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Sex/Gender-Based Disparities in Early Transplant Access by Attributed Cause of Kidney Disease–Evidence from a Multiregional Cohort in the Southeast United States

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Introduction: We examined sex/gender disparities across the continuum of transplant care by attributed cause of end-stage kidney disease (ESKD).

Methods: All adults (18–79 years; $N = 43,548$) with new-onset ESKD in Georgia, North Carolina, or South Carolina between 2015 and 2019 were identified from the United States Renal Data System (USRDS). Individuals were linked to the Early Steps to Transplant Access Registry (E-STAR) to obtain data on referral and evaluation. Waitlisting data was ascertained from USRDS. Using a Cox-proportional hazards model, with follow-up through 2020, we assessed the association between sex/gender and referral within 12 months (among all incident dialysis patients), evaluation start within 6 months (among referred patients), and waitlisting (among all evaluated patients) by attributed cause of ESKD (type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, glomerulonephritis, cystic disease, and other).

Results: Overall, women (vs. men) with type 2 diabetes-attributed ESKD were 13% (crude hazard ratio [HR]: 0.87 [0.83–0.91]), 14% (crude HR: 0.86 [0.81–0.91]), and 14% (crude HR: 0.86 [0.78–0.94]) less likely to be referred, evaluated, and waitlisted, respectively. Women (vs. men) with hypertension-attributed ESKD were 14% (crude HR: 0.86 [0.82–0.90]) and 8% (crude HR: 0.92 [0.87–0.98]) less likely to be referred and evaluated, respectively, but similarly likely to be waitlisted once evaluated (crude HR: 1.06 [0.97–1.15]). For all other attributed causes of ESKD, there was no sex/gender disparity in referral, evaluation, or waitlisting rates.

Conclusion: In the Southeast United States, sex/gender disparities in early access to kidney transplantation are specific to people with ESKD attributed to type 2 diabetes and hypertension.

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Women with ESKD are less likely to be waitlisted for or receive a kidney transplant as compared with men, even after adjustment for several demographic and clinical factors[1–5] and despite similar or better posttransplant survival.[4,6–8] Some evidence also demonstrates that this disparity extends to the earlier and necessary prewaitlisting transplant steps of referral and evaluation. For example, in the Southeast United States, we have shown that women are approximately 14% and 6% less likely to be referred and evaluated for a transplant as compared to men.[9–12]

Reasons for this disparity have not been delineated, though some evidence, largely from single-center studies, include greater provider perceptions of frailty regarding female (particularly among older women) candidates,[13] higher levels of obesity,[6,14] higher psychosocial and health-related concerns among women versus men,[15] and a lack of provider

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awareness of sex/gender-related disparities[16] (sex/gender terminology is used herein to better reflect the multifaceted complexity of the socialization, history, biology, health, and evolution that shape sex/gender constructs).[17] Few studies, however, have examined whether there is variability in access to transplantation by sex/gender depending on the attributed cause of ESKD. Some conditions that cause ESKD may not affect men and women equally and therefore may contribute to the observed sex/gender disparities in transplant access. One United States-based study showed that the sex/gender disparity in rates of waitlisting and transplant was not consistent across all causes of ESKD, with the sex/gender disparity being most notable among patients with ESKD attributed to type 2 diabetes.[5] Similarly, a 2012 French study demonstrated that older women with diabetes were less likely to be waistlited.[18] It remains unknown whether attributed cause of ESKD impacts sex/gender disparities at upstream transplant steps of referral and evaluation, with important implications for access to downstream steps of waitlisting and transplant.

In this study, we examined sex/gender disparities across the continuum of early transplant steps from referral to waitlisting among patients initiating dialysis across 3 states in the Southeastern United States by attributed cause of ESKD.

METHODS

Study Population

In this study, we included all adult patients with ESKD (aged 18 to <80 years) initiating dialysis between January 1, 2015 and December 31, 2019 in End-stage Renal Disease Network 6 (comprised of the states of Georgia, North Carolina, and South Carolina) from the USRDS, a national registry of all patients with ESKD in the United States initiating kidney replacement therapy. Individuals were linked to patient-level referral and evaluation data obtained from the E-STAR,[19,20] a voluntary registry of transplant referral and evaluation forms collected from all 9 adult transplant centers in End-stage Renal Disease Network 6 (i.e., 100% capture for this region). We excluded patients who were missing information on race ($n = 505$) or attributed cause of ESKD ($n = 656$), and those who were listed as unsuitable transplant candidates on the USRDS Centers for Medicare and Medicaid Services (CMS) 2728 form (i.e., medically unfit, unsuitable due to age, or psychologically unfit; $n = 1257$). The final cohort included 43,548 people with incident ESKD and potentially eligible for a kidney transplant between 2015 and 2019 (Figure 1).

Sex/Gender

The primary exposure variable in this study was termed sex/gender and was determined from the CMS form 2728 completed within 45 days of dialysis initiation whereby dialysis center staff document "sex". For the period of study, there was not a nonbinary option on CMS form 2728 and thus all patients are assigned to "male" or "female," herein referred to as "men" and "women."

Outcomes

We examined 3 primary outcomes: referral, evaluation start, and waitlisting. Referral date, ascertained from

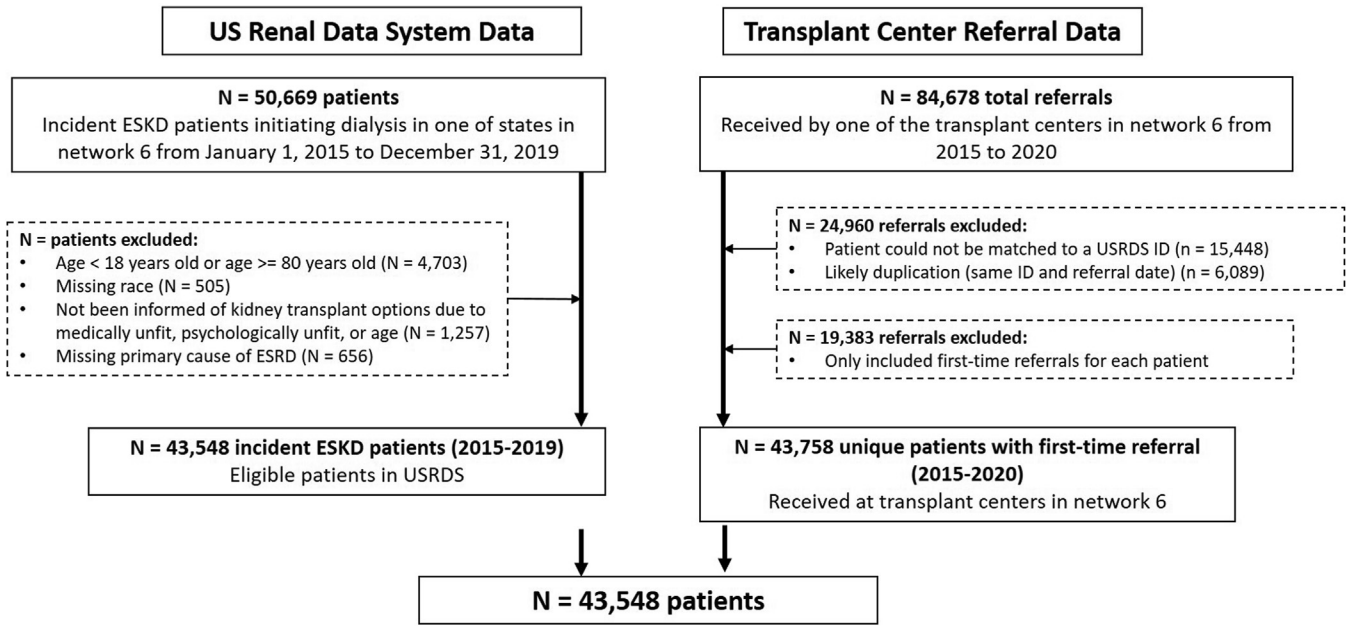

Figure 1. Flow diagram of study inclusion and exclusion criteria for study population. GA, Georgia; ID, identification; NC, North Carolina; SC, South Carolina; USRDS, United States Renal Data System.

E-STAR, was defined as the date when 1 of the 9 transplant centers received a referral form for a kidney transplant evaluation for a given patient, typically by a nephrologist or dialysis facility provider. Referrals in this study were defined as referral within 12 months of dialysis start among all patients with incident ESKD because dialysis facilities are required to educate patients with ESKD about transplant within 60 days of dialysis start. We considered a first referral within 12 months of initiating dialysis as a proxy for access to appropriate care as in our other work.[9,10,20] Although patients can be referred more than once (to the same center or a different center), we restricted the analyses to the first referral event in the study period. For patients who were preemptively referred (i.e., had a referral date prior to dialysis initiation), we defined follow-up time (i.e., time from dialysis to referral) as 1-day. Evaluation start, ascertained from E-STAR, was defined as the date when a patient physically initiated a required component of the transplant evaluation, including first visit to the transplant center, visit to a satellite clinic, or attendance at a required transplant education course. We examined evaluation start within 6 months of the patient's first referral date among those referred for transplant.[20] Six months was chosen because the median time to evaluation start among waitlisting patients in previous analysis has shown to be 91 days (interquartile range: 81–107).[20] Waitlisting date, ascertained from USRDS, was defined as the date that a patient was added to the waitlist for a kidney transplant and was determined among all patients who had started the transplant evaluation process, and also among all patients on incident dialysis (regardless of whether they had started the evaluation process). For patients who were preemptively waitlisted (i.e., had a waitlisting date prior to dialysis initiation), we defined follow-up time (i.e., time from dialysis to waitlist) as 1-day.

Covariates

Patient-level characteristics, as recorded in USRDS, were ascertained from the CMS form 2728. Key variables of interest included attributed cause of ESKD (type 2 diabetes, type 1 diabetes, hypertension, glomerulonephritis, cystic disease, and other), age (categorized for analysis into 18–44, 45–64, and 65–80 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and "Other," where "Other" is made up of Middle Eastern, American Indian or Alaskan Native, Asian, Indian, Pacific Islander, and multiracial), and obesity as measured by body mass index (BMI) (underweight: <18.5 kg/m^2, normal weight: 18.5–24 kg/m^2, overweight: 25–29 kg/m^2, obese class I: 30–34 kg/m^2, obese class II: 35–40 kg/m^2; and obese class III: >40 kg/m^2). Other variables of interest included access to pre-ESKD nephrology care (yes, no), comorbidities (smoking status, congestive heart failure, diabetes, atherosclerotic heart disease, other cardiac disease, cerebrovascular disease, peripheral vascular disease, and cancer), transplant education (informed of transplant yes/no) and insurance status (no insurance, Medicaid, Medicare, private, or other). For insurance status, where patients indicated they had >1 insurance provider, we categorized them using a hierarchy of private, Medicaid, Medicare, and other. For all nonprimary variables, excluding pre-ESKD nephrology care, $<5\%$ of data were missing. For pre-ESKD nephrology care, 12.9% of data were missing. Therefore, primary multivariable analyses, described below, do not adjust for pre-ESKD nephrology care. In sensitivity analyses, we also adjusted for pre-ESKD nephrology care among those with nonmissing data.

Dialysis facility-level characteristics (i.e., the facility from which patients started dialysis and were or were not referred to a transplant center) were determined from the facility file in USRDS and included profit status (for-profit or not-for-profit), facility type (free-standing or not), facility size, and patient to social worker ratio. Neighborhood-level characteristics were determined from the American Community Survey using patient 5-digit ZIP code linked to USRDS data and included poverty ($\geq$ or $<$ 20% of ZIP code living in poverty), average percentage Black, and average percentage of high school graduates.

Statistical Analysis

Differences in baseline demographic and clinical characteristics by sex/gender and primary cause of ESKD and were summarized using frequencies and proportions or means and SDs, as appropriate.

For the outcome of referral, all individuals initiating dialysis were followed-up with from the date of dialysis initiation until 12-month referral date, date of death, or end of follow-up (12 months from dialysis start or December 31, 2020), whichever occurred first. For the outcome of evaluation, individuals who had been referred were followed-up with from date of first referral until 6-month evaluation start date, date of death, or end of follow-up (6 months from referral date or December 31, 2020), whichever occurred first. For the outcome of waitlisting among patients who had started the evaluation process, individuals were followed-up with from evaluation start date until waitlisting date, date of death, or end of follow-up (November 13, 2020), whichever occurred first; and analysis was restricted to those who had started the evaluation process before November 13, 2020. For

waitlisting among all patients on incident dialysis, individuals were followed from dialysis start date to waitlisting date, date of death, or end of follow-up (November 13, 2020). Cumulative incidence was estimated and plotted over time for each of referral, evaluation, and waitlisting in men and women separately.

To assess the association between sex/gender and each outcome (referral, evaluation start, or waitlisting), stratified by attributed cause of ESKD, we used Cox proportional hazards models. Because the relationship between sex/gender and each outcome could not be confounded by other variables, that is, it is not possible for other variables to causally influence sex/gender, we presented crude risks as our primary analysis. However, we included multivariable adjusted models to explore if differences in transplant access were explained by underlying risk factors or comorbidities, which we interpret as potential mediators of the associations under study. In our minimally adjusted model, we adjusted for age, race, and obesity. In fully adjusted models, we adjusted for age, race, obesity, comorbidities, whether patient has been informed of kidney transplant options, insurance status, census variables (neighborhood poverty level, average % Black, and average % high school graduates) and facility characteristics (for-profit or not, freestanding facility or not, facility size, and patient to social worker ratio). We included a random intercept at the dialysis facility's level to allow for intrafacility correlation.

In sensitivity analyses, we stratified the association between sex/gender and each outcome by race, age, and obesity among people with type 2 diabetes and hypertension attributed ESKD to explore possible effect modification by these factors. This analysis was limited to type 2 diabetes and hypertension owing to limited power in other attributed ESKD groups for a 3-way stratification. In additional sensitivity analyses, we performed competing risk analyses using Fine-Gray models treating death or living donor transplant as a competing risk for all outcomes. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R version 4.0.2 (R Core Team, 2020) with "survival" (Therneau, 2020). Figures were created in R version 4.2.3 with package "forestploter" (Dayimu A, 2023). This study adheres to the STROBE guidelines for observational studies (see Supplementary Material), adheres to the Declaration of Helsinki, and was approved by the institutional review board at Emory University (IRB00113572). The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

RESULTS

Baseline Characteristics

We included 43,548 adult patients with ESKD initiating dialysis (mean [SD] age: 58.8 [13.4] years; 44.4% women; and 52.9% Black) in Georgia, South Carolina, and North Carolina between December 2015 and December 2019. Overall, more than 75% of ESKD was attributed to type 2 diabetes or hypertension. More specifically, 4.2%, 42.2%, 35.5%, 7.5%, 2.5%, and 8.2% of incident ESKD was attributed to type 1 diabetes, type 2 diabetes, hypertension, glomerulonephritis, cystic kidney disease, and other, respectively (Table 1). By sex/gender, women (vs. men) were more likely to have type 2 diabetes as the primary cause of ESKD, be Black, have a higher BMI, have Medicaid insurance, have pre-ESKD care, and to live in a neighborhood with a higher poverty level and greater proportion of Black residents (Table 1). Men and women were similarly likely to be informed of transplant as a treatment option, to have similar dialysis-facility level factors (i.e., for-profit status, facility type and size, and patient-to-social worker ratio), and to have similar neighborhood-level education. In addition, comorbidities were similar between men and women; excluding diabetes, which was more common among women, and prior tobacco use, which was more common among men.

Those with ESKD attributed to type 2 diabetes were older at ESKD onset, had a higher proportion of people with Medicare as primary insurance, have a higher BMI, and most likely to have cardiovascular comorbidities compared with all other causes of ESKD. People with ESKD attributed to hypertension had a higher proportion of people who were Black, and lived in neighborhoods with higher poverty, greater proportion of Black residents, and lower education as compared with all other causes of ESKD (Supplementary Table S1).

Association Between Sex/Gender and Referral, Evaluation, and Waitlisting

Among all patients with incident ESKD, 45.2%/48.7% (%women/%men) were referred within 12 months, 54.3%/57.4% started the evaluation within 6 months among those referred, 48.9%/49.4% were waitlisted among those who started the evaluation, and 17.4%/20.0% were waitlisted among all patients with incident dialysis (Table 2). Median (interquartile range) time to each outcome was shorter in women versus men. Overall, women were 14% less likely to be waitlisted compared to men (crude HR: 0.86 [0.82–0.90]). By transplant step, women were 10% (0.90 [95% CI: 0.88–0.93]) less likely to be referred within 12 months among incident dialysis patients, 8% (0.92 [0.89–0.96]) less

Table 1. Characteristics of patients with incident ESKD from 2015 to 2019, overall and stratified by sex/gender, in the Southeast United States

Characteristics	Total	Women	Men
N (%)	43,548 (100.0)	19,344 (44.4)	24,204 (55.6)
Patient-level characteristics			
Attributed cause of ESKD			
Type 1 diabetes	1810 (4.2)	862 (4.5)	948 (3.9)
Type 2 diabetes	18,366 (42.2)	8438 (43.6)	9928 (41.0)
Hypertension	15,452 (35.5)	6478 (33.5)	8974 (37.1)
Glomerulonephritis	3261 (7.5)	1606 (8.3)	1655 (6.8)
Cystic kidney	1093 (2.5)	515 (2.7)	578 (2.4)
Other	3566 (8.2)	1445 (7.5)	2121 (8.8)
Age			
Mean ± SD	58.8 ± 13.2	59.3 ± 13.3	58.4 ± 13.1
18–29	1275 (2.9)	625 (3.2)	650 (2.7)
30–39	2914 (6.7)	1262 (6.5)	1652 (6.8)
40–49	5877 (13.5)	2356 (12.2)	3521 (14.6)
50–59	10,000 (23.0)	4168 (21.6)	5832 (24.1)
60–69	13,280 (30.5)	6160 (31.8)	7120 (29.4)
70–79	10,202 (23.4)	4773 (24.7)	5429 (22.4)
Race/ethnicity group			
Non-Hispanic White	18,172 (41.7)	7510 (38.8)	10,662 (44.1)
Black	23,055 (52.9)	10,906 (56.4)	12,149 (50.2)
Hispanic	1316 (3.0)	494 (2.6)	822 (3.4)
Other	1005 (2.3)	434 (2.2)	571 (2.4)
Insurance status			
Medicaid	9484 (21.8)	5376 (27.8)	4108 (17.0)
Medicare	17,381 (39.9)	7744 (40.0)	9637 (39.8)
Employer	8848 (20.3)	3565 (18.4)	5283 (21.8)
Other	3647 (8.4)	1143 (5.9)	2504 (10.4)
None	4188 (9.6)	1516 (7.4)	2672 (11.0)
Obesity (BMI, kg/m^2)			
Mean ± SD	30.6 ± 8.32	31.6 ± 9.1	29.8 ± 7.6
Obesity			
Underweight	1188 (2.7)	596 (3.1)	592 (2.5)
Normal	10,414 (24.0)	4297 (22.3)	6117 (25.4)
Overweight	11,748 (27.1)	4474 (23.3)	7274 (30.2)
Obese class I	9139 (21.1)	3947 (20.5)	5192 (21.5)
Obese class II	5472 (12.6)	2762 (14.4)	2710 (11.2)
Obese class III	5400 (12.5)	3167 (16.5)	2233 (9.3)
Comorbidities			
Congestive heart failure	11,504 (26.4)	5276 (27.3)	6228 (25.7)
Atherosclerotic heart disease	3710 (8.5)	1470 (7.6)	2240 (9.3)
Other cardiac disease	7399 (17.0)	3064 (15.8)	4335 (17.9)
Cerebrovascular disease	3965 (9.1)	1801 (9.3)	2164 (8.9)
Peripheral vascular disease	3278 (7.5)	1260 (6.5)	2018 (8.3)
Hypertension	39,359 (90.4)	17,523 (90.6)	21,836 (90.2)
Diabetes	26,581 (61.0)	12,268 (63.4)	14,313 (59.1)
COPD	3643 (8.4)	1765 (9.1)	1878 (7.8)
Cancer	2383 (5.5)	943 (4.9)	1440 (6.0)
Tobacco Use	3802 (8.7)	1359 (7.0)	2443 (10.1)
Pre-ESRD nephrology care	30,129 (79.5)	13,626 (80.9)	16,503 (78.3)
Patient has been informed of kidney transplant options	39,328 (92.2)	17,487 (92.4)	21,841 (92.0)
Neighborhood-Level Characteristics			
Neighborhood poverty level			
< 20% (low poverty)	25,611 (59.7)	11,002 (57.6)	14,609 (61.3)
≥ 20% (high poverty)	17,325 (40.4)	8085 (42.4)	9240 (38.7)
Average % Black (mean ± SD)	34.1 ± 23.7	35.4 ± 23.9	33.1 ± 23.5
Average % high school graduates (mean ± SD)	85.2 ± 6.8	85.0 ± 6.6	85.3 ± 6.9

(Continued on following page)

Table 1. (Continued) Characteristics of patients with incident ESKD from 2015 to 2019, overall and stratified by sex/gender, in the Southeast United States

Characteristics	Total	Women	Men
Dialysis-Facility Characteristics			
For-profit	37,425 (86.8)	16,735 (87.3)	20,690 (86.4)
Freestanding facility	41,756 (96.8)	18,616 (97.1)	23,140 (96.6)
Facility size (# of patients, mean ± SD)	89.7 ± 52.3	90.3 ± 52.5	89.2 ± 52.2
Patient to social worker ratio (mean ± SD)	76.8 ± 32.1	77.2 ± 31.9	76.5 ± 32.3

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESKD, end-stage kidney disease; SD, standard deviation
Data are *N* (%) unless otherwise specified.
Percentage of missing value in each variable:
Obesity: 0.43%.
Pre-ESKD nephrology care: 12.94%.
Patient has been informed of kidney transplant options: 2.01%.
Neighborhood poverty level: 1.41%.
For-profit, Freestanding facility, and Facility size (# of patients): 0.97%.
Average % Black and Average % high school graduates: 1.35%.
Patient to social worker ratio: 4.71%.

likely to start the evaluation within 6 months among those referred, but similarly likely to be waitlisted among those evaluated (0.98 [0.93–1.03]) (Table 2). Patterns were similar in minimally and fully adjusted multivariable models, but effect sizes reduced.

Association Between Sex/Gender and Referral, Evaluation, and Waitlisting by Attributed Cause of ESKD

Cumulative incidence of referral, evaluation, and waitlisting by attributed cause of ESKD and sex/gender is shown in Figure 2. Briefly, patients with ESKD with cystic disease-attributed ESKD had the highest cumulative incidence of each outcome, whereas people with diabetes (either type 1 or type 2) had the lowest. This was true in both men and women though cumulative incidence was generally higher in men for people with diabetes. Overall, women (vs. men) with type 2 diabetes-attributed ESKD and hypertension-attributed ESKD were 13% (crude HR: 0.87 [0.83–0.91]) and 14% (0.86 [0.82–0.90] less likely to be waitlisted among all incident patients with ESKD, respectively; whereas there were no sex/gender disparities in overall waitlisting rates for other causes of ESKD (Figure 3). By transplant step, women with type 2 diabetes-attributed ESKD were 13%, 14%, and 14% less likely to be referred (among incident dialysis patients), evaluated (among referred patients), and waitlisted (among patients who started the evaluation), respectively; compared to men with type 2 diabetes-attributed ESKD (Figure 4). Women with hypertension-attributed ESKD were 14% and 8% less likely to be referred and evaluated, respectively, but similarly likely to be waitlisted once evaluated (1.06 [0.97–1.15]). For all other causes of ESKD, there was no sex/gender disparity in referral, evaluation, or waitlisting rates, with 1 exception: in fully adjusted models only, women with cystic kidney disease-attributed ESKD were 28% (1.28 [1.06–1.56])

Table 2. Association of sex/gender with 12-month referral, 6-month evaluation start, and waitlisting among patients initiating dialysis between 2015 and 2019, with follow-up through 2020 in the Southeast United States

Number of events and models	12-month referral (Among patients on incident dialysis)	6-month evaluation start (Among referred patients)	Waitlisting (Among evaluated patients)	Waitlisting[d] (Among patients on incident dialysis)
Outcomes				
Men	11,797 (48.7)	7905 (57.4)	4139 (49.4)	4847 (20.0)
Women	8742 (45.2)	5438 (54.3)	2862 (48.7)	3360 (17.4)
Time to outcome (d), median (IQR)				
Men	66 (1–201)	45 (17–86)	103 (1–268)	225 (1–474)
Women	57 (1–191)	44 (15–91)	90 (1–252)	203 (1–451)
Overall models[a]				
Crude	0.90 (0.88–0.93)	0.92 (0.89–0.96)	0.98 (0.93–1.03)	0.86 (0.82–0.90)
Minimally adjusted[b]	0.94 (0.92–0.99)	0.95 (0.92–0.98)	1.00 (0.95–1.05)	0.92 (0.88–0.97)
Fully adjusted[c]	0.96 (0.93–0.99)	0.96 (0.92–0.99)	1.02 (0.96–1.07)	0.86 (0.91–1.01)

IQR, interquartile range.
[a]Compares hazard rate of each outcome in women vs. men.
[b]Adjusted for attributed cause of ESKD, age group, race/ethnicity, and obesity status.
[c]Adjusted for attributed cause of ESKD, age group, race/ethnicity, obesity status, comorbidities, patient has been informed of kidney transplant options or not, insurance status, census variables (neighborhood poverty level, average % of black, and average % high school graduates), and facility characteristics (for-profit or not, freestanding facility or not, facility size, and patient to social worker ratio).
[d]The different numbers between waitlisting among evaluated patients and waitlisting among all dialysis patients are due to the former (waitlisting among evaluated patients) being restricted, by date, to those who had started the evaluation .g

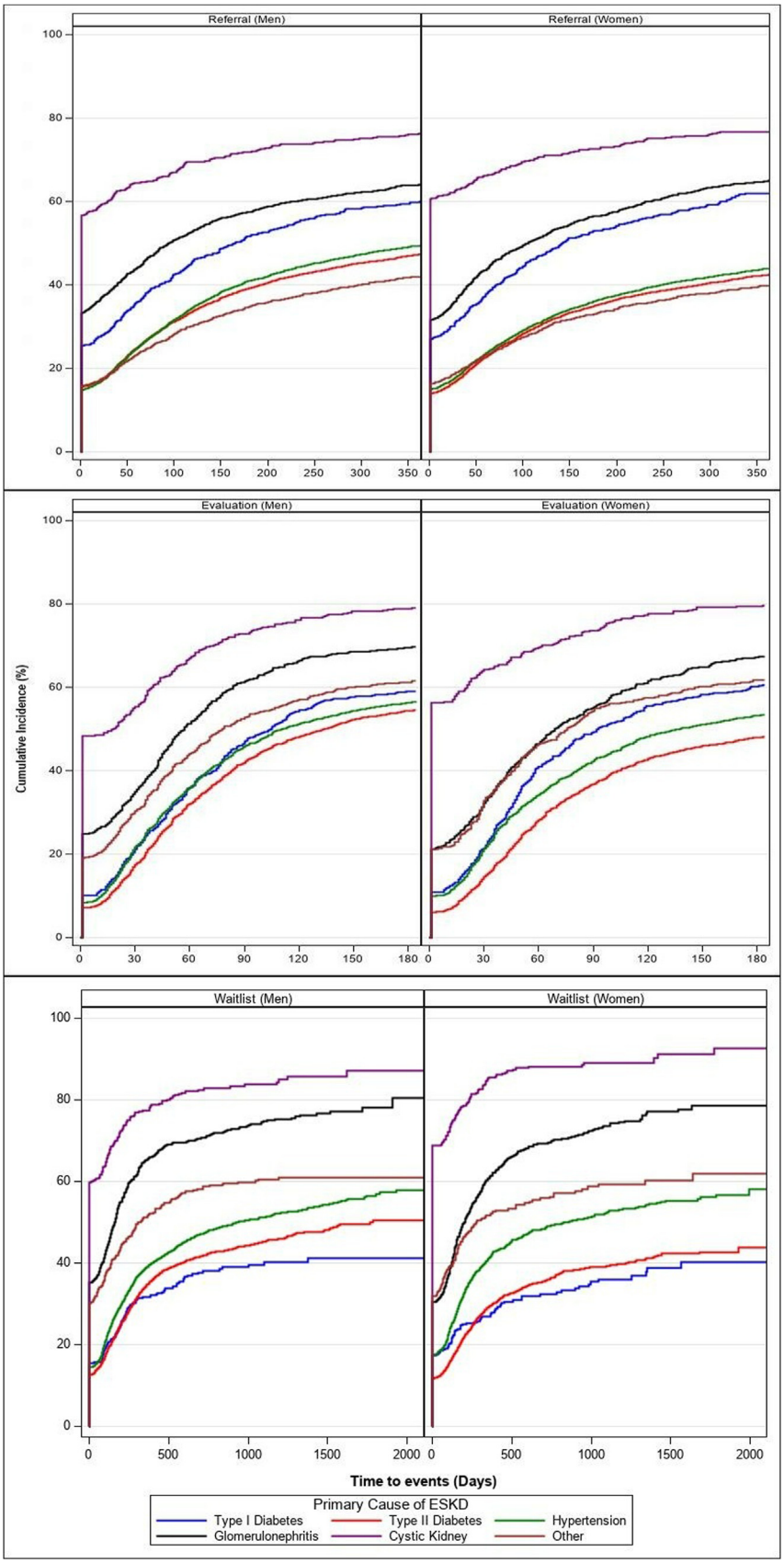

Figure 2. Cumulative incidence of 12-month referral (among patients on incident dialysis), 6-month evaluation, and waitlisting in men and women with ESKD.

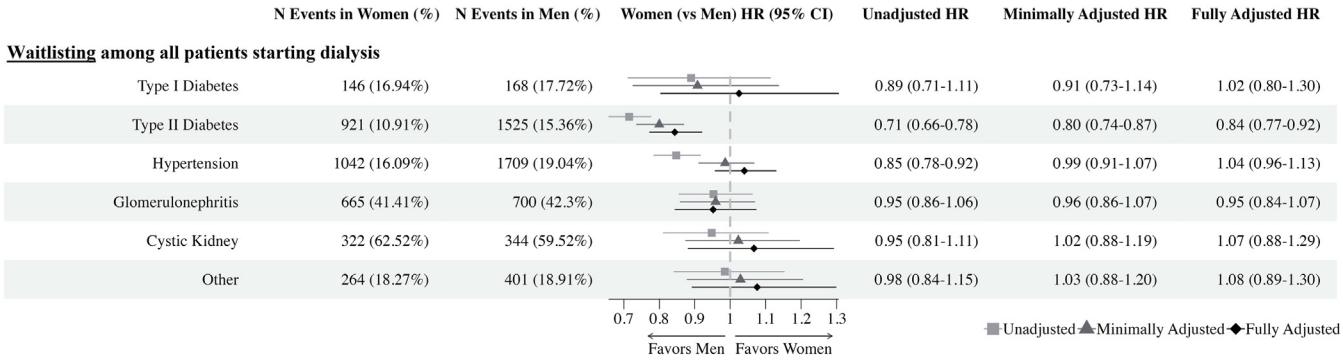

Figure 3. Hazard of waitlisting among women versus men by attributed cause of ESKD among incident patients on dialysis between 2015 and 2019, with follow-up through November 2020, in the Southeast United States.

times more likely to be waitlisted once they had begun the evaluation process, as compared with men with cystic kidney disease.

Sensitivity Analyses

Among people with type 2 diabetes or hypertension-attributed ESKD, there were differences in the sex/gender disparity by race and ethnicity, age, and obesity status, and by transplant step. For example, non-Hispanic White women with type 2 diabetes and hypertension were 22% and 26% less likely to be referred, respectively compared to men of the same race, whereas non-Hispanic Black women with type 2 diabetes and hypertension were 9% and 11% less likely to be referred, respectively (Supplementary Tables S2 and S3). For outcomes of evaluation and waitlisting, differences in the sex/gender disparity by race and ethnicity were small. By age, both young (18–29 years) and older (≥60 years) women with type 2 diabetes were less likely to be referred compared to men of the same age, whereas this was only true for older women (≥70 years) with hypertension. By obesity, in general, obese women with type 2 diabetes or hypertension-attributed ESKD were less likely to be referred, evaluated, and waitlisted than men of the same weight.

Patterns of sex/gender disparities with referral, evaluation, and waitlisting were similar when considering the competing risk of both death and living donor (Supplementary Table S4), and with additional adjustment for pre-ESKD nephrology care (Supplementary Table S5).

DISCUSSION

In the Southeast United States, we show that sex/gender disparities in referral and start of the transplant evaluation are specific to ESKD caused by type 2 diabetes or hypertension, and vary by race and ethnicity, age, and obesity. Disparities in access to waitlisting among patients who start the evaluation process are specific to women with type 2 diabetes-attributed ESKD. For all other causes of ESKD, no sex/gender disparities were identified in access to transplant from referral to waitlisting in crude models. This study adds important information to a growing area of research documenting sex/gender disparities in prewaitlisting transplant steps, showing that efforts to improve access for women at earlier transplant steps (i.e., referral) may have the greatest impact. These results also highlight the need to collect national data on prewaitlisting steps to identify where in the transplant process inequities are occurring, and among which subgroup of the population they are concentrated.[21] In particular, we show that intervention efforts focusing on women with type 2 diabetes or hypertension, which constitute 75% of all ESKD cases, should be prioritized.

Using novel referral and evaluation data, our findings build on previous work by identifying where in the transplant process sex/gender disparities by attributed cause of ESKD exist. For example, we show that sex/gender disparities in transplant access are specific to women with type 2 diabetes and hypertension and add new information that these disparities occur most prominently at upstream transplant steps of referral and evaluation. In another United States study of downstream transplant steps of waitlisting and deceased donor transplantation, women with ESKD due to type 2 diabetes were 27% less likely to be waitlisted and 11% less likely to access a deceased donor once waitlisted, compared to men with ESKD attributed to type 2 diabetes.[5] In the current study, women with type 2 diabetes were 13% less likely to be waitlisted among all patients initiating dialysis as compared to men. The smaller effect sizes in the current study are most likely explained by a longer study period in the study by Ahearn *et al*. (2005–2017 compared to 2015–2020 in our study) that occurred largely prior to the new Kidney Allocation System, which was rolled out in December 2014. And in a 2012 study, French women were 31% less likely to be waitlisted overall as compared to men, and this increased to 49% among

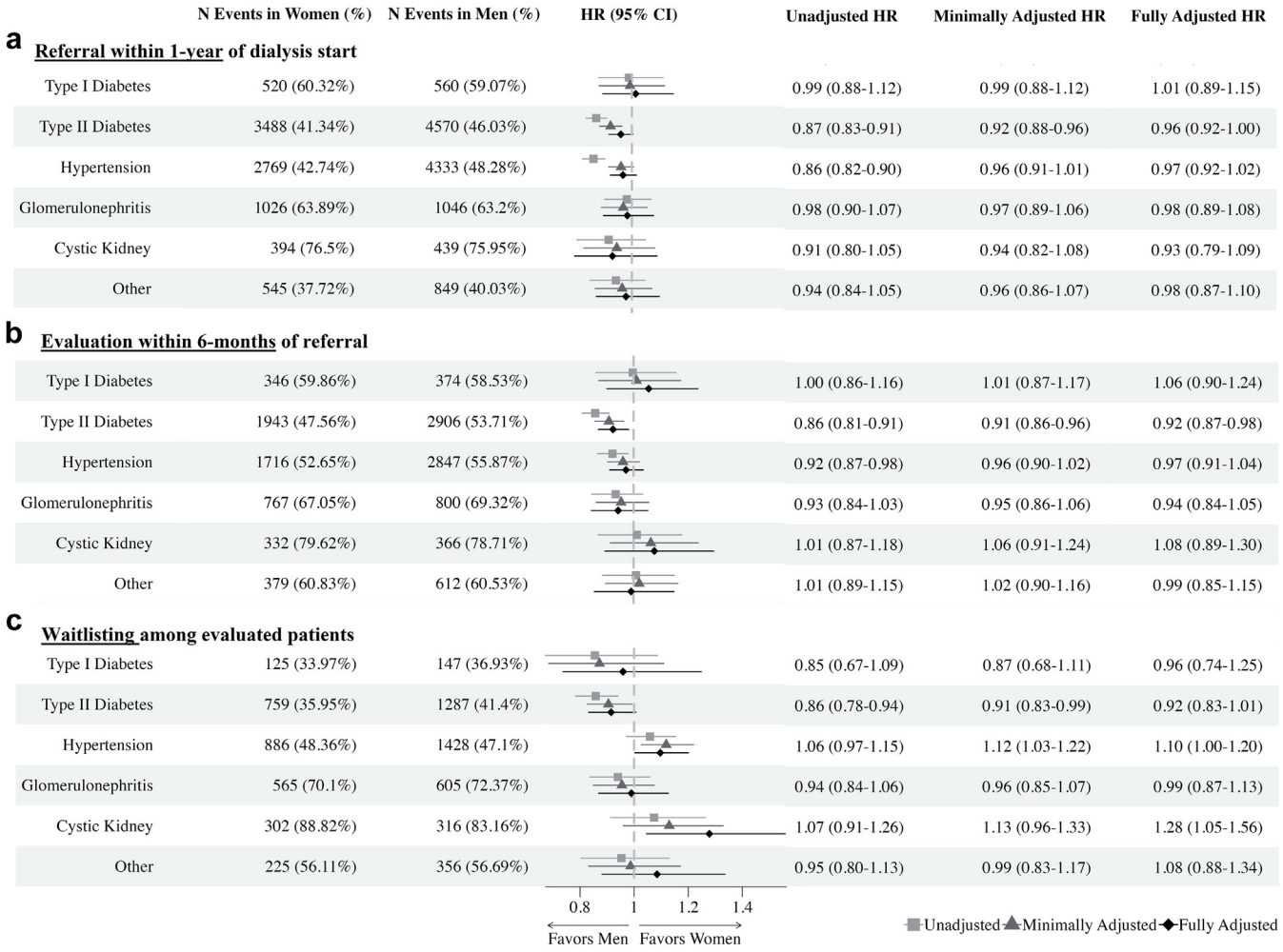

Figure 4. Hazard of (a) 12-month referral (among patients on incident dialysis), (b) 6-month evaluation start (among referred patients), and (c) waitlisting (among those who started the evaluation) in women versus men by attributed cause of ESKD between 2015 and 2019, with follow-up through November 2020, in the Southeast United States.

women older than 60 years with diabetes (vs. older men with diabetes).[18] These higher estimates are explained by the use of a logistic regression model that did not consider differential follow-up time. When survival time was considered, effect sizes were reflective of the current study's findings.[18]

People with ESKD attributed to type 2 diabetes or hypertension are at elevated risk for cardiovascular disease, and this may, in part, explain reduced access to transplant. In our data, people with type 2 diabetes or hypertension had a higher risk of prevalent cardiovascular comorbidities relative to other causes of ESKD. However, the prevalence of cardiovascular comorbidities was largely similar in men and women, and models that adjusted for these comorbidities did not fully attenuate the observed association between sex/gender and transplant access in people with type 2 diabetes or hypertension, suggesting this does not explain our observations. Further, adults with type 2 diabetes or hypertension in our study were more likely to be obese compared to other causes of ESKD. Our prior work, and confirmed in the current study, has shown that sex/gender disparities in access to referral is modified by obesity such that women with higher BMI have reduced access relative to men of the same BMI.[9] It is possible, therefore, that providers' perceptions of transplant eligibility in women, for the same set of comorbidities as men, plays a role. In particular, providers' perceptions of frailty, especially among older women, may contribute to sex/gender-based disparities. Previous studies, and confirmed in the current study, show that older women are less likely to be referred[9] or waitlisted[2] for a transplant compared to men of the same age. Unfortunately, frailty is not captured in our data and therefore cannot be explored in the current study.

It is also likely that social determinants of health play a large role in explaining sex/gender-based disparities in transplant access. ESKD caused by type 2 diabetes or hypertension, compared to ESKD caused by

glomerulonephritis, type 1 diabetes, or cystic disease, are arguably more likely to be influenced by upstream social determinants of health, which are known risk factors for the development of type 2 diabetes and hypertension,[22,23] and subsequent ESKD. Indeed, in our study, people with type 2 diabetes or hypertension were more likely to have Medicaid insurance, self-reported Black race, and live in neighborhoods with a higher proportion of Black residents and higher poverty. These factors are also more common among women (vs. men) with ESKD. These risk factors accrue over the individuals' life course and contribute to more rapid progression from chronic kidney disease (CKD) to ESKD, inadequate dialysis treatment, reduced access to kidney transplantation, and poor health outcomes[24]; although mechanisms are not well understood. Additional factors such as caregiving burden (i.e., children and elderly parents), risk aversion,[25] and poor self-advocacy,[26] disproportionately experienced by women, may also play a role. Regardless, there are implications for providers caring for patients with CKD and type 2 diabetes or hypertension that can be enacted now to improve equitable transplant access. For example, risk factor modification such as early use of antihyperglycemic and antihypertensive treatment may be prioritized to improve transplant eligibility among women with CKD. Further, referral to nephrologists prior to ESKD, education on transplant as a treatment option, and early referral to a transplant center for evaluation could also be prioritized among women with ESKD due to type 2 diabetes and hypertension to reduce sex/gender-based disparities in overall transplant access.

The key strength of this study includes the use of novel referral data across all 9 transplant centers in Georgia, North Carolina, and South Carolina, through the E-STAR database,[19] linked to the national USRDS registry allowing us to examine each step of the transplant process among the appropriate denominator population (i.e., all patients on incident dialysis, all referred patients, and all evaluated patients). However, there are some limitations to be considered. First, our results are generalizable only to the Southeastern United States, which has a larger Black population, higher burden of chronic disease, and lower transplant rates compared with other regions in the United States.[4,27,28] Second, patients who may have initiated dialysis in the region but were referred to transplant centers outside of Georgia, North Carolina, and South Carolina were excluded from the study population. However, based on previous literature, we expect this to be a small proportion (i.e., $<10\%$).[20] Third, USRDS captures all patients initiating kidney replacement therapy (either dialysis or transplant). It therefore does not include late-stage CKD patients who may self-refer or be referred from a nephrologist. Findings of this work are therefore limited to individuals with ESKD initiating kidney replacement therapy. However, we believe this represents the majority of individuals being referred for a transplant. For example, in Figure 1, we report that approximately 18% of individuals who were referred to a transplant center could not be linked to USRDS. We believe this represents the smaller proportion of referred patients who have late-stage CKD. Fourth, this study is limited to data routinely captured in dialysis and transplant centers. We are therefore unable to examine the impact of several potentially important factors, such as income, education status, caregiving burden, or frailty. Finally, sex/gender, as determined from CMS 2728, is assigned by the provider at kidney replacement therapy initiation and does not necessarily reflect patient self-identified sex/gender. Therefore, findings of this study will be influenced by provider perceptions of sex/gender.

Conclusions

In the Southeast United States, sex/gender disparities in early access to kidney transplantation are specific to people with ESKD attributed to type 2 diabetes and hypertension, which constitute the majority ($\sim$75%) of all ESKD, and are greatest at earlier transplant steps (i.e., referral and evaluation). An understanding of the underlying mechanisms driving these disparities is needed to inform the design of interventions and policies to improve transplant access for women with ESKD.

DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHOR CONTRIBUTIONS

JLH conceived the study, contributed to study design, oversaw analysis, and wrote the manuscript. MD conducted all analyses and reviewed/edited the manuscript. SOP contributed to funding and data acquisition, provided intellectual input, and reviewed/edited the manuscript. AG assisted in analysis and reviewed/edited the manuscript. DD and AR contributed to study design, provided intellectual input, and reviewed/edited the manuscript. REP contributed to data acquisition, study conceptualization, provided intellectual input, and reviewed/edited the manuscript. All authors approve the final version of this manuscript. JLH is the guarantor of this work and takes responsibility for final responsibility for the decision to submit for publication.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Baseline characteristics of patients with incident ESKD, by gender, in the Southeast US, 2015-2019.

Table S2. Association of sex/gender with 12-month referral, 6-month evaluation start, and waitlisting among patients with type 2 diabetes-attributed ESKD initiating dialysis between 2015 and 2019, with follow-up through 2020, by race, age, and obesity, in Southeast United States.

Table S3. Association of sex/gender with 12-month referral, 6-month evaluation start, and waitlisting among patients with hypertension-attributed ESKD initiating dialysis between 2015 and 2019, with follow-up through 2020, by race, age, and obesity, in Southeast United States.

Table S4. Hazard of 12-month referral, 6-month evaluation start, and waitlisting in women vs. men and by attributed cause of ESKD, in the Southeast United States, accounting for competing risk of death and transplant (deceased or living donor).

Table S5. Hazard of 12-month referral, 6-month evaluation start, and waitlisting in women vs. men and by attributed cause of ESKD, in the Southeast United States, with additional adjustment for pre-ESKD nephrology care.

STROBE Statement—Checklist of items that should be included in reports of cohort studies.

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