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Title: Using race to estimate glomerular filtration and its impact in kidney transplantation.

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Running Head: eGFR, Race and Kidney Transplantation

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Abstract:

Since direct measurement of glomerular filtration rate (GFR) is time consuming and more expensive, estimated GFR (eGFR) based on measured laboratory values is widely used to determine kidney function. Commonly used formulae to calculate eGFR are dependent on variables which include filtration markers like serum creatinine and patient characteristics including race. Medical algorithms which utilize race are increasingly being scrutinized, as race is recognized to be a social construct rather than a biologic one. eGFR calculations have important implications for kidney transplantation, both in the listing of candidates as well as in the evaluation of potential kidney donors. This review considers the specific implications of race based eGFR calculations on recipient evaluation and on decisions related to living kidney donation. We suggest a potential policy solution to ensure that racial and ethnic minority patients are not disadvantaged by eGFR as a result of current calculation methods.

Background

The accurate assessment of glomerular filtration rate (GFR) defines severity of kidney dysfunction, informs the need for therapeutic adjustments including drug dosing, and predicts likelihood of progression to end stage kidney disease (ESKD). Ideally, critical decisions including the initiation of dialysis for ESKD, and qualifying to begin accruing waiting time on the kidney transplant waiting list, should be based on GFR that is determined by measurement or creatinine clearance. Unfortunately, direct measurement of GFR is time consuming, incur additional costs and is not immune to measurement error (1). Consequently, serum creatinine (Cr) based formulas are widely used to calculate an estimated GFR (eGFR) in both clinical practice and epidemiologic research.

The 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation includes the variables age, sex, and race (specified as black versus non-black) (2) and is superior to the modification of diet in renal disease (MDRD) eGFR equation in accurately predicting true measured GFR (mGFR). The CKD-EPI development dataset included 2601 black patients (31.5% of the total population), of whom the largest proportion was from the African American Study of Kidney Disease and Hypertension, in which race was self- reported. The MDRD dataset population included 197 black (13.1%) and 1304 white patients (86.8%) with no information on how race was determined. The equations assign a race coefficient of 1.16 (CKD-EPI) and 1.21 (MDRD) to patients identified as black, resulting in 16% and 21% respective increases in eGFR for black patients with the same age, sex and creatinine.(2, 3) Interestingly, this black coefficient did not perform well in African populations, where removal of the coefficient improved their accuracy.(4) Alternatively, eGFR can be calculated using the cystatin C (GFR_{cys}) equation, in which the black coefficient decreases significantly to 1.06. (5) Unfortunately, as each relies on race, the results are subject to bias and error for mixed race individuals as well as black patients of different ethnicity (e.g. Afro-Caribbean, Afro-American, African).

Race is well recognized to be a social construct rather than a biologic one.(6, 7) Consequently, medical decision making tools that rely on race are being increasingly scrutinized. Enanya *et al.* note the significant possible harm of estimating a biologic measure (eGFR) with potentially biased parameters, given that race is not objectively measured nor defined.(6) The authors argue that patient race should guide clinical care only if its use confers substantial benefit which cannot be achieved through other feasible approaches, patients who reject race categorization are accommodated fairly, and its use is transparent. The use of race in eGFR equations does not appear to meet these criteria. This conclusion has also been shared by the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN), who recently formed a joint task force to "focus on the use of race to estimate GFR".(8)

Current kidney allocation policy and clinical management are directly impacted by inaccuracy in eGFR measurements, which are believed to be "objective" measures of organ function. Errors and biases have specific implications on recipient evaluation, wait-listing, and access to transplantation. The use of race based eGFR may also adversely affect living kidney donation. Thus, we suggest a potential short-term policy solution to ensure that racial and ethnic minority patients are not disadvantaged by current calculation methods.

eGFR and Chronic Kidney Disease (CKD) Progression

Accurate assessment of GFR is important to predict progression of CKD and is vital for appropriate ESKD planning, including timing for referral to transplant evaluation. There are well documented differences in expected rates of progression of CKD to ESKD between black and non-black populations(9-11). Compared to white patients, black women are 2-fold more likely and black men 3.5 times more likely to progress to ESKD over 5 years.(10) The multifactorial reasons for more rapid progression include genetic risks, differential access to health care, and coexisting risks including obesity and hypertension.(12) Biological factors such as possession of 2 apolipoprotein L1 (*APOL1*) renal risk variants (RRV) have also been associated with more rapid progression to ESKD, which is more common in persons of African ancestry (2 RRV in 10-15%; 1 RRV in 35-40%).(13, 14) (Figure 1) Consequently, among CKD patients, black individuals with similar GFRs would be expected to reach ESKD sooner than whites.

Risk prediction tools such as the Centers for Disease Control and Prevention CKD Surveillance System calculator unfortunately do not reflect these observed risks.(15) Consider a 50 year old, 70 kg male with DM and a Cr of 2.5 mg/dL. The CKD-EPI eGFR is 33 mL/min per 1.73 m^2 if black and 29 mL/min per 1.73 m^2 otherwise. Using these estimates, a white patient has a predicted ESKD risk of 4.5% -23.2% in two years while a patient classified as black has only a 3.0% -16.3% risk. This eGFR tool suggests that the black patient would have up to 30% lower likelihood of progression than his white counterpart, based on assumptions about his race alone, despite clinical evidence to the contrary.(16-18) These predictions have substantial implications for patient education and timely planning for renal replacement therapy. Further complicating this picture is the consideration of the mixed-race patient. Patients may be inappropriately categorized as black, rendering their eGFR higher, leading to inappropriate care decisions, including delayed referral to a transplant center.

As many nephrologists use an eGFR cutoff of 20-30 mL/min to initiate transplant evaluation, eGFR errors can result in delayed referral of patients considered “black” by their clinicians. Delayed evaluation contributes to a delay in listing of black patients.(19, 20) Current analyses demonstrate that black patients with ESKD are 24% less likely to be waitlisted than whites (relative risk [RR]: 0.76 (95% confidence interval [95% CI], 0.69 to 0.83) even after accounting for socioeconomic status and comorbidity (RR 0.90; 95% CI, 0.83 to 0.97). Replacement of current race based eGFR equations with precise, race-neutral equations when available or with mGFR may assist black patients in accessing transplant care in a more timely and efficient manner.

Transplant policy and eGFR

In order to establish an equitable system to allocate available deceased donor organs in the United States, strict acceptance criteria have been established by the Organ Procurement and Transplantation Network (OPTN). Under the revised kidney allocation system (KAS), patients qualify for waiting time points once they have initiated chronic dialysis or have documentation of a creatinine clearance, GFR or eGFR of ≤ 20 mL/min, unadjusted for body surface area. The KAS revision also credits time on dialysis prior to waitlisting to ensure equitable access for patients who previously suffered due to late referral for transplant evaluation.(21) The reasons for late referral to kidney transplant (KT) are multifactorial, but error in eGFR is a likely contributor.(22)

Misclassification errors may also reduce access to the waiting list for black patients, who despite having more rapid declines in kidney function, need a higher creatinine than white patients to be eligible to begin accruing waiting time for a kidney transplant. This policy reduces likelihood of preemptive KT for black patients, which has been demonstrated to have superior long-term outcomes.(23, 24) As a result, black patients more frequently experience the increased mortality risk associated with dialysis.

Substitution of 'Race' with APOL1 genotype analysis:

The use of *APOL1* analysis instead of race has the ability to impact many aspects of transplantation. (26) Kidney Donor Risk Index (KDRI) which was developed to evaluate organ offers by predicting allograft longevity, includes black race as a risk factor. Replacing race with *APOL1* analysis revised KDRI and improved the score for the 85% of AA donors who possessed 0/1 RRV. In those who possessed 2 RRV's it conferred a hazard ratio 1.51 times that associated with 0/1 RRV indicating that using *APOL1* genotype improved the performance of KDRI substantially. Similarly, Kidney Donor Profile Index (KDPI) for an AA deceased kidney donor with 0/1 *APOL1* renal-risk variants would decrease by 18 percentage points, whereas the KDPI for AA donors with 2 renal-risk variants would increase by 19 points. Consequently, the KDPI for organs recovered from black donors with 0-1 variants, would approximate the median for all deceased kidney donors, but the KDPI for the 2 RRV donor group reaches the range where kidneys are likely to fare poorly, and substantially impact recipient choice. In both these situations substituting 'self-identified race' with a genotype analysis potentially improves the risk profile as well as ensures proper allocation of organs that have a higher risk of failure to appropriate recipients.(25) The currently underway *'APOL1* Long-term Outcomes' (APOLLO) U01 study seeks to generate data within a prospective national cohort to inform the role of *APOL1* genotyping in allocation policy and living donor evaluation. (26)

Impact of Race Based eGFR on Living Donation

Living donor kidney transplant (LDKT) is considered the optimal care for patients with advanced CKD in need of kidney replacement therapy. LDKT allows for preemptive KT and is associated with improved survival.(23, 27) Historically, black patients have had limited access to living donation (LD) compared to their white counterparts.(28-30) The priority in the evaluation of living kidney donors is safety. Clinicians are directed to ensure the donor candidate does not pose unacceptable risk for post-donation ESKD. (31) Most importantly, the evaluation team must ensure there is adequate kidney function in the donor such that the recipient benefits and the donor is healthy.(32) As previously discussed, at baseline black individuals have a higher risk of CKD and CKD progression than their white counterparts.(10) In addition, there is a well-documented increased risk for future development of CKD and progression to ESKD following donation among black donors. Balancing the need for LDKT donor safety requires accurate information on which to base decisions.

The use of race-based estimates of GFR presents unique challenges for LDKT. First, the use of current race-based eGFR equations may overestimate the true renal reserve in black potential donors. Although U.S. National OPTN Policy requires confirmatory measurements with mGFR or mCrCl,(33), if eGFR is used in the decision making process, there remains the potential for its overestimation, thereby increasing donor risk.

Second, without careful application of race-neutral eGFR, otherwise acceptable black LD candidates could be inaccurately excluded from donor evaluation on the basis on established center cutoffs for minimal eGFR. These exclusions would be expected to happen in the population of candidates with eGFR within 5-10 mL/min of acceptability. For example, to streamline the evaluation, some programs exclude donor candidates with eGFR <60 ml/min per 1.73 m2 without proceeding to mCrCl or mGFR. These potential donors would be screened out prior to confirmatory testing, exacerbating the disparity in access (29)

Finally, as previously noted, the case of the mixed-race donor creates a particular challenge to LD evaluation and estimation of future health risk. To address these concerns, accurate estimates of GFR must be available or mGFR used.

Proposal

The use of race-based equations as the basis for listing for transplantation should be minimized and eliminated once appropriate race neutral equations are developed. In the short term, utilization of $eGFR_{cys}$ based estimates of GFR should be considered for all patients, particularly black patients who may

be disadvantaged with creatinine based eGFR estimates. Over time, the OPTN should move to use only race neutral equations once the nephrology community develops them.

In the case of LD, centers should be encouraged to consider revising thresholds for donor evaluation, particularly among black patients. Use of $eGFR_{cys}$, rather than creatinine-based estimates should be considered for initial screening. In addition, transplant centers need to comply with UNOS policy to determine candidacy based on mGFR.

Moving forward, the OPTN should consider requiring alternatives to the current creatinine based eGFR equations which include race such as GFR_{cys}. Additional markers to assess GFR including β trace protein and β-2 microglobulin that have stronger associations with adverse outcomes than creatinine, and are less influenced by race, should also be evaluated.(34) Specifically, research is needed to determine if the novel methods of eGFR assessment improve accuracy, generalizability, and reliability by eliminating the need to specify patient race.(5)

Finally, the transplant community should partner with NKF, ASN, and others to emphasize the need for early referral for evaluation among patients categorized as black and reported to have higher eGFR based on standard reporting. Perhaps these patients should be referred with an eGFR of 30-35, especially in patients with risk factors including hypertension, diabetes, high-grade proteinuria or known genetic risk (e.g. 2 *APOL1* RRV). If transplant programs do not see patients until they have already developed ESKD, any benefit of reform in measurement of eGFR will be eliminated.

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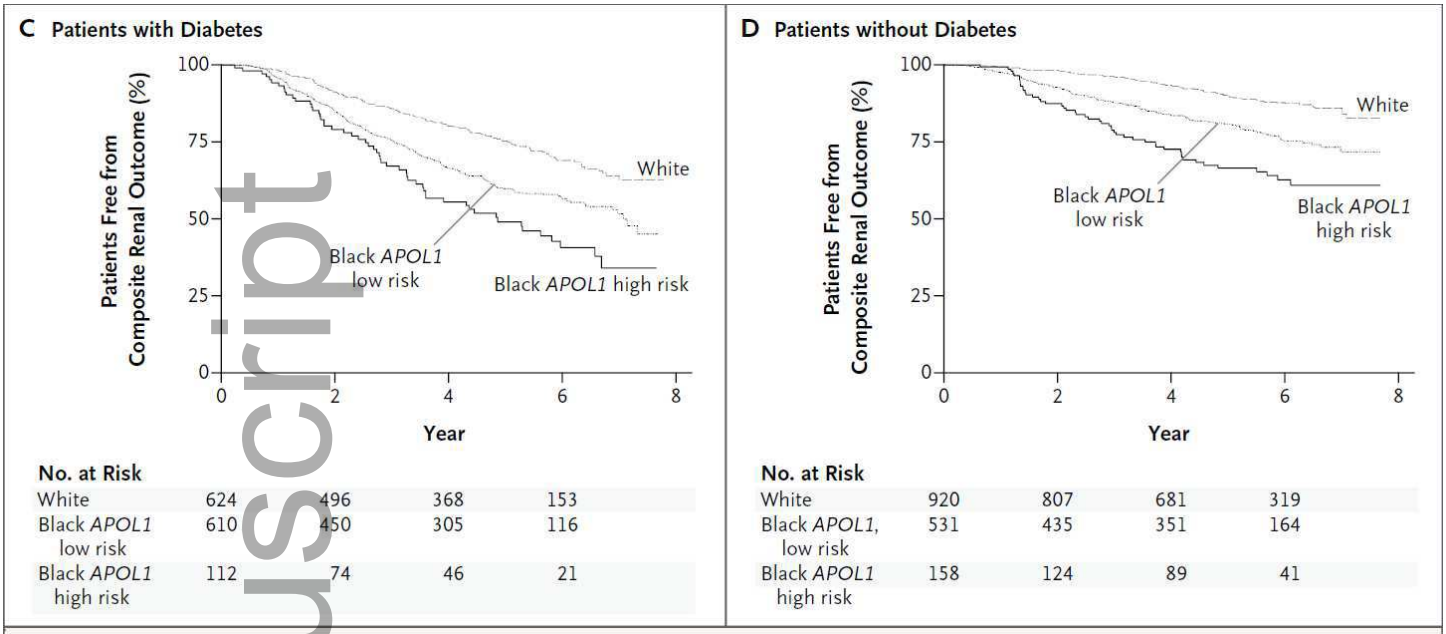
Figure 1: Comparisons of the Estimated Glomerular Filtration Rate (eGFR) Slope and Proportion of Patients Free from a Primary Outcome Event in the CRIC Study.



Between-Group Comparisons of the Estimated Glomerular Filtration Rate (eGFR) Slope and Proportion of Patients Free from a Primary Outcome Event in the CRIC Study.

In the Chronic Renal Insufficiency Cohort (CRIC) study, the primary outcomes were the eGFR slope and a composite of end-stage renal disease or a reduction of 50% in the eGFR from baseline. Shown are the proportions of white patients and black patients in the *APOL1* high-risk and low-risk groups who were free from the primary outcome of end-stage renal disease or a reduction of 50% in the eGFR from baseline, among patients with diabetes (Panel C) and among those without diabetes (Panel D).