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Laken Smothers Date

Effect modifiers of sex disparities in kidney transplantation referral rates among adults with end-stage kidney disease (ESKD) in the Southeastern U.S.

By

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Epidemiology

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By

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Abstract

Effect modifiers of sex disparities in kidney transplantation referral rates among adults with end-stage kidney disease (ESKD) in the Southeastern U.S.
By Laken Smothers

Background & Aims: Males with end-stage kidney disease (ESKD) are more likely to be referred for and receive a kidney transplant compared to females, though reasons for this disparity are unknown. In this study, we examine the role of age, race/ethnicity, and obesity as potential effect modifiers in the association between sex and kidney transplant referral rates.
Methods: We identified all adults (18-80 years) with ESKD from the US Renal Data System in Georgia, North Carolina, and South Carolina between January 2012 and December 2015, and linked to referral data obtained from transplant centers, with follow-up through December 2016,. Using a mixed-effects multivariate Cox Proportional Hazards model adjusted for several patient-level characteristics and accounting for clustering by dialysis facility, we assessed the association between sex and 12-month referral (from dialysis initiation). Interaction terms were included for age, race/ethnicity, and body mass index (BMI), and results stratified accordingly.
Results: Among 31,881 ESKD patients, 31.1% (n=9,928) were referred within 12-months . Overall, females were 13% less likely to be referred for a kidney transplant as compared with males in fully adjusted models (HR: 0.87; 95% CI: 0.83,0.91). Interaction terms for age, race/ethnicity, and BMI were significant. Females aged 45-64 and 65-80 were 0.90 (0.85, 0.96) and 0.75 (0.68, 0.82) less likely to be referred compared to males of the same age. Non-Hispanic White and Non-Hispanic Black females were 0.79 (0.73, 0.85) and 0.91 (0.86, 0.97) less likely to be referred compared to males of the same race/ethnicity. For all other race and age subgroups, no sex difference in referral rates was observed. For obesity, females were 9-29% less likely to be referred across all BMI groups, excluding BMI 30-34.9 where referral rates were similar in males and females.
Conclusion: In a Southeastern US population, we show that the sex disparity in referral rates appears to be specific to older, Non-Hispanic Black and White females, and most BMI groups, excluding BMI 30-34.9. Interventions to reduce sex disparities in kidney transplant referral rates should consider the potential effects of age, race/ethnicity, and obesity.

Effect modifiers of sex disparities in kidney transplantation referral rates among adults with end-stage kidney disease (ESKD) in the Southeastern U.S.

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INTRODUCTION

In the United States, the prevalence of end stage kidney disease (ESKD) has continued to rise, with over 785,000 receiving treatment (either dialysis or transplantation) for ESKD in 2018[1]. Kidney transplantation is the preferred treatment as it provides a better quality of life, longer survival, and lower hospitalization rates compared with those remaining on dialysis[2]. However, a relative donor shortage means not all ESKD patients will receive a lifesaving transplant.

The process of receiving a transplant can be complex and disparities in access can occur at each step (**Figure 1**). First, ESKD patients must indicate an interest in kidney transplantation (Step 1). Next, eligible ESKD patients must be referred (Step 2) for transplant evaluation (Step 3) at a transplant center by a physician or dialysis facility. After completing the pre-transplant evaluation (Step 4), most patients are placed on the deceased donor waitlist (Step 5) until an organ becomes available (Step 6). In 2017, only 13.2% of incident ESKD patients were placed on the deceased donor waitlist or received a transplant within one year of ESKD diagnosis[1].

Disparities have been identified at multiple steps in the transplant process. For example, it has been well described that Blacks have a lower rate of transplant compared with Whites, despite a higher burden of ESKD[1,3-5]. Commonly cited reasons for racial disparities in transplant include racial differences in preference for kidney transplantation, barriers to starting or completing the evaluation process, and increased time on the waitlist compared to Whites[1,4]. Studies have also found that older (vs. younger) age is associated with a lower rate of referral among incident ESKD patients in Georgia, North Carolina, and South Carolina[4,6]. Researchers have cited perceptions about older age and frailty as contraindications for transplant as possible drivers of age disparities in transplant access[4,6]. Additionally, a smaller number of studies have described disparities in waiting time for transplant based on degree of obesity whereby the likelihood of receiving a transplant decreases as the grade of obesity increases[7]. Provider bias in choosing optimum candidates for transplantation and increased likelihood of being bypassed for organ offers has been cited as potential reasons for this observed disparity[7,8].

Sex disparities in later steps of the transplant process (i.e. waitlisting and transplant) whereby women are less likely to receive a transplant as compared to men is also well documented. Reasons for this sex disparity are not well elucidated. Potential non-biological mechanisms include: conservative treatment preferences among older females[9,10]; females may be less likely to have discussions about kidney transplantation with their medical provider[11]; and physician biases[12]. Other studies have suggested a potential role of age, race, and obesity in explaining sex disparities in later steps to transplant[8,13-15]. For example, Segev et al. found that in a national U.S. study from 2000 to 2005, the likelihood of a woman having access to transplantation decreased by 7% for every decade increase in age[13]. In another U.S. study of the association of obesity with access to transplantation among incident ESKD patients between 1995 and 2007, Gill et al. found that women classified as level 1 obese (body mass index (BMI) 30-34.9 kg/m^2) were 11% (HR: 0.89 (95%CI: 0.86, 0.92) less likely to receive transplantation compared to women with a normal BMI (10.0-24.9 kg/m^2), while for men the opposite was observed. Men classified as level 1 obese were 24% more likely to receive a transplant compared to normal weight men[8]. Additionally in Monson et al., a study examining factors associated with rate of renal transplant evaluation completion among the renal transplant patient population at the University of Illinois between 2009 and 2010, researchers found a significant interaction between race/ethnicity and sex[14]. For example, Hispanic men, Hispanic women, and White men, as compared with Black men, had a 2.75, 1.96, and 1.99 times higher rate of completion, respectively. However, Black and White women did not have a significantly different rate of completion compared to black men[14].

Whether sex disparities exist at earlier steps, and whether age, race/ethnicity, and obesity also play a role in modifying sex disparities at earlier steps of the transplant process, i.e. referral, is less well known due to the lack of national surveillance data on early transplant steps. Several studies have found that females are less likely to be referred for a transplant as compared with males[4,6], though few have explored reasons why. Some evidence suggest that barriers at later steps in the transplant process are not always the same as barriers in earlier steps. For example, in a study examining variation in dialysis facility referral in Georgia, Patzer et al. found that Blacks were 23% less likely to be waitlisted compared to Whites[4], but were in fact 22% more likely to be referred compared to Whites. In another study in the Southeastern United States, between 2012-2016, non-Hispanic Black patients were 22% more likely to be referred for a transplant in Georgia, but were 7% less likely to be evaluated compared to non-Hispanic Whites in Georgia, North Carolina, and South Carolina[6]. These studies highlight the need to understand barriers occurring across the spectrum of the transplant process so that interventions to reduce disparities in transplant access can be targeted appropriately. This is particularly pertinent to the Southeastern US, a region with one of the highest burdens of ESKD and one the lowest rates of kidney transplant in the US[1].

Study Aims

In this study, we will examine the association between sex and 12-month referral rates across three states in the Southeastern US (Georgia (GA), North Carolina (NC), and South Carolina (SC)) and examine the potential effect modification by age, race/ethnicity, and obesity.

Identifying possible modifiers of this association can help clarify mechanisms by which sex impacts access to transplant. Doing so, may help identify possible interventions to reduce sex disparities in transplant access.

METHODS

Study Population

The primary study population was identified from the United States Renal Data System (USRDS). The USRDS is a national registry of all ESKD patients in the United States initiating renal replacement therapy (RRT)[1]. Using the USRDS, we identified all adult ESKD patients (aged 18-80 years) initiating dialysis in GA, NC, and SC between January 1, 2012 and December 31, 2015, with follow-up through December 31, 2016 to ensure a minimum of 12-months follow-up for all patients. Individuals were linked to kidney transplant referral data collected from adult transplant centers in Island Peer Review Organization, Inc. (IPRO) Network 6 in the same period. Network 6 is the ESKD Network of the South Atlantic that serves GA, NC, and SC and collects data to measure dialysis and ESKD-related processes and outcomes. We excluded patients who were preemptively referred for a transplant (N=3,633), or were missing information on sex, race/ethnicity, age, or BMI (n=1,222). The final cohort included 31,881 people with incident ESKD**, Figure 2**.

Data Collection and Measurement

The primary outcome for this study was 12-month referral, defined as the first referral from a dialysis facility for transplant evaluation within one year of dialysis initiation, as determined from referral forms routinely collected from all nine adult transplant centers in GA, NC, and SC. This data has been used in previous studies to examine disparities in referral rates in the Southeast[4,6,16].

Primary variables of interest were ascertained from CMS form 2728, which is completed by providers within 45 days of ESKD diagnosis for all patients. Key variables of interest included sex (male, female), age (18-44, 45-64, and 65-80), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other race), and BMI (<18.5, 18.5-24, 25-29, 30-34, 35-40, and ≥40 kg/m^2). Other variables of interest included primary cause of ESKD (diabetes, hypertension, glomerulonephritis, other) access to pre-ESKD care (yes, no), comorbidities (smoking status, congestive heart failure, diabetes, atherosclerotic heart disease, other cardiac disease, cerebrovascular disease, and peripheral vascular disease), and insurance status (no insurance, Medicaid, Medicare, private, or other). For insurance status, where patients indicated they had more than one insurance provider, we categorized them using the hierarchy of private, Medicaid, Medicare, and other.

Statistical Analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) and R (R Core Team, 2020) with ‘survival’ (Therneau, 2020). Differences in baseline demographic and clinical characteristics by sex were examined using Chi-square tests for categorical variables, independent t-tests for normally distributed continuous variables, and two-sample Mann-Whitney U tests for non-normally distributed continuous variables. The normality assumption was tested for all continuous variables using density plots. Individuals were followed from date of dialysis initiation until 12-month referral date, date of death, or end of follow-up (12-months from dialysis start), whichever occurred first. To assess the association between sex and 12-month referral, we used Cox proportional hazard models, censored for death, with Hazard Ratios (HR) and 95% Confidence Intervals (CI) reported. To account for clustering of patients within dialysis facilities, dialysis facility was modeled as a random effect. To examine the effect of several confounders on the association between sex and 12-month referral, we added variables to the model using a forward stepwise approach as follows: model 1 adjusted for age, race/ethnicity, and insurance type; model 2 adjusted for model 1 plus primary cause of ESKD, pre-ESKD care, and BMI; model 3 adjusted for model 2 plus comorbidities. Individuals missing data for any of the variables in the model were excluded from analysis by R, however for all variables less than 13% of data was missing. The final model included variables significantly associated with 12-month referral in multivariate analysis with $p<0.05$. The proportional hazards (PH) assumption was assessed graphically using log-negative-log plots, see **Supplementary Figures 1-4**, and statistically using goodness of fit testing.

We tested for interactions between age (18-44, 45-64, and 65-80), BMI (<18.5, 18.5-24, 25-29, 30-34, 35-39, ≥40 kg/m^2) and race/ethnicity (Non-Hispanic Black, non-Hispanic White, Hispanic, and Other) with sex. Given the lack of statistical power inherent in interaction tests, we considered interactions to be significant when $p<0.2$[17]. Where the interaction was significant, we stratified analyses by that factor. This study was approved by the institutional review board at Emory University (IRB00079596).

RESULTS

Baseline characteristics

This study included 31,881 adult ESKD patients initiating dialysis (median age 62.0, 55.2% male) in GA, SC, and NC between January 2012 and December 2015. At dialysis initiation, females (vs. males) were more likely to be Non-Hispanic Black, have a BMI ≥35 kg/m2, be Medicaid insured, have diabetes as primary cause of ESKD, have pre-ESKD care, and some comorbidities (diabetes, congestive heart failure, cerebrovascular disease), **Table 1**. In contrast, males (vs. females) were more likely to have hypertension as a primary cause of ESKD, and some comorbidities (current smoker, peripheral vascular disease, other cardiac disease, and cancer).

Association between sex and 12-month referral

Among 31,881 adult ESKD patients, 31.1% were referred within 12 months of dialysis initiation. In crude models, females were 16% less likely (0.84 (0.80, 0.87)) to be referred within 12 months for transplant. After adjustment for age, race, and insurance status, females were 12% less likely to be referred (0.88 (0.85, 0.92)). In final multivariate models females were 13% (0.87 (0.83, 0.91)) less likely to be referred within 12-months as compared to males, **Table 2**. Factors associated with 12-month referral are reported in **Table 3** and include insurance status, primary cause of ESKD, pre-ESKD care, and all comorbidities, excluding diabetes. For key variables of age, race/ethnicity, and obesity the following was observed: adults aged 45-64 and 65-80 were 0.71 (0.67-0.75) and 0.33 (0.31-0.35) less likely to be referred within 12-months as compared to adults aged 18-44; Non-Hispanic Black, Hispanic, and other race/ethnicity adults were 1.24 (1.18-1.30), 1.26 (1.12-1.43), and 1.44 (1.23-1.68) times more likely to be referred compared with non-Hispanic White adults; and compared to normal weight adults, adults with BMI 25-29.9, 30-34.9, and 35-39.9 had a 1.11(1.04-1.18), 1.19 (1.11-1.26), and 1.16 (1.07-1.25) increased rate of 12-month referral. For adults with BMI <18.5 or ≥40 kg/m^2, there was a 0.81 (0.70-0.94) and 0.88 (0.81-0.95) lower hazard of referral compared to normal weight adults.

Significant interactions were found for age (p<0.001), race/ethnicity (p=0.004), and BMI (p=0.14). The addition of the age interaction term attenuated the association between sex and 12-month referral (HR: 0.93 (0.85-1.02)), **Table 4,** but race (0.80 (0.74, 0.86)) and BMI (0.88 (0.80, 0.97)) did not. By age, females aged 45-64 and 65-80 were 0.90 (0.85, 0.96) and 0.75 (0.85, 0.96) times less likely to be referred within 12 months as compared to males of the same age, while females aged 18-44 had no difference in rate of referral as compared with men (0.95 (0.86, 1.04), **Figure 3a and Supplementary Table 1**. By race/ethnicity, Non-Hispanic Black females and Non-Hispanic White females were 0.91 (0.86, 0.97) and 0.79 (0.73, 0.86) less likely to be referred within 12 months compared to Non-Hispanic Black and Non-Hispanic males, respectively**.** In contrast Hispanic and 'other race' females had no difference in rate of referral compared to Hispanic and other race males (0.82 (0.63, 1.06) and (0.93 (0.67, 1.28), respectively), **Figure 3b and Supplementary Table 1**. By BMI, females with a BMI <18.5, 18.5-24.9, 25-29.9, 35-39.9, and ≥40 kg/m^2 were 0.71 (0.52, 0.97), 0.90 (0.82, 0.99), 0.91 (0.84, 0.99), 0.79 (0.70, 0.89), and 0.79 (0.69, 0.89) less likely to be referred within 12 months compared to males in the same BMI category, while females with a BMI between 30 and 34.9 kg/m^2 had the same rate of referral as their male counterparts, 0.92 (0.84, 1.01), **Figure 3c and Supplementary Table 1**.

DISCUSSION

In this study of Southeastern US adults with incident ESKD, we show that females are 13% less likely to be referred for a transplant within 12-months of dialysis initiation compared to males. This association was modified by age, race, and obesity. For example, while younger females (18-44 years) had the same rate of referral as males of the same age, older females were less likely to be referred than their male counterparts, with this disparity increasing with increasing age. Further, while Hispanic and other race/ethnicity females had the same rate of referral as their male counterparts, Non-Hispanic White and Non-Hispanic Black females had a 21% and 9% lower rate of 12-month referral compared to Non-Hispanic Black and non-Hispanic Whites males, respectively. Females with a BMI between 30-34.9 kg/m^2 had no difference in referral rate compared to males with the same BMI, while females in all other BMI categories had a 9-29% lower rate of referral compared to their male counterparts. The results of this study suggest that the observed sex disparities in referral for kidney transplant may be age-, race-, and BMI- specific and subsequent interventions designed to reduce sex disparities should consider the role age, race/ethnicity, and obesity play in access to referral.

Our finding that females were less likely to be referred as compared to males is consistent with prior literature that females were 11-14% less likely to be referred within 12-months of starting dialysis[4,6] in the Southeast, using the same dataset. Though few other studies have examined sex disparities in the referral step specifically, our results are in line with other studies that report sex disparities in later steps of transplant. For example, Patzer et al. showed that females, compared to males, had a 6% lower rate of transplant evaluation start in the Southeastern United States[6], and Shaubel et al. showed that Canadian women had a 20% lower rate of kidney transplant overall compared to males[15]. While the reasons for these sex disparities are still unclear, some potential hypotheses include lower probability of discussing transplant as a treatment option with women, women's attitudes toward transplant, and provider bias as potential reasons for the observed sex disparity at the referral step[11,18]. For example, a single center study by Salter et al. among individuals who recently initiated hemodialysis treatment at a Maryland dialysis facility, showed that women were 45% more likely to not discuss kidney transplant with a medical professional compared with men[11]. Another study, in which patients at dialysis centers in Maryland were surveyed between 2009 and 2012, also suggests that women are less likely to 'want' to receive a transplant compared to men[19]. In this study Salter et al. found that females initiating dialysis were 72% more likely to report having high-health related concerns and 55% more likely to report having psychosocial concerns about kidney transplant compared to males[19]. Lastly, another study conducted in a single dialysis facility demonstrated that providers may view women as more frail compared to men, and so are less likely to refer them to a transplant[20]. Salter et al. suggests that among individuals classified as frail by a nurse practitioner, women were more likely to be misclassified as frail, however female sex did not have a significant association with misclassification by a nephrologist[20]. The results suggest that though females may be subject to a higher level of perceived frailty, more research is needed to clarify whether providers involved in the transplant process are contributing to this bias.

Our analysis that age modifies the relationship between sex and transplant referral is consistent with some other studies examining later steps of the transplant process. For example, in a national cohort of first-onset ESKD patients between 2000 and 2005, females older than 75 years were 59% less likely to receive a live donor transplant compared to males of the same age with the same comorbidities[13]. This disparity was not observed in younger age groups (e.g. 18-45)[13], a finding similar to the current study. Additionally, Segev et al. suggested that these differences may be due to perceptions of older women's frailty and whether they are an optimum candidate to receive a transplant. However mortality differences between males and females post-kidney transplant have not been observed among the kidney transplant population in the United States[1]. In a study examining factors associated with perceived frailty and misclassification of frailty by healthcare providers among adults undergoing hemodialysis at a single dialysis center in Maryland, Salter et al. shows that older age was associated with a 36% higher odds of nephrologist perceived frailty for every 5 year increase in age[20]. The results of the current study suggest that older women are less likely to be referred for transplant and this likely affects downstream steps such as waitlisting and transplant. Furthermore, in our analysis the addition of age as an interaction term completely attenuated the association between sex and referral rates, suggesting that age may be the main factor explaining sex disparities in transplant referral.

This is the first study to examine the interaction between sex and race, and referral rates, but our findings are similar to prior literature examining the interaction between sex and race at later steps[15]. In a nation-wide Canadian study between January 1981 and December 1996, White, Asian Indian, Black, North American Indian, and Asian adult males had a 18%, 67%, 66%, 42%, and 23% higher rate of transplant compared to their female counterparts, respectively[15]. Males in the 'other or unknown' race/ethnicity group did not have a significantly different rate of transplant compared to females. In the current study, we did not find differences in referral rates between males and females of Hispanic or other race/ethnicity, but we cannot rule out that we may have been underpowered to detect an association due to smaller sample sizes in these groups. Researchers cited cultural differences in views about transplantation or willingness to offer an organ to their family members as potential reasons why there were differences between rate of transplantation by race and ethnicity group[15], however this does not fully explain the interaction between sex and race. The mechanisms behind race as a significant effect modifier of sex and rate of referral warrant further analysis.

In this study, BMI was a significant modifier of sex and 12-month referral. This finding is in line with a previous study, Gill et al., which found that BMI was a significant modifier of the association between sex and likelihood of activation on the waitlist in a U.S. cohort captured between 1995 and 2007[8]. Taken together, this suggests that obesity may play an important role in transplant access at both early and later steps of transplantation. In our analysis we found that BMI did not attenuate a large portion of the disparity between males and females in regard to referral rate, and for most BMI groups, the relationship between sex and referral rates was similar, suggesting that it plays a minor role in modification of the association of sex and 12-month referral. Obesity-specific criteria for transplant eligibility varies between transplant centers[21], and may play a role in referral rates as those who do not meet the criteria are often referred to other services (e.g. weight management), delaying transplant referral. In the current study, we did not examine the role of center-specific obesity criteria on rates of referral, but the impact of center variation in BMI cutoffs on early steps of the kidney transplantation process should be investigated in future studies.

The key strength of this study includes the use of routinely collected referral data across 9 transplant centers in GA, NC and SC, linked to the national USRDS registry. However, there are some limitations to be considered. First, our results are generalizable only to the Southeastern US and to individuals who begin dialysis as their first mode of kidney replacement therapy. In this study, we excluded ESKD patients who were preemptively referred, waitlisted, or transplanted. These patients were, in general, younger and had less comorbidities than those included in the current study, and were more likely to have had pre-ESKD care and private health insurance, **Supplementary Table 2**. In addition, the Southeastern US has a higher proportion of Blacks, higher burden of chronic disease, and lower transplant rates compared to other regions in the US and so results of the current study may not be generalizable outside of the Southeastern U.S[1,22,23]. Second, patients who may have initiated dialysis in the region, but were referred to transplant centers outside of GA, NC, and SC were excluded from the study population. However, based on previous literature we expect this to be a small proportion (i.e. <10%)[6]. Third, this study is limited to data routinely captured in dialysis and transplant centers. We are therefore unable to adjust for several potentially important factors such as income and education status. Further, CMS form 2728 only captures information on comorbidities at time of ESKD diagnosis, and does not indicate the severity of these comorbidities. As a result, we cannot rule out the possibility of residual confounding in this study. Finally, for some smaller subgroups such as Hispanic and other race/ethnicity groups, we may not have had enough statistical power to detect significant associations. Future studies using national data should be conducted to confirm our findings.

In conclusion, we found that females in the Southeastern United States were 13% less likely to be referred for transplant within 12 months of dialysis initiation as compared to males. Furthermore, we found that age, race, and obesity modified this association such that older, non-Hispanic Black and non-Hispanic White females, and most BMI groups, excluding BMI 30-34.9 were less likely to be referred compared to their male counterparts. Future studies should examine whether these factors explain the sex disparity at referral in other US regions and nationally. Additionally, future interventions to reduce sex disparities in access to kidney transplant should consider the role that age, race/ethnicity, and obesity play in modifying the association between sex and transplant referral.

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TABLES

Table 1. Baseline characteristics of incident adult ESKD patients in GA, SC, and NC, by sex, 2012-2015

	Total	**Male**	**Female**	**P-value**
N(%)	31,881(100.0)	17,612 (55.2)	14,269 (44.8)	
Demographic Characteristics				
Age in years, median (IQR)	62.0 (52.0-70.0)	63.0 (53.0-70.0)	61.0 (51.0-69.0)	<0.001
Age category (%)				<0.001
18-44	13.9	14.6	13.0	
45-64	44.1	45.2	42.8	
65-80	42.0	40.3	44.2	
Race/Ethnicity (%)				<0.001
Non-Hispanic White	41.5	44.0	38.5	
Non-Hispanic Black	54.1	51.3	57.5	
Hispanic	2.7	3.0	2.2	
Other	1.8	1.8	1.7	
Insurance Type (%)				<0.001
Private	18.8	20.2	17.0	
Medicaid	25.1	19.5	32.1	
Medicare	39.5	40.5	38.3	
Other	6.5	8.4	4.3	
No insurance coverage	10.1	11.5	8.5	
Clinical Characteristics				
BMI (kg/m^2), median (IQR)	29.1 (24.5-35.1)	28.4 (24.2-33.7)	30.1 (24.9-36.8)	<0.001
BMI (kg/m^2)				<0.001
<18.5	3.2	2.9	3.5	
18.5-24.9	24.8	26.9	22.2	
25-30	26.4	28.7	23.4	
30-35	20.5	20.8	20.1	
35-40	12.1	10.8	13.6	
≥40	13.1	9.9	17.1	
Primary Cause of ESKD* (%)				<0.001
Diabetes	44.7	42.8	47.0	
Hypertension	36.2	37.7	34.2	
Glomerulonephritis	6.8	6.2	7.6	
Other	12.4	13.3	11.2	
Pre-ESKD nephrology care* (%)				<0.001
Yes	71.0	69.6	72.8	
Comorbidities* (%)				
Current Smoker	9.2	10.7	7.3	<0.001
Congestive heart failure	27.8	26.9	28.9	<0.001
Atherosclerotic heart disease	10.4	11.1	9.6	<0.001
Other cardiac disease	17.9	18.9	16.7	<0.001
Diabetes	58.8	56.7	61.5	<0.001
Cerebrovascular vascular disease	9.3	8.8	9.8	<0.01
Peripheral vascular	9.1	10.0	8.1	<0.001
Cancer	6.5	6.9	6.1	<0.01

*27 (0.1%) of patients missing primary cause of ESKD, 4,885 (12.2%) missing pre-ESKD nephrology care, 16 (<0.1%) missing information on comorbidities

**Abbreviations: BMI= body mass index, ESKD= End Stage Kidney Disease, SD= standard deviation

Table 2. Hazard Ratios (95% CI) of the association between sex and 12-month referral among incident ESKD patients in GA, NC, and SC, 2012-2016, in multivariate models using a forward stepwise approach

	Crude model	**Model 1***	**Model 2†**	**Model 3‡**
Male	Reference	Reference	Reference	Reference
Female	0.84 (0.80, 0.87)	0.88 (0.85, 0.92)	0.88 (0.84, 0.92)	0.87 (0.83, 0.91)

*Model 1: adjust for race, age, and insurance status
†Model 2: model 1 + primary cause of ESRD, BMI, pre-ESRD care
‡Model 3: (model 2 + comorbidities

Table 3. Association of ESKD patient characteristics with 12-month referral in GA, NC, and SC, 2012-2016.

	Bivariate model HR (95% CI)	**Multivariate model*** HR (95% CI)
Sex		
Male	Reference	Reference
Female	0.84 (0.80, 0.87)	0.87 (0.83, 0.91)
Age		
18-44	Reference	Reference
45-64	0.66 (0.63, 0.70)	0.71 (0.67, 0.75)
65-80	0.29 (0.28, 0.31)	0.33 (0.31, 0.35)
Race/Ethnicity		
Non-Hispanic White	Reference	Reference
Non-Hispanic Black	1.46 (1.40, 1.53)	1.24 (1.18, 1.30)
Hispanic	1.62 (1.44, 1.81)	1.26 (1.12, 1.43)
Other	1.52 (1.31, 1.77)	1.44 (1.23, 1.68)
BMI (kg/m^2)		
<18.5	0.80 (0.70, 0.92)	0.81 (0.70, 0.94)
18.5-24.9	Reference	Reference
25-29.9	1.15 (1.08, 1.21)	1.11 (1.04, 1.18)
30-34.9	1.26 (1.19, 1.34)	1.19 (1.11, 1.26)
35-39.9	1.26 (1.18, 1.35)	1.16 (1.07, 1.25)
≥40	1.05 (0.98, 1.13)	0.88 (0.81, 0.95)
Insurance status		
Private	Reference	Reference
Medicaid	0.67 (0.63, 0.71)	0.67 (0.63, 0.71)
Medicare	0.03 (0.50, 0.56)	0.80 (0.75, 0.85)
Other	0.78 (0.71, 0.85)	0.75 (0.68, 0.83)
No insurance coverage	0.98 (0.92, 1.04)	0.80 (0.75, 0.86)
Primary Cause of ESKD		
Diabetes	Reference	Reference
Hypertension	1.04 (1.00, 1.09)	1.01 (0.95, 1.07)
Glomerulonephritis	1.34 (1.24, 1.44)	1.05 (0.96, 1.15)
Other	0.75 (0.70, 0.81)	0.73 (0.67, 0.80)
Pre-ESKD nephrology care		
No	Reference	Reference
Yes	0.98 (0.93, 1.02)	1.11 (1.06, 1.16)
Comorbidities		
Current smoker	1.03 (0.96, 1.10)	0.93 (0.86, 1.00)
Congestive heart failure	0.75 (0.72, 0.79)	0.89 (0.84, 0.94)
Atherosclerotic heart disease	0.64 (0.59, 0.70)	0.84 (0.77, 0.92)
Other cardiac disease	0.68 (0.64, 0.72)	0.84 (0.79, 0.90)
Diabetes	0.92 (0.88, 0.96)	0.97 (0.92, 1.03)
Cerebrovascular vascular disease	0.69 (0.63, 0.75)	0.78 (0.72, 0.85)
Peripheral vascular	0.70 (0.64, 0.76)	0.87 (0.80, 0.96)
Cancer	0.48 (0.43, 0.54)	0.64 (0.57, 0.73)

*The multivariate model examined the association between each patient characteristic and referral within one year of dialysis initiation, adjusted for all of the patient characteristics in the table.

Table 4. Hazard Ratio (95%CI) of the association between sex and 12-month referral in multivariate models, and in models including an interaction term for age, race/ethnicity, and BMI

	Multivariate model	**Model + Interaction term (age)**	**Model + Interaction term (race)**	**Model + Interaction term (BMI)**
Male	Reference	Reference	Reference	Reference
Female	0.87 (0.83, 0.91)	0.93 (0.85, 1.02)	0.80 (0.74, 0.86)	0.88 (0.80, 0.97)

FIGURES

Figure 1. Key steps in access to kidney transplantation

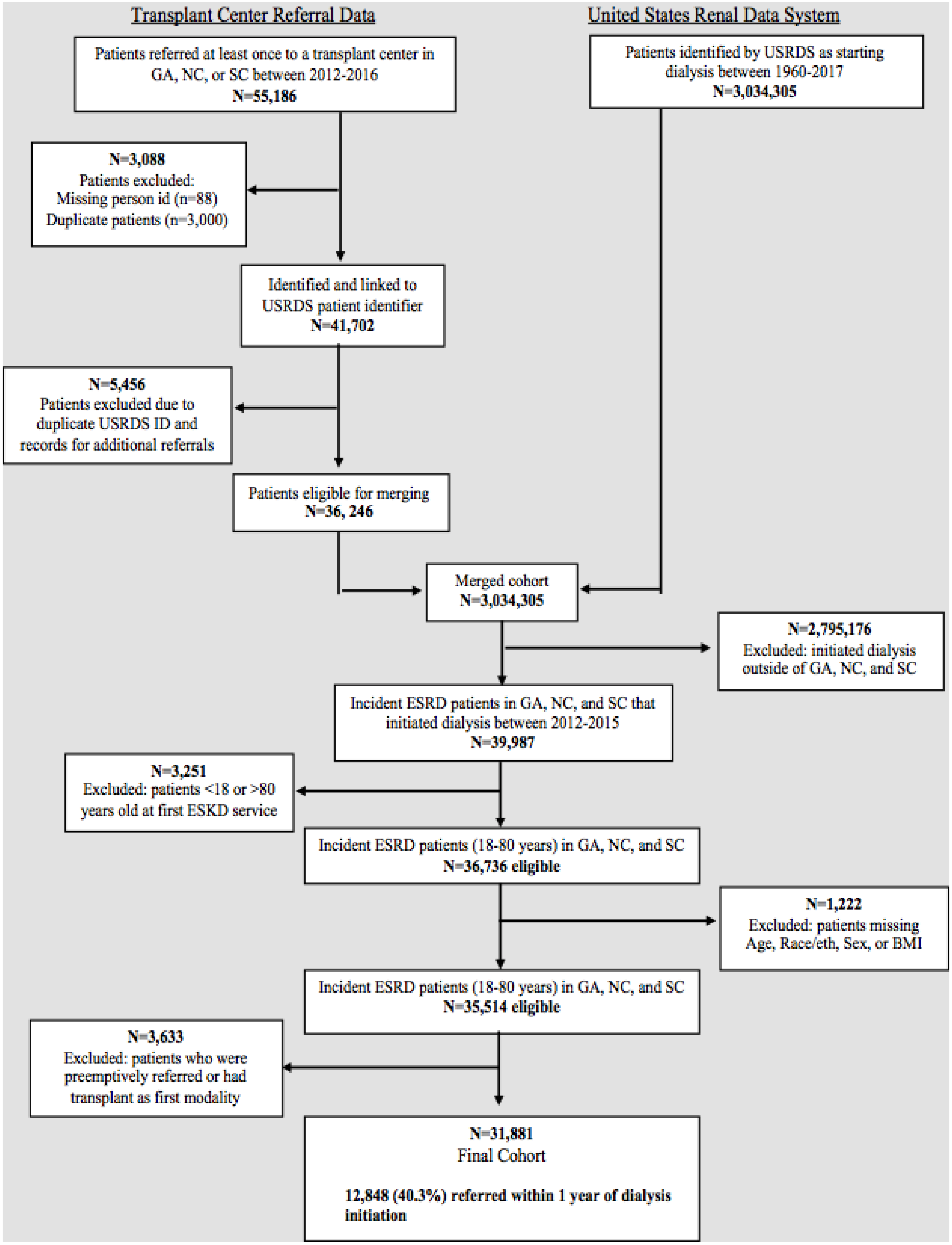


Figure 2. Flow diagram of study inclusion and exclusion criteria for study population (2012-2015)

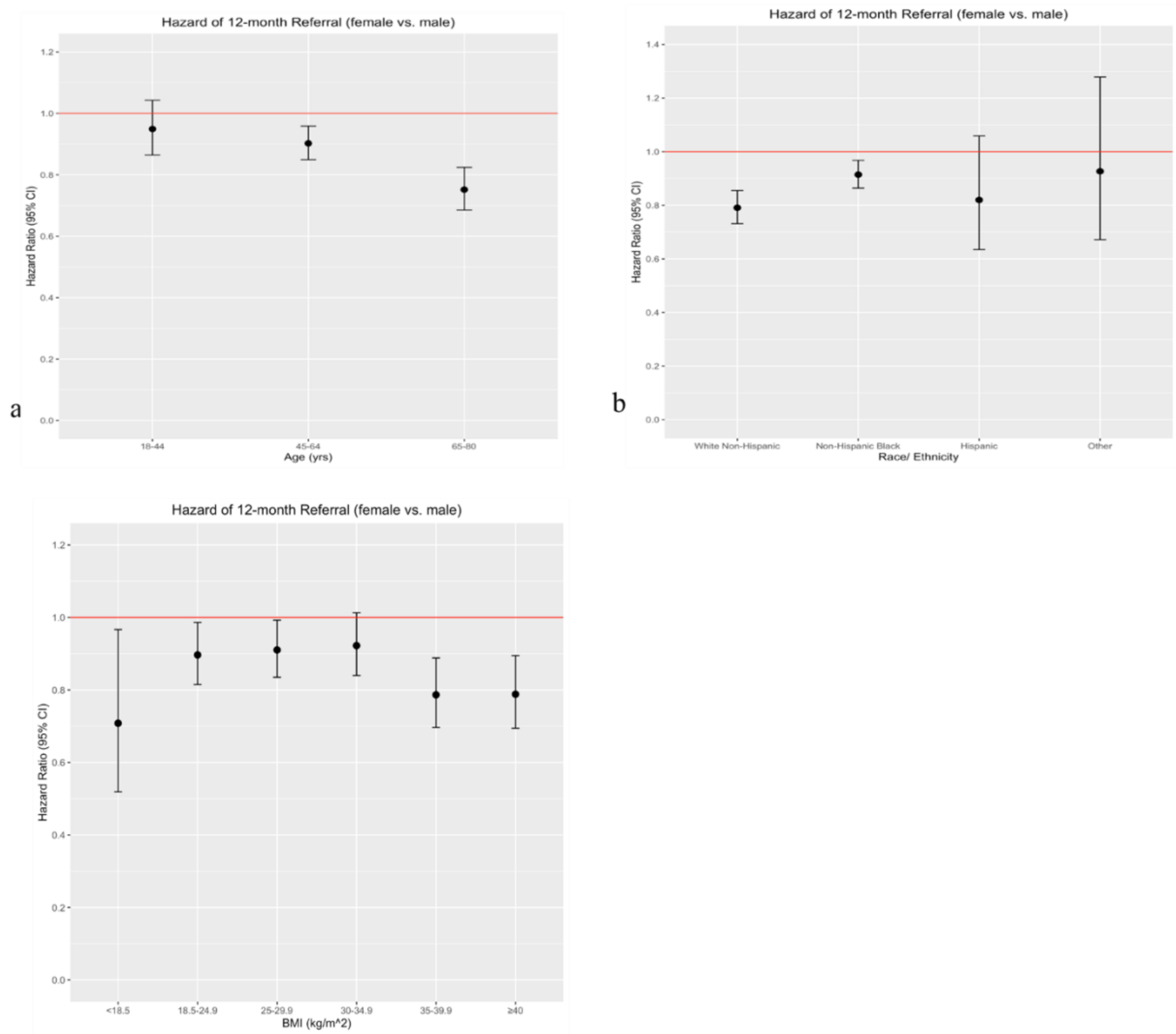


Figure 3. Association between 12-month referral and sex Stratified by (a) Age (b) race, and (c) BMI. The reference line of 1 (in red) indicates no difference in referral rates between males and females

APPENDIX

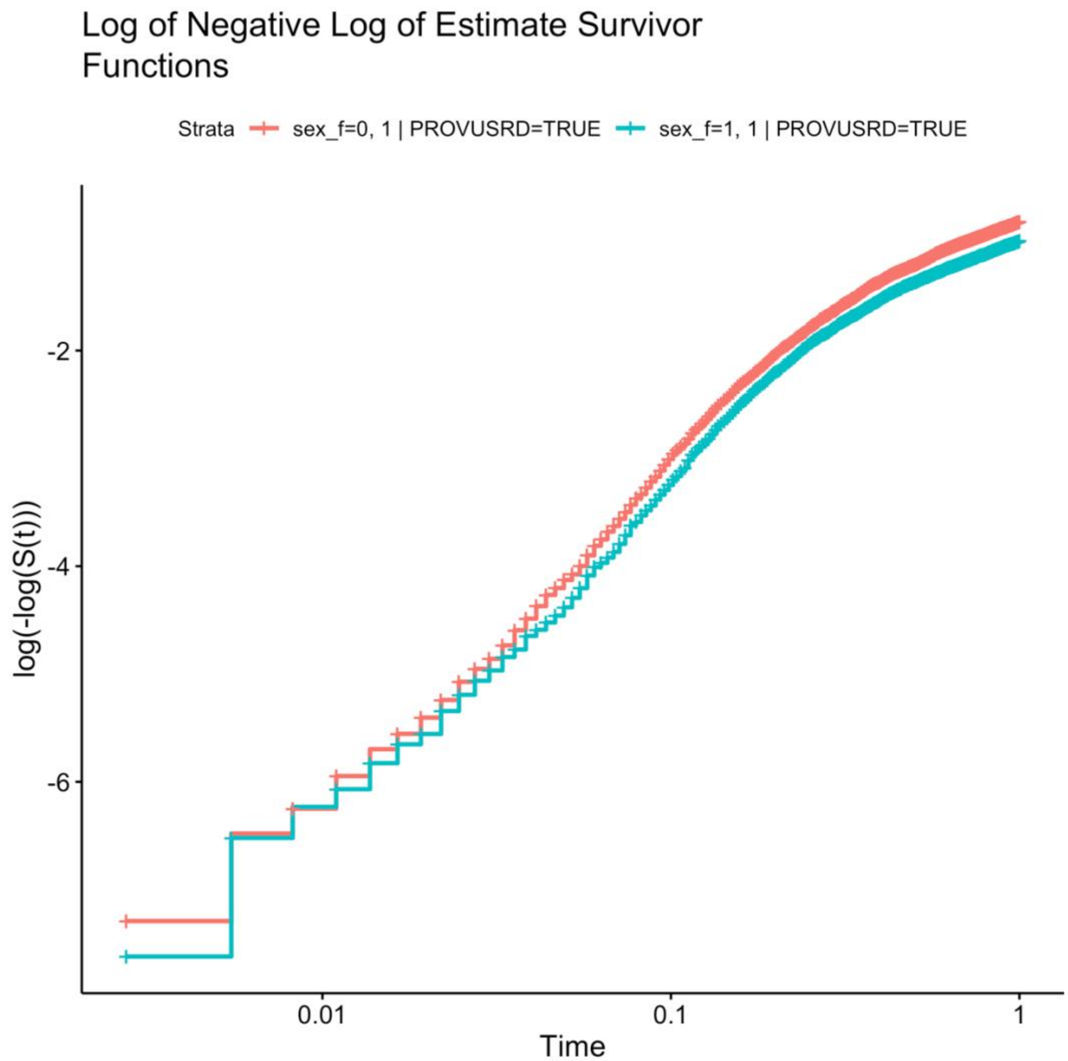
Supplementary Table I. Association between sex and 12-month referral stratified by age, race/ethnicity, and BMI

	12-month referral (N)	**12-month referral HR (95% CI)**
Age category		
18-44	2354	0.95 (0.86, 1.04)
45-64	5241	0.90 (0.85, 0.96)
65-80	2333	0.75 (0.69, 0.82)
Race/Ethnicity		
White, non-Hispanic	3277	0.79 (0.73, 0.85)
Non-Hispanic Black	6106	0.91 (0.86, 0.97)
Hispanic	342	0.82 (0.63, 1.06)
Other	203	0.93 (0.67, 1.28)
BMI (kg/m^2)		
<18.5	2241	0.71 (0.52, 0.97)
18.5-24.9	228	0.90 (0.82, 0.99)
25-29.9	2692	0.91 (0.84, 0.99)
30-34.9	2225	0.92 (0.84, 1.01)
35-39.9	1322	0.79 (0.70, 0.89)
≥40	1220	0.79 (0.69, 0.89)

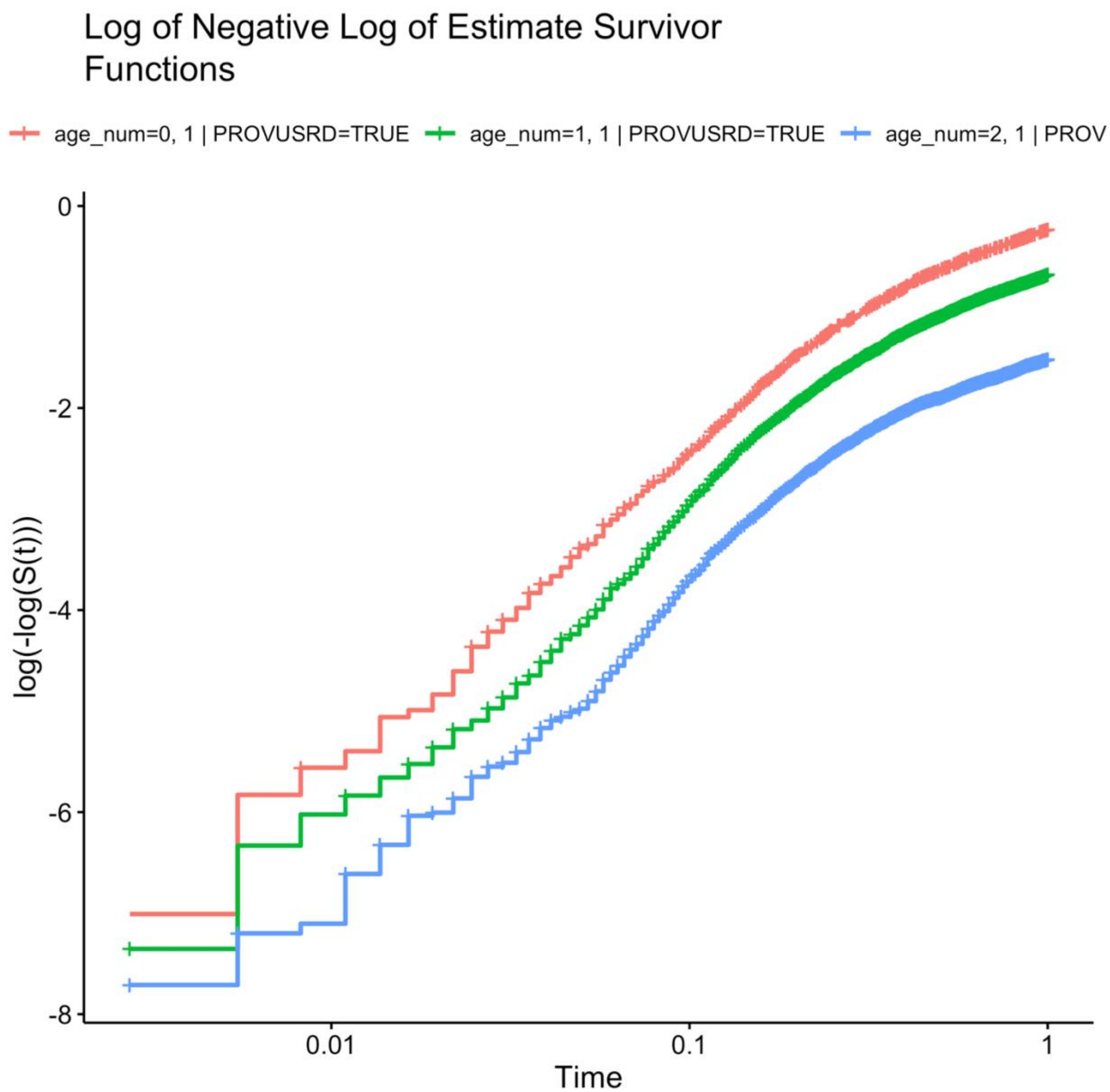
Supplementary Table II. Baseline characteristics of included study population as compared with pre-emptively referred or transplanted ESKD patients.

Variables	**Study population (included)**	**Pre-preemptively referred or transplanted (excluded)**	**p-value**
N	31,881	3,633	
Sex (%)			
male	55.2	56.7	0.1
Age in years, median (IQR)	62.0 (52.0-70.0)	56.0 (45.0-64.0)	<0.001
Age category (%)			<0.001
18-44	13.9	24.0	
45-64	44.1	51.8	
65-80	42.0	24.2	
Race/Ethnicity (%)			0.007
non-Hispanic White,	41.5	42.2	
Non-Hispanic Black	54.1	52.5	
Hispanic	2.7	2.8	
Other	1.8	2.5	
Insurance Type (%)			<0.001
Employer Group	18.8	41.9	
Medicaid	25.1	17.6	
Medicare	39.5	30.1	
Other	6.5	7.3	
No insurance coverage	10.1	3.1	
Clinical Characteristics			
BMI (kg/m^2), median (IQR)	29.1 (24.5-35.1)	29.4 (25.2-34.6)	0.09
BMI (kg/m^2) (%)			<0.001
<18.5	3.2	1.4	
18-5-24.9	24.8	22.6	
25-29.9	26.4	29.3	
30-34.9	20.5	23.4	
35-39.9	12.1	14.9	
≥40	13.1	8.5	
Primary Cause of ESKD (%)			<0.001
Diabetes	44.7	43.3	
Hypertension	36.2	29.9	
Glomerulonephritis	6.8	13.7	
Other	12.4	13.1	
Pre-ESKD nephrology care (%)			<0.001
Yes	71.0	93.8	
Comorbidities (%)			
Current Smoker	9.2	5.1	<0.001
Congestive heart failure	27.8	13.3	<0.001
Atherosclerotic heart disease	10.4	6.3	<0.001
Other cardiac disease	17.9	10.4	<0.001
Diabetes	58.8	55.0	<0.001
Cerebrovascular vascular disease	9.3	4.4	<0.001
Peripheral vascular	9.1	5.8	<0.001
Cancer	6.5	3.5	<0.001

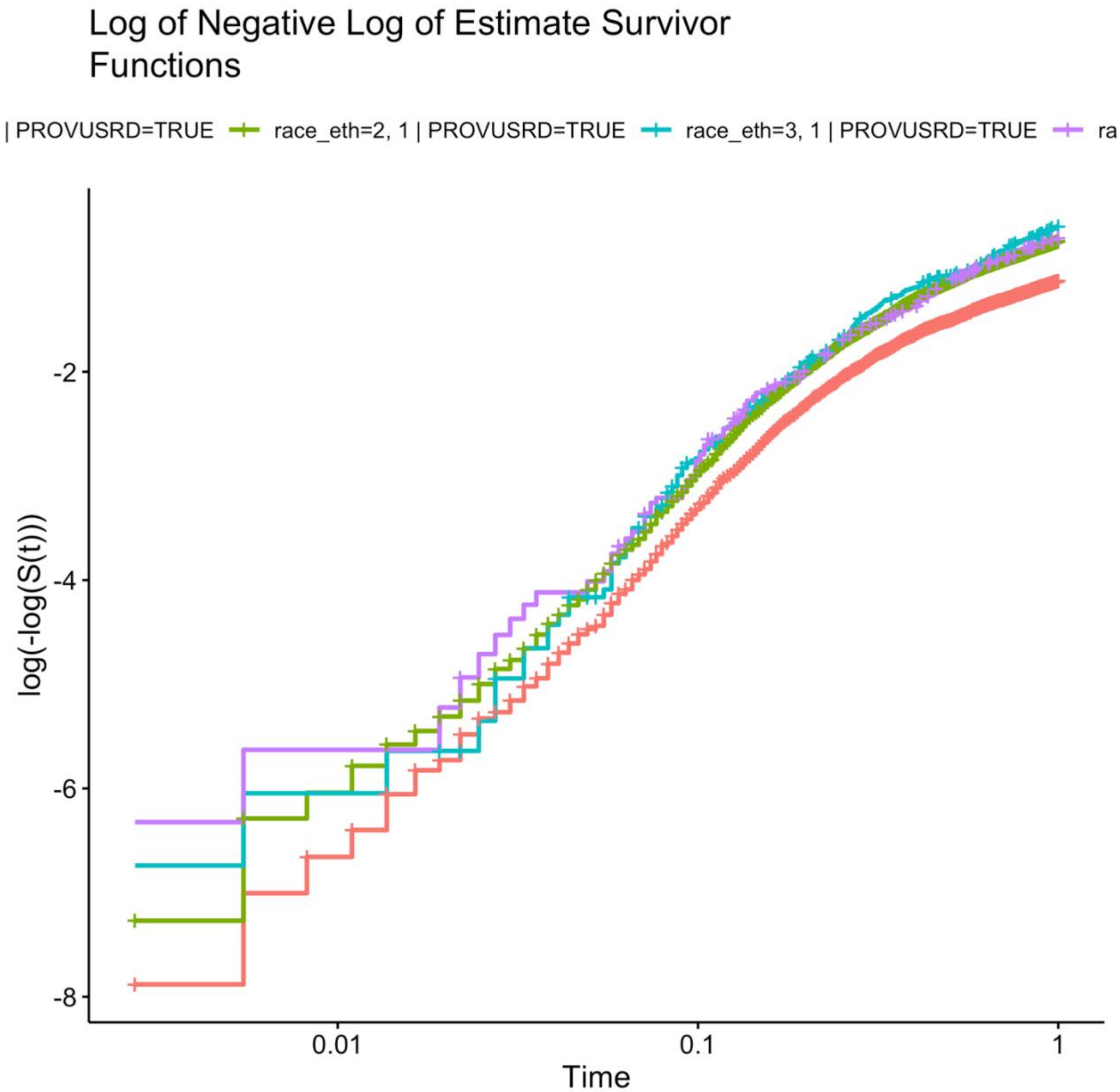
[*] Among those excluded 32 (0.9%) of patients were preemptively transplanted while the remaining 3,601 patients were preemptively referred



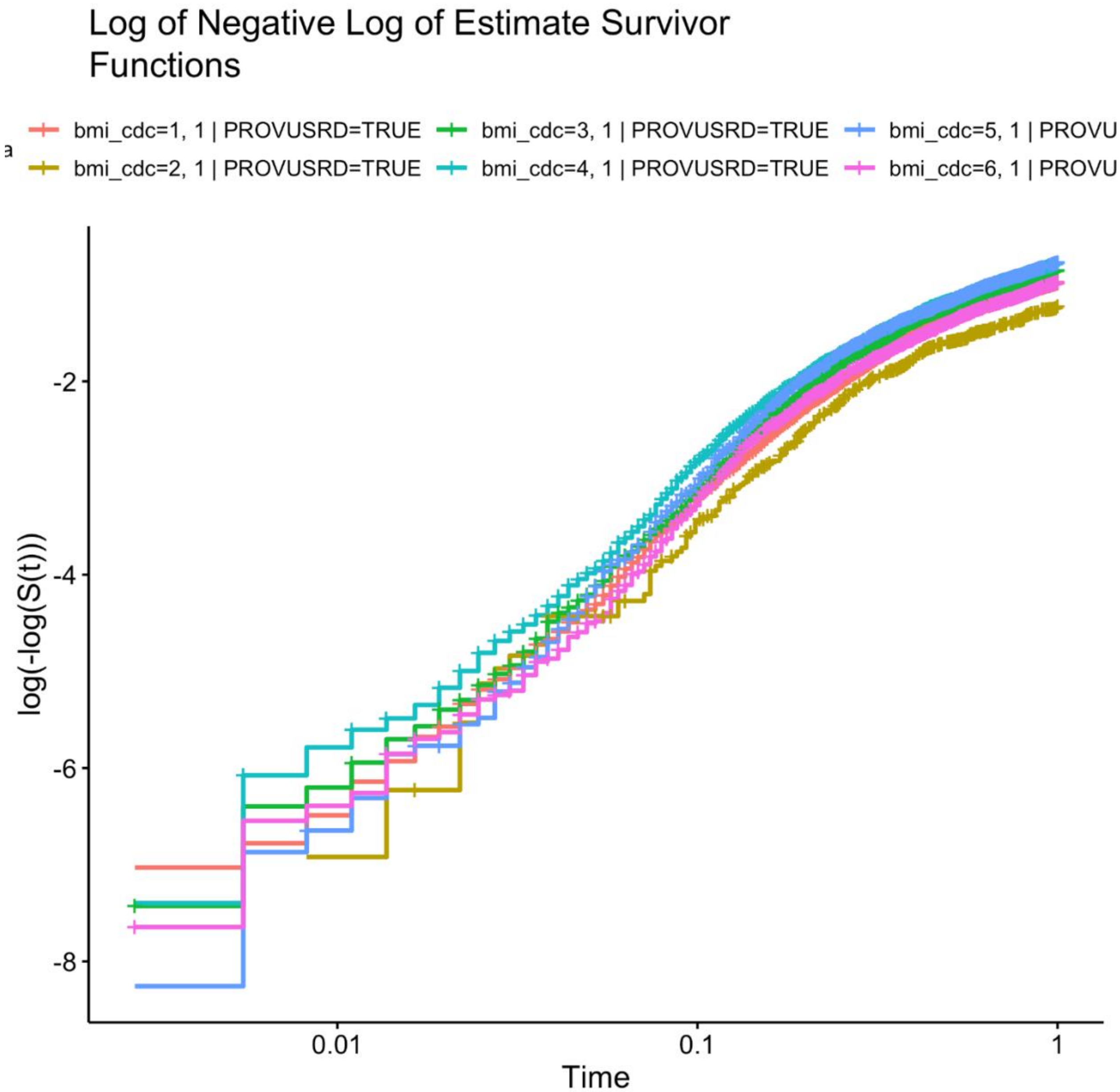
Supplementary Figure 1. Graph testing proportional hazards assumption for sex (Females=1; Males=0).



Supplementary Figure 2. Graph testing proportional hazards assumption for age (0=18-44; 1=45-64; 2=65-80).



Supplementary Figure 3. Graph testing proportional hazards assumption for race/ethnicity (Red=White-Non Hispanic; Green=Non-Hispanic Black; Blue=Hispanic; Purple=Other).



Supplementary Figure 4. Graph testing proportional hazards assumption for BMI (kg/m^2) (Red=<18.5; Gold=18.5-24.9; Green=25-29,9; Light Blue=30-34.9; Blue=35-39.9; Pink=≥40).