Achieving Equity for Liver Transplantation Recipients With Chronic Kidney Disease

SEE ARTICLE ON PAGE 959

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 mortality after liver transplantation, with >10% increase in 5-year mortality in those with serum creatinine >2.0 mg/dl prior to liver transplantation surgery. Data demonstrating a clear survival benefit of simultaneous liver and kidney (SLK) transplantation in patients with ESLD having advanced kidney dysfunction have led to an increase in the number of SLK transplants over the years in the United States.

The risk of end-stage kidney disease (ESKD) requiring dialysis ranges from 2% to 5% per year after transplantation.[1] Following the implementation of the Model for End-Stage Liver Disease (MELD) score for liver allocation by the 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 with 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 for 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 transplantation programs.[3]

Access to SLK listing is particularly important for Black individuals given the high rate of kidney failure among this group compared with other races. Recently published data suggest that the adjusted risk of ESKD after liver transplantation for Black recipients was increased by twofold and the median time to ESKD was much shorter for Blacks compared with Whites.[4] Any validated estimated glomerular filtration rate (eGFR) equation or measured glomerular filtration rate (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 four-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. Currently, laboratories provide two values for eGFR for an individual, one for self-identified Black individual and the other for non-Black individual, resulting in provider bias and uncertainty for those of mixed race. Current national events around racial injustice have prompted the medical community to revisit use of race in medical equations and explore strategies to ameliorate some of the existing

Abbreviations: AKI, acute kidney injury; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; ESLD, end-stage liver disease; GFR, glomerular filtration rate; KAL, kidney after liver; LTA, liver transplantation alone; MDRD-4, four-variable Modification of Diet in Renal Disease; MELD, Model for End-Stage Liver Disease; SLK, simultaneous liver and kidney; UNOS, United Network for Organ Sharing.

Address reprint requests to Darshana M. Dadhania, M.D., M.S., Weill Cornell Medicine – New York Presbyterian Hospital, New York, NY. Telephone: 212 746 4430; FAX: 212 746 6894; E–mail: dmd2001@med.cornell.edu

Darshana M. Dadhania consults for Care Dx. She has received grants from CSL Behring and AlloVir Inc.

Received March 25, 2022; accepted March 25, 2022.

© 2022 American Association for the Study of Liver Diseases

View this article online at wileyonlinelibrary.com.

DOI 10.1002/lt.26464

disparities in care and access. Prompted by these sentiments, the National Kidney Foundation/American Society of Nephrology 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]

In this issue of *Liver Transplantation*, Panchal and colleagues investigated the impact of removing the race variable from the MDRD and CKD-EPI equations on Black patients' eligibility for an SLK transplant.[6] The authors performed a retrospective analysis of all patients listed for either a liver or SLK in the UNOS database and examined whether the likelihood of meeting the criteria for SLK using either the CKD or sustained acute kidney injury (AKI) pathway was higher if race was eliminated from the eGFR equations. For the entire cohort of 7937 Black patients, the median value of the minimum waitlist eGFR was 7 mL/min/1.73 m^2 lower when race was removed from the MDRD-4 equation.[6] The findings were similar with the CKD-EPI equation, and the impact of removing race from the 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 with those without ESLD. The observed difference in eGFR with and without the race variable in those with lower creatinine values (<2.5 mg/dL) suggests that Black patients with ESLD are at a greater risk for disparities in health care access.

In this investigation, the authors demonstrated that the percentage of Black patients classified as 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 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 a higher percentage of reclassification to ESLD with CKD compared with Black men ($P < 0.05$).[6] This is not surprising given that women have lower muscle mass compared with 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 the eGFR equation with and without the race variable. By eliminating the race variable in the eGFR equation and reclassifying Black patients with ESLD, the percentage of patients with ESLD and CKD who had received LTA increased by 4.7% to 6.2% and the percentage of patients with SLK transplants decreased by 5.5% to 8.4%.[6] Furthermore, 1.7% to 2.1% of those reclassified as having CKD by using the eGFR equation without the race variable received a kidney transplantation within 1 year of the liver transplantation, suggesting that patients meeting the safety net criteria could have been identified earlier. These data clearly demonstrate that Black patients 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 improve access to SLK transplantation. In addition to moving toward 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 needs to be addressed with a strong emphasis on the race-free equation, and (3) novel approaches for race- and sex-independent accurate eGFR assessment in patients with ESLD need to be investigated.

Recent investigations suggest that listing of Black patients for SLK or KAL does not mirror that of Whites and there may be unidentified barriers to early listing of Black patients for SLK 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 among the LTA recipients (16% versus 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 those receiving an SLK (7% versus 16%), suggesting the possibility of disparity in access to KAL transplantation.[7]

The transplantation community has 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., the

authors used the current eGFR equations and removed the race variable to demonstrate the impact on Black patients. Inker and colleagues recently studied and compared this approach with a new race-free eGFR equation, and their work was published in a recent issue of the *New England Journal of Medicine*.[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) equation had clinically acceptable agreement with measured GFR for both race groups. This is an important step toward 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) equation has not been studied in a large cohort of patients with ESLD, especially because the creatinine measurement in a patient with ESLD is impacted by sarcopenia, liver dysfunction, and increased volume of distribution. Cystatin C is another endogenous biomarker investigated for GFR estimation. 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) equation was associated with lower bias and greater agreement with the measured GFR compared with the new eGFR (creatinine).[8] Although cystatin C levels may be less impacted by sarcopenia and liver dysfunction, cystatin C measurement is also influenced by factors such as sexual hormones, thyroid function, and inflammation, and 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 patients with ESLD at risk for CKD, independent of race and sex.

Given the increased mortality risk among SLK and KAL recipients compared with SPK or kidney-alone transplantation recipients, the "utility" of kidney organs for SLK and KAL has been raised. A recent investigation evaluating the "utility" of kidney allografts for SLK transplantations suggests that the kidney allograft lifespan is shortened by approximately 1 year in patients with SLK as compared with 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 about "equity." Clearly the data suggest that Black recipients with ESKD following liver transplantation have a significantly higher risk of mortality compared with White recipients; 5-year survival with ESKD was reduced by 54% in Black patients versus 30% in White patients.[4] By continuing to use the 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 transplantation will be impeded.

Darshana M. Dadhania, M.D., M.S.[1]
Mona D. Doshi, M.B.B.S.[2]
[1]Division of Nephrology and Hypertension
Weill Cornell Medicine – New York Presbyterian Hospital
New York, NY
[2]Department of Medicine
Division of Nephrology
University of Michigan
Ann Arbor, MI

REFERENCES

1) Hussain SM, Sureshkumar KK. Refining the role of simultaneous liver kidney transplantation. J Clin Transl Hepatol 2018;6:289-295.
2) Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, et al. OPTN/SRTR 2017 annual data report: liver. Am J Transplant 2019;19(suppl 2):184-283.
3) Luo X, Massie AB, Haugen CE, Choudhury R, Ruck JM, Shaffer AA, et al. Baseline and center-level variation in simultaneous liver-kidney listing in the United States. Transplantation 2018;102:609-615.
4) Alvarado M, Schaubel DE, Reddy KR, Bittermann T. Black race is associated with higher rates of early-onset end-stage renal disease and increased mortality following liver transplantation. Liver Transpl 2021;27:1154-1164.
5) Delgado C, Baweja M, Burrows NR, Crews DC, Eneanya ND, Gadegbeku CA, et al. Reassessing the inclusion of race in diagnosing kidney diseases: an interim report from the NKF-ASN task force. Am J Kidney Dis 2021;78:103-115.
6) Panchal S, Serper M, Bittermann T, Asrani SK, Goldberg DS, Mahmud N. Impact of race-adjusted glomerular filtration rate estimation on eligibility for simultaneous liver-kidney transplantation. Liver Transpl 2022;28:959-968.
7) Jay CL, Washburn WK, Rogers J, Harriman D, Heimbach J, Stratta RJ. Difference in survival in early kidney after liver transplantation compared with simultaneous liver-kidney transplantation: evaluating the potential of the "safety net". J Am Coll Surg 2020;230:463-473.
8) Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385:1737-1749.
9) Cheng XS, Stedman MR, Chertow GM, Kim WR, Tan JC. Utility in treating kidney failure in end-stage liver disease with simultaneous liver-kidney transplantation. Transplantation 2017;101:1111-1119.