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Achieving Equity for Liver Transplant Recipients with Chronic Kidney Disease

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Kidney dysfunction has been associated with increased patient morbidity and mortality among multiorgan transplant recipients, including liver transplant recipients. A number of factors contribute to acute and chronic kidney injury in patients with end-stage liver disease (ESLD) including hemodynamic disturbances, drug toxicity, and progression of underlying kidney disease. . Baseline kidney function reflecting renal reserve is an important predictor of patient

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mortality post liver transplantation, with >10% increase in 5-year mortality in those with serum creatinine >2.0mg/dL prior to liver transplant surgery. Data demonstrating a clear survival benefit of simultaneous liver and kidney (SLK) transplantation in end-stage liver disease (ESLD) patients with advanced kidney dysfunction has led to an increase in the number of SLK transplants over the years in the U.S.

The risk of end-stage kidney disease (ESKD) requiring dialysis ranges from 2% to 5% per year after transplantation.[1] Implementation of Model for End-Stage Liver Disease Score (MELD) for liver allocation by United Network for Organ Sharing (UNOS) there was a significant increase in the number of SLK transplants. Historical investigation of liver transplant recipients demonstrates that both SLK and early kidney after liver (KAL) transplant recipients had lower patient adjusted mortality compared to those with liver transplant alone (LTA) and ESKD. As a result, the current UNOS policy for allocation of kidneys to liver transplant candidates defines the criteria for SLK transplantation as well as early KAL transplantation under the 'safety net' policy.[2] However, the ability to predict who will and will not develop ESKD following liver transplantation remains an important unmet challenge. There is significant variability in the listing practices across transplant programs. [3]

Access to SLK listing is particularly important for Black individuals given the high rate of kidney failure among Black individuals compared to other races. Recently published data suggests that the adjusted risk of ESKD post liver transplantation for Black recipients was increased by 2-fold and the median time to ESRD was much shorter for Blacks compared to Whites.[4] Any validated eGFR equation or measured GFR can be used when listing a patient for SLK as per the UNOS policy. The most common equations used for eGFR measurement are the 4-variable modification of diet in renal disease (MDRD-4) and the chronic kidney disease epidemiology collaboration (CKD-EPI), both of which include the Black race variable in the equation. The race adjustment assigns a higher GFR to Black patients for the same level of serum creatinine. As a result there is a concern that race-based GFR estimation may potentially reduce access to SLK and KAL for Black patients, despite the well documented higher prevalence of kidney disease.

Currently the laboratories provide two values of GFR for an individual, one for Black and one for non-Black, resulting in provider bias and uncertainty for those of mixed race. The increasing national events around racial injustice has prompted the medical community to revisit use of race in medical equations and explore strategies to ameliorate some of the existing disparities in care and access. Prompted by these sentiments, the NKF/ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases developed a new refitted CKD-EPI formula to estimate GFR without race coefficient.[5]

Prompted by these sentiments, Panchal and colleagues in this edition of *Liver Transplantation*, the authors investigated the impact of the removing race variable from MDRD and CKD-EPI equations on Black patients' eligibility for a SLK transplant.[6] The authors performed a retrospective analysis of the listing data for all patients listed for either a liver or SLK over a 17 year period using the UNOS database and examined if the likelihood of meeting the criteria for SLK using either the CKD or sustained AKI pathway was higher if race was eliminated from the eGFR equations. For the entire cohort of 7,937 Black patients, the median value of the minimum waitlist eGFR was 7ml/min/1.73m^2 lower when race was removed from the MDRD-4 equation.[6] The findings were similar with CKD-EPI equation and the impact of removing race from eGFR equation was greater for those with serum creatinine values that were numerically lower. It is already well known that given the incidence of sarcopenia in patients with ESLD, the numerical serum creatinine value is lower compared to those without ESLD. The observed difference in eGFR with and without race variable in those with lower creatinine values (<2.5mg/dL) suggests that Black patients with ESLD are at greater risk for disparities in health care access.

In this investigation, the authors demonstrated that the percentage of Black patients classified has having CKD using the CKD-EPI equation increased from 21.5% to 27.1% by eliminating the race variable, resulting in a reclassification of 5.6% of the Black patients to ESLD with CKD.[6] Similarly, the percentage of Black patients meeting the SLK waitlist criteria increased significantly ($p<0.05$) and resulted in a 23.7% increase in SLK transplant candidacy. Of interest,

Black women had higher percentage of reclassification to ESLD with CKD compared to men ($p<0.05$).[6] This is not surprising given that women have lower muscle mass compared to men and the impact of eliminating the race variable was greater at lower numerical creatinine values. Similar trends were noted when examining the AKI pathway but the findings were not statistically significant.

Although the mortality was numerically higher, there was no statistically significant difference in waitlist mortality between Black patients who met the SLK transplant listing criteria using eGFR equation with and without race variable. By eliminating the race variable in the eGFR equation and reclassifying the Black patients with ESLD, the percentage of patients with ESLD and CKD who received LTA increased by 4.7% to 6.2% and the percentage of patients receiving SLK transplants decreased by 5.5% to 8.4%.[6] Furthermore, 1.7% to 2.1% of those reclassified as having CKD by using an eGFR equation without the race variable received a kidney transplant within one-year of the liver transplant, suggesting that patients meeting the safety net criteria could have been identified earlier. These data identify the number of patients who would benefit and receive improved level of care if a race-free equation were used for listing patients for SLK.

Several factors need to be considered to decrease health care disparities among patients with ESLD and access to SLK transplantation. In addition to moving towards a race-free GFR equation, (1) the current barriers to prompt listing and utilization of the 'safety net' need to be addressed, (2) heterogeneity in the assessment of eGFR across centers need to be addressed with a strong emphasis on the race-free equation and (3) novel approaches to race and gender independent accurate eGFR assessment in ESLD patients need to be investigated.

Recent investigations suggest that listing of Black patients for SLK or LAK does not mirror that of Whites and there may be unidentified barriers to early listing of Black patients for SLK early as well as to the use of the 'safety net'. In an analysis of the UNOS data from 2002 to 2018, the authors found the proportion of Black individuals among the SLK recipients to be much larger

than the proportion in LTA recipients (16% vs. 9%), suggesting that Blacks are more likely to be sicker and have more advanced liver disease at the time of listing. Furthermore, the proportion of Black patients receiving a KAL was much lower than SLK (7% vs. 16%), suggesting the possibility of disparity in access to kidney after liver transplantation.[7]

The transplant community has raised significant concerns about the use of race in the eGFR equation and the potential for health care disparities given that race is a social construct rather than a biologic construct. Furthermore, the growing multiracial population invalidates the use of self-reported race in medical decisions. In the current publication by Panchal et al. they used the current eGFR equations and removed the race variable to demonstrate the impact on Black patients. This approach was recently studied and compared to a new race-free eGFR equation using creatinine in a publication in a NEJM publication by Inker and colleagues.[8] The authors demonstrated that the new race-free eGFR (creatinine) equation is associated with less bias than the current equations with removal of the race variable. Furthermore, the new race-free eGFR(creatinine) had clinically acceptable agreement with measured GFR for both race groups. This is an important step towards implementing a race-free eGFR equation in clinical practice. Given the complexities of estimating eGFR in patients with ESLD and the potential disparities in access to SLK transplantation, developing policies to use the validated race-free eGFR equation across institutions for SLK listing will be imperative.

It is important to note that this new eGFR(creatinine) has not been studied in large cohort of ESLD patients, especially since the creatinine measurement in an ESLD patient in impacted by sarcopenia, liver dysfunction, and increased volume of distribution. Cystatin C, another endogenous biomarker investigated for GFR estimation, is also influenced by factors such as sexual hormones, thyroid function, and inflammation. Inker and colleagues did develop a novel race-free based eGFR equation using creatinine and cystatin C. The authors demonstrated that the new eGFR(creatinine-cystatin C) was associated with the lower bias and greater agreement with the measured GFR compared to the new eGFR(creatinine).[8] Although cystatin C levels may be less impacted by sarcopenia and liver dysfunction, cystatin C based equations have not been

studied in the ELSD population. There is a need for novel investigations to identify the best biomarkers and equations to identify ESLD patients at risk for CKD, independent of race.

Given the relatively increased mortality risk among SLK and KAL recipients compared to SPK or kidney-alone transplant recipients, the 'utility' of kidney organs for SLK and KAL has been raised. Recent investigation evaluating the 'utility' of kidney allografts for SLK transplants suggests the kidney allograft lifespan is shortened by approximately one-year in patients with SLK as compared to those with SPK or kidney alone transplantation in the pre-MELD and MELD era.[9] However, the use of Black race in the eGFR equation is not about 'utility' but rather 'equity'. Clearly the data suggests that Black recipients with ESKD following liver transplantation have significantly higher risk of mortality compared to White recipients; 5-year survival with ESKD was reduced by 54% in Black vs. 30% in White patients.[4] By continuing to use Black race in the equation for eGFR, the diagnosis of CKD will be delayed in this vulnerable population and access to SLK and the much needed 'safety net' for early KAL transplant will be impeded.

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