Modification of eGFR formulas using estimates of fat-infiltration from MRI: a preliminary study in cirrhosis patients

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Introduction: Renal function is a critical factor in determining the priority of liver-transplant candidates. From serum creatinine or cystatin C measurements, glomerular filtration rate (GFR) is estimated and incorporated into a patient's MELD score to assess how urgently a transplant is required. GFR is generally derived from serum measurements using the Modification of Diet in Renal Disease (MDRD) formula for creatinine and the CKD-EPI formula for cystatin C[1,2]. And while relatively accurate for the general population, these formulas may overestimate GFR in patients with low muscle-mass, such as those with cirrhosis[2]. Overestimation of GFR in cirrhotics amounts to lowering the transplant-priority of a population which is typically most in-need. In this study, we aim to calibrate the GFR formulas to account for reduced muscle-mass in cirrhosis patients. Since these patients routinely undergo liver examinations with MRI, we can gain a more direct estimate of whole-body muscle composition by examining MR images. Here, we evaluate the benefit of incorporating such measurements into the estimation of GFR with the MDRD and CKD-EPI formulas.

Methods: 38 patients (21 male, 17 female; ages 36-81) with liver cirrhosis (MELD scores: 4-27) were included in this IRB-approved study. Reference GFR values were obtained from 99m-Tc DTPA clearance ("nucs") on the same day as the MR exam. Serum creatinine and cystatin C measurements were obtained from blood samples. At 3T (TimTrio, Siemens), a multi-slice axial T1w gradient-echo sequence was prescribed to cover the entire liver: TR 163 ms, TE 3.5 ms, flip angle 70°, FOV 340x400 mm, matrix size 270x320, slice thickness 6 mm). The fraction of fat in the erector spinae (ES) muscles was then measured at the level of the L3-L4 vertebrae by manually segmenting the pertinent slice of the in-phase MR acquisition (Figure 1). This slice-location was chosen for segmentation because previous studies have linked paraspinal fat-infiltration at this location to whole-body muscle-composition and overall health[2,3,4].

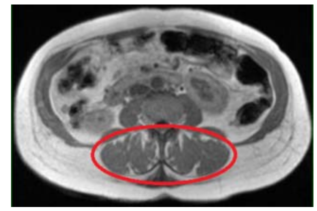

Figure 1: Axial in-phase image used to segment fat fraction of the erector spinae muscles (circled in red)

We began modification of the GFR formulas by re-fitting their coefficients using the nucs GFR values as the target. We then incorporated estimates of fat-fraction from the MR images into the formulas as a multiplication factor, $(f/f_{avg})^c$, where f is the L3-L4 fat fraction, f_{avg} is the average fat-fraction across all subjects, and c is a new coefficient to be fit. Pearson's correlation coefficients (r) were computed between reference GFRs and estimated GFRs (eGFRs) before and after formula modification.

Results: Correlation between reference nucs and eGFRs for the MDRD and CKD-EPI equations before and after the incorporation of fat fraction is shown in Figure 2. With r = 0.57, the original MDRD formula (Fig 2a) placed 60% of cases within 30% of the reference GFR. Incorporation of fat-fraction improved the correlation to r = 0.70, with 76% of cases within 30% of reference (Fig 2b). The original CKD-EPI formula showed a correlation of r = 0.55, with 65% of cases within 30% of reference (Fig 2c). Addition of patient fat-fraction raised the correlation to r = 0.72 with 74% of cases within 30% of reference (Fig 2c). The optimized coefficients for our modified MDRD and CKD-EPI formulas are shown in equations (1) and (2).

(1) $eGFR_{MDRD} = 300 \times Scr^{-0.7} \times Age^{-0.4} \times (f/f_{avg})^{0.17} \times [0.75\ if\ black] \times [0.74\ if\ female]$

(2) $eGFR_{CKD-EPI} = 141 \times \min(Scys/1.4, 1)^{-0.9} \times \max(Scys/1.4, 1)^{0.8} \times 0.9^{Age} \times (f/f_{avg})^{0.15} \times [0.75\ if\ female]$

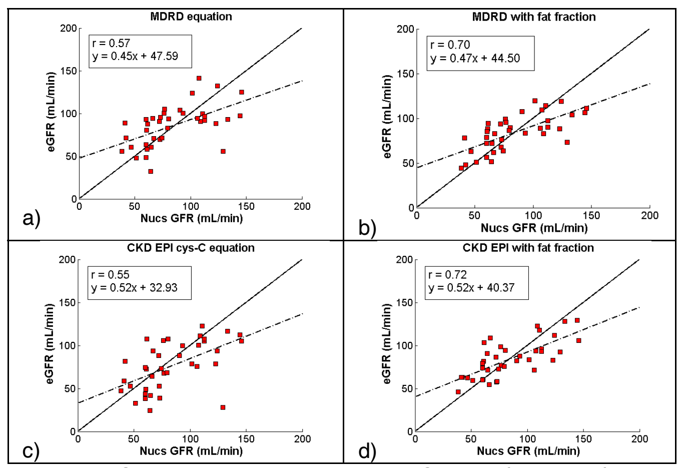

Figure 2: Correlation between nucs and eGFRs before and after the incorporation of ES-muscle fat-fraction

Among patients with mild cirrhosis (MELD < 10), the average improvement in GFR accuracy was 5%. Those with more moderate cirrhosis (MELD ≥ 10) showed an average improvement of 7%.

Discussion: GFR values estimated with the unmodified MDRD or CKD-EPI formulas show poor correlation with the reference standard. By incorporating patient fat-fraction as an estimate of whole-body muscle composition, we were able to improve the accuracy of eGFR measurements. GFR values for patients with more moderate cirrhosis showed slightly more of an improvement than those from patients with only mild illness, likely because they have experienced greater muscle-loss along with their greater disease-severity. Further investigation with a wider range of cirrhosis-severity will help to establish this finding.

A major limitation of this study is the lack of multiple populations in which to separately develop and validate our equations, but these will be included in future work comprising larger datasets. Regardless, the importance of more direct estimates of whole-body muscle composition in calculating eGFR is clearly shown.

Conclusion: The MDRD and CKD-EPI formulas do not adequately account for the muscle-build of cirrhotic patients. A simple measurement of fat infiltration in the paraspinal muscles, obtained from a routine liver examination, can provide a more direct estimate of total-body muscle composition and improve eGFR accuracy. This result highlights systematic differences in non-GFR determinants of serum creatinine and cystatin C levels that investigators should be aware of when looking to apply these formulas to particular patient populations.

References: [1]Levey et al. Annals Int Med 1999;130(6):461-70. [2]Inker et al. N Engl J Med 2012;367:20-9. [3]Kang et al. Clin Rad 2007;62:479-86. [4]Zoico et al. J Gerontol A Biol Sci Med Sci 2010;3:295-9. [4]D'hooge et al. J Man Ther 2012.