 918), n (%)	No. of male deaths (N = 1248), n (%)	*P*
10–19	0 (0%)	1 (0.02%)	1.00	0 (0%)	0 (0%)	–
20–29	74 (2.06%)	107 (2.04%)	0.95	19 (2.07%)	20 (1.60%)	0.42
30–39	132 (3.68%)	131 (2.50%)	**<0.01**	37 (4.03%)	38 (3.04%)	0.22
≥40	71 (1.98%)	105 (2.01%)	0.93	33 (3.59%)	35 (2.80%)	0.30
Total	277 (7.72%)	344 (6.57%)	**0.04**	89 (9.69%)	93 (7.45%)	0.06

Statistically significant *P* values are denoted in bold.MELD-Na, Model for End-stage Liver Disease-Sodium.

proportionate to the frequency of indication in respective groups. Taken together, these observations may suggest more uniform and appropriate candidate selection with the application of standardized 2017 listing criteria, as many of the disparities in outcomes pre-policy change are no longer observed post-policy change.

When considering each listing group separately, Black patients did not experience any significant differences in the likelihood of death, transplantation, or delisting for clinical deterioration, although they were more likely to be delisted for clinical improvement pre-policy change compared with White patients. Asian and Hispanic patients were less likely to undergo transplantation compared with White patients, and Hispanic patients were more likely to be delisted for clinical deterioration pre-policy change compared with post-policy change. However, these patterns were no longer significant post-policy change, again supporting the idea that standardized listing criteria may have improved candidate selection.

A higher serum creatinine was observed for male patients compared with female patients post-policy change, although MELD equalized between the sexes (rising from 24 to 25 for female patients and remaining at 25 for male patients), possibly suggesting that a greater number of sicker female patients (perhaps in ways not captured by MELD, such as frailty) were listed post-policy change. Compared with the observed increase in creatinine for female patients pre- versus post-policy change, a larger relative increase in creatinine was observed in male patients, perhaps because only male patients with renal dysfunction beyond an objective threshold were considered for SLK listing in the post-policy change period.

It is worth noting that the demographics of patients listed for SLK and LT have changed over time, with more listings overall and a rising proportion of female patients listed for ALD and MASLD.[24,25,32] There are several notable differences between the patterns observed in SLK and LT populations in this study. First, the relative waitlist times for male and female patients are inverse in the pre- and post-policy change periods—overall waitlist time decreased for both SLK and LT patients in the post-group, but female SLK patients had shorter waitlist times than male SLK patients, whereas female LT patients had longer waitlist times than male LT patients. Second, female LT candidates are less likely than male candidates to undergo transplantation pre- and post-policy change, whereas female SLK candidates have a significantly lower likelihood of transplantation pre-policy change but a nonsignificant increased likelihood of transplantation post-policy change. Finally, although ALD and MASLD are more common in both SLK and LT patients post-policy change, these indications for transplant are only significant predictors in waitlist outcomes for LT patients, not in SLK patients. Similarly, ethnicity is a nonsignificant predictor of outcomes in SLK but not LT patients in the post-policy change group. Together, these observations suggest the SLK population is a unique subset of patients requiring LT.

The reclassification of MELD to MELD 3.0 more commonly upclassified female patients than male patients, as expected on the basis of its incorporation of patient sex to assign points. The MELD 3.0 incorporates hypoalbuminemia as a marker of disease severity. This likely explains why some male patients in our population also benefited from reclassification from MELD to MELD 3.0 and perhaps why female patients with high MELDs (30–39) may have been downclassified by MELD 3.0 if they were in a phase of clinical deterioration requiring supplemental albumin for the treatment of AKI, hepatorenal syndrome, or hypotension. The discrepancy between MELD and MELD 3.0 was most apparent in patients

with an MELD score of <30. Patients with a MELD score of ≥30 are sick enough to be near the top of the organ waitlist in most UNOS regions regardless of blood type; however, in the more moderately ill groups, this reclassification may have had a more significant clinical impact in their waitlist time, as highlighted by the significantly higher likelihood of female death in patients with MELDs upclassified using MELD 3.0.

Consistent with prior work by Kim et al, this report suggests that MELD 3.0 may mitigate observed sex disparities on not only LT but also specifically SLK waitlist outcomes because there was an association between the magnitude of MELD/MELD 3.0 discrepancy and the likelihood of transplantation. Additionally, both female patients and patients who died on the waitlist were significantly more likely to be upclassified using MELD 3.0 (even more so for female patients who died on the waitlist). The association between MELD 3.0 reclassification and waitlist death further supports that MELD and MELD-Na may have underrepresented the severity of patients' clinical status with disproportionate effects on female SLK candidates compared with male candidates. The use of MELD 3.0 in the SLK population may capture disease severity more accurately and thus offer waitlist time benefits for these patients. To our knowledge, this is the first time that the MELD 3.0 has been applied to the SLK population, specifically, with results that show benefits for female transplant candidates similar to those described in the initial article by Kim et al.[3]

Notably, several changes to organ allocation systems occurred during the study period—the implementation of the MELD-Na score for organ allocation (2016),[33] the redistribution of donation service area and transplant region boundaries (2018, 2020),[34,35] and the modification of MELD exception point assignment (2019).[36] These changes would have uniformly affected organ access for both sexes throughout the country with no specific impact on SLK candidates. Therefore, it is felt that these policy changes do not confound the analysis of the 2017 SLK policy, which, unlike the aforementioned policy changes, has a basis for differentially impacting male and female patients.

Additionally, when comparing patients listed for SLK with those listed for LT, differences in SLK versus LT patient demographics are observed, including mean age, MELD, creatinine, and indication for listing. Age, MELD, and creatinine were all higher in SLK patients regardless of the listing period, further suggesting that, with the exception of those who are acutely ill with very high MELDs, SLK candidates with moderately high MELDs from chronic multiorgan dysfunction may be sicker than LT patients. The relative pattern of demographic changes is similar in SLK and LT patients over time (eg, older, higher MELD, less HCV), and yet the significant predictors of waitlist outcomes among SLK patients still differ post-policy change, further highlighting SLK patients as a unique group in which to study MELD 3.0 impact.

There are several limitations to this study, including its retrospective nature and the use of registry data with limited granularity to evaluate clinical characteristics (including HLA sensitization) that may affect listing and waitlist outcomes. The goal of the SLK policy change was to standardize criteria for which patients should be considered for SLK listing; however, the available data only allow analysis of those patients who are ultimately listed and lack any information about whether a uniform approach to referring and accepting patients for listing exists. It is worth noting that the relevance of these findings is affected by the recent adoption of the MELD 3.0 allocation score, although our analysis of MELD 3.0 reclassification suggests benefits for female patients. More work remains to be done with respect to eliminating sex-based differences in transplantation listing and outcomes. Future research may evaluate additional waitlist time for those awaiting smaller organs and consider a data-driven algorithm for exception points for these patients as well as sex-based differences in referral and time to transplant evaluation completion. Our findings provide additional support for the MELD 3.0 benefit specifically in SLK patients (not previously examined as a unique subset) and also support the expectation for continued mitigation of sex disparities on the SLK waitlist using the 2017 standardized listing criteria and MELD 3.0.

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