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Author names in bold designate shared co-first authorship.

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Letter to the Editor: Glomerular Filtration Rate Assessment in Liver Disease (GRAIL): Are We There Yet?

TO THE EDITOR:

Renal dysfunction is common in liver cirrhosis, and it is associated with poor prognosis. However, we still have major limitations when assessing renal function in patients with cirrhosis. Current available methods are biased and have a tendency to consistently overestimate glomerular filtration rates (GFRs).

We read with great interest the article by Asrani et al.[1] regarding the development of a GFR model in patients with liver disease, before and after liver transplant (LT), the glomerular filtration rate assessment in liver disease (GRAIL).

Indeed, the need for a new mathematical formula for GFR in cirrhosis is of concern. Kalafateli et al. also developed a formula, the Royal Free Hospital Cirrhosis (RFHC) for estimation of GFR in stable patients being evaluated for liver transplantation.[2]

The RFHC comprises age, sex, creatinine, urea, international normalized ratio, and ascites whereas GRAIL is based on sex, age, ethnicity, creatinine, blood urea nitrogen, and albumin. There are some important differences between the two. First, GRAIL comprises ethnicity, a well-known factor that affects GFR estimation in the general population.[3] Even though these data are well established in the general population, the effect in the population with cirrhosis is still unknown. The RFHC did not include ethnicity, mostly because of type 2 error. Serum albumin levels in GRAIL can be altered because of recent albumin infusions and therefore overestimate GFR. The assessment of ascites in the RFHC poses a problem given that it is a subjective measure.

One pitfall for both equations is that a marker for muscle mass estimation was not incorporated. Decreased muscle mass has a great impact on overestimation of kidney function, especially in male patients with cirrhosis, as shown in a recent study.[4]

Even though, as stated by the researchers, the GRAIL model is skewed to predict lower GFR, it would be interesting to see how this equation would have compared to the RFHC. Further validation studies are required for both formulas; however, we are finally on the path to conceive a better GFR formula in the population with cirrhosis.

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Potential conflict of interest: Nothing to report.

REPLY:

We appreciate the interest in our work. Drs. Carvao and Jasmins highlight several important points.

First, serum creatinine, sodium, and estimated glomerular filtration rate (eGFR) are all imperfect surrogates of renal function in patients with cirrhosis. This is especially true in patients with decompensated liver disease, whereby the influence of extrahepatic factors may impede accurate estimation. Often, renal function is dependent on where the patient lies on the acute kidney injury/chronic kidney disease continuum, the degree of liver dysfunction, and other relevant patient characteristics. Developing an estimating equation for each and every subset of cirrhosis is untenable. One also assumes steady state in predictive models, but manipulation or alterations are possible across the breadth of current glomerular filtration rate (GFR) estimating equations. This includes changes in relevant parameters with diuresis (serum creatinine, serum sodium), changes with use of anticoagulation or nutrition (prothrombin time), changes with volume management (albumin, degree of ascites), changes with muscle mass (gender), or assessment of whether serum creatinine is reflective of acute kidney injury or chronic kidney disease or a combination thereof. Notwithstanding these factors, there is a need to include objective measures in predictive models.

In our study, the use of glomerular filtration rate assessment in liver disease (GRAIL) to identify low GFR may be helpful for clinically relevant decisions before and after transplantation.[1] Although a direct comparison was not carried out with the royal free hospital equation, the addition of ascites or serum sodium did not improve performance characteristics. The addition of ascites had marginal improvement in bias (eGFr–GFR 6.7 mL/min/1.73 m^2 with ascites versus 7.1 mL/min/1.73 m^2), but the differences were not clinically significant and the need to have an objective set allowed us to further remove it from model building. In a subsequent study, replacing serum creatinine with GRAIL (as compared with other estimates of GFR) in the Model for End-Stage Liver Disease ascites–sodium score improved the prediction of wait-list mortality, especially for women and those with the highest disease severity.[2]

Second, measured GFR remains important. There is a need to identify specific scenarios whereby estimating equations may not be enough: The clinician may be forced to instead obtain measured GFR, however onerous or expensive.[3]

Finally, accurate estimation of renal function in the future may rely on combining factors that capture separate surrogates of renal structure and function, as well as take the clinical context into consideration. Given the pervasive and dynamic effect of renal dysfunction in patients with liver disease, and coupled with the increasing burden of cirrhosis worldwide, continued refinement of current models is warranted.

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