Editorial

JOURNAL OF HEPATOLOGY

Assessment of renal function in cirrhosis: Sarcopenia, gender and ethnicity matter

Claire Francoz[1,2,*], Elsa Sola[3,4,5,6]

[1]*Hepatology and Liver Intensive Care, Hospital Beaujon, Clichy, France;* [2]*INSERM U1149, Centre de Recherche sur l'Inflammation, Paris, France;* [3]*Liver Unit, Hospital Clínic Barcelona, Barcelona, Spain;* [4]*University of Barcelona, Barcelona, Spain;* [5]*Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain;* [6]*CIBER de Enfermedades Hepáticas y Digestivas, Barcelona, Spain*

See Article, pages 847–854

Kidney dysfunction is common in patients with advanced cirrhosis[1–3] and a number of studies have shown that impaired kidney function has a negative impact on outcomes.[4] As a result, serum creatinine has been incorporated into the model for end-stage liver disease (MELD) score,[4] which is a robust tool to predict short-term mortality in patients with cirrhosis. Since then, the MELD score has been widely adopted in liver transplantation for prioritization in organ allocation. Even though creatinine level has an independent prognostic value, it is an inaccurate marker of renal function in cirrhosis. Indeed, serum creatinine concentration is influenced by several factors unrelated to renal function, including skeletal muscle mass. In this context, it is well recognized that women have lower serum creatinine levels than men, as on average they have a lower muscle mass.[5] Hence, for a similar glomerular filtration rate (GFR), women have lower serum creatinine, lower MELD score, lower priority for liver transplantation and higher risk of death on the waiting list.[6,7]

The gold standard method for measuring GFR is the clearance of radioactive (^{125}I-iothalamate, ^{51}Cr-EDTA and ^{99m}Tc-diethylene triamine penta-acetic) or non-radioactive (inulin and iohexol) exogenous filtration markers. Unfortunately, these techniques are costly, time-consuming and impractical for routine use. For many years, creatinine-based equations are widely used in the general population to estimate GFR. Not surprisingly, in patients with advanced cirrhosis, all of these equations tend to overestimate true GFR since they are based on serum creatinine.[8] Cystatin C, which is less influenced by extra renal factors and especially gender, age, inflammation and muscle mass, has been considered a potential alternative to serum creatinine for estimating GFR. Several cystatin C-based equations, which have been derived in the general population,[9] have been proposed and tested in patients with cirrhosis. However, none of them was shown to be clearly superior to creatinine-based equations.[10] By contrast, equations combining cystatin C and serum creatinine may have a greater precision and accuracy to assess GFR in specific populations, especially those with low muscle mass.[10] In patients with cirrhosis, while studies have demonstrated that equations combining serum creatinine and cystatin C may better predict GFR compared to serum creatinine-based equations, the performance of cystatin C-based equations was lower than that reported in the general population.[11]

Overestimation of renal function when using serum creatinine concentration, as well as creatinine-based equations, is due, at least in part, to sarcopenia. Inaccuracies of creatinine and creatinine-based equations are a major concern when assessing kidney function in female patients but also in any sarcopenic patients with cirrhosis. Therefore, we need to better assess interactions between muscle mass, creatinine and GFR in order to improve and to adjust equations to muscle mass and gender.

In the study by Yoo *et al.* published in this issue of the *Journal of Hepatology*,[12] the authors confirmed in a large cohort of patients with cirrhosis that both Modified Diet in Renal Disease using the creatinine-based 4 variables (MDRD4) equation and a cystatin C-derived equation overestimate true GFR measured by ^{51}Cr-EDTA clearance. Overestimation of true GFR by the MDRD4 equation was observed in about 50% of patients, confirming that MDRD4 should be interpreted with caution in patients with cirrhosis. While previous studies showed that ascites and advanced age were independently associated with inaccuracies of MDRD4 for estimating GFR,[13] this study suggests that sarcopenia, in addition to female gender and Child-Pugh score, were independent risk factors for overestimation. However, when male and female patients were analyzed separately, sarcopenia was only associated with overestimation of true GFR in males, not in females.

A growing number of studies have shown that decreased muscle mass is associated with a worse outcome in patients with cirrhosis, independent of the MELD score.[14] However, recent studies have shown that the deleterious impact of sarcopenia is only observed in men[15] while low subcutaneous

Keywords: Renal function; Sarcopenia; Glomerular filtration rate; Cystatin C, Cirrhosis.
Received 4 February 2019; accepted 11 February 2019
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2018.12.030.
* Corresponding author. Address: Service d'Hépatologie, Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy, France. Tel.: +33 140875291.
E-mail address: claire.francoz@bjn.aphp.fr (C. Francoz).

adipose tissue, but not skeletal muscle mass, may be associated with a higher risk of waiting list mortality in females.[15] This study by Yoo and colleagues reinforce the concept of a close relationship between renal function, sarcopenia and outcome in cirrhosis. The lack of a significant impact of sarcopenia on the accuracy of the MDRD4 equation, or on mortality, in female patients may result from their lower muscle mass relative to male patients.

These findings have important implications. However, whether these results obtained in a large population from Korea can be extrapolated to other populations is uncertain. Indeed, since body composition is highly different across different ethnicities, the accuracy of GFR estimates using serum creatinine, which directly derives from muscle mass, has to be reassessed in different populations.

The MDRD4 equation, which is recommended by the National Kidney Foundation Kidney Disease Outcome Quality Initiative, derives from a large US population that almost only includes Caucasian and African American patients.[16] Investigators in Asia subsequently assessed the performance of GFR equations in different countries with different Asian ethnic populations.[17] Investigators in China and Japan found some biases in MDRD equations and developed ethnic-based coefficients for adjustment. For instance, in Chinese patients, MDRD4 had to be adjusted by a coefficient of 1.233 while in Japanese patients, the coefficient was 0.763.[17] In Korean patients, the coefficient for MDRD4 equation was 0.99096.[17] The need for different coefficients illustrates differences in terms of muscle mass, even in Asian patients coming from relatively close geographic areas. Differences may be even larger when considering Caucasian, African or African American patients.

Asian patients are reported to have lower muscle mass than Northern Europeans and African-Americans.[18] By contrast, Asian people have a higher percentage of body fat and more central fat accumulation than Caucasians.[19] Asian women have a greater fat percentage than men and this fat accumulation may explain, in part, their lower muscle mass due to the negative effect of fat on muscle protein synthesis. Therefore, the results presented by Yoo *et al.* must be confirmed in a non-Asian population.

Plasma cystatin C is a promising marker, not so much for assessing renal function, but rather for predicting kidney dysfunction and mortality in patients with decompensated cirrhosis.[20] Yoo and colleagues confirmed that cystatin C may accurately predict both acute kidney injury and survival in patients with cirrhosis. Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells and eliminated almost exclusively by glomerular filtration, without any tubular secretion. In contrast to serum creatinine, serum cystatin C is independent of gender, age, muscle mass, inflammation and malignancy and it is not affected by serum bilirubin level. However, a reference method for cystatin C dosage is lacking. In addition, genetic variability in cystatin C production or metabolism has been reported recently, with single-nucleotide polymorphisms on chromosome 20 containing cystatin genes, which are characterized by multiple cystatin-like sequences.[21] This genetic variability may explain lower plasma cystatin C concentration. For instance, the presence of the T allele of rs13038305 is associated with 6.4% lower concentration of cystatin C.[22]

The assessment of renal function in patients with advanced cirrhosis remains a challenging issue, since current surrogate markers are biased. Equations are influenced by a number of factors including gender and ethnicity. Due to the impact of inaccurate assessment of renal function in specific conditions, such as prioritization for liver transplantation, these factors should be considered in future studies.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.004.

References

[1] Gines A, Escorsell A, Gines P, Salo J, Jimenez W, Inglada L, et al. Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites. Gastroenterology 1993;105:229–236.
[2] Huelin P, Piano S, Sola E, Stanco M, Sole C, Moreira R, et al. Validation of a staging system for acute kidney injury in patients with cirrhosis and association with acute-on-chronic liver failure. Clin Gastroenterol Hepatol 2017;15, 438–445e435.
[3] Salerno F, Borroni G, Moser P, Badalamenti S, Cassara L, Maggi A, et al. Survival and prognostic factors of cirrhotic patients with ascites: a study of 134 outpatients. Am J Gastroenterol 1993;88:514–519.
[4] Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
[5] Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. Annu Rev Med 1988;39:465–490.
[6] Cholongitas E, Marelli L, Kerry A, Goodier DW, Nair D, Thomas M, et al. Female liver transplant recipients with the same GFR as male recipients have lower MELD scores–a systematic bias. Am J Transplant 2007;7:685–692.
[7] Mindikoglu AL, Regev A, Seliger SL, Magder LS. Gender disparity in liver transplant waiting-list mortality: the importance of kidney function. Liver Transpl 2010;16:1147–1157.
[8] Sherman DS, Fish DN, Teitelbaum I. Assessing renal function in cirrhotic patients: problems and pitfalls. Am J Kidney Dis 2003;41:269–278.
[9] Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367:20–29.
[10] Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, et al. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. Am J Kidney Dis 2008;51:395–406.
[11] Mindikoglu AL, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. Hepatology 2014;59:1532–1542.
[12] Yoo JJ, Kim SG, Kim YS, Lee B, Lee MH, Jeong SW, et al. Estimation of renal function in patients with liver cirrhosis: Impact of muscle mass and sex. J Hepatol 2019;70:847–854.
[13] Francoz C, Prie D, Abdelrazek W, Moreau R, Mandot A, Belghiti J, et al. Inaccuracies of creatinine and creatinine-based equations in candidates for liver transplantation with low creatinine: impact on the model for end-stage liver disease score. Liver Transpl 2010;16:1169–1177.
[14] Durand F, Buyse S, Francoz C, Laouenan C, Bruno O, Belghiti J, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. J Hepatol 2014;60:1151–1157.
[15] Ebadi M, Tandon P, Moctezuma-Velazquez C, Ghosh S, Baracos VE, Mazurak VC, et al. Low subcutaneous adiposity associates with higher mortality in female patients with cirrhosis. J Hepatol 2018;69:608–616.
[16] Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a

new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470.
[17] Teo BW, Zhang L, Guh JY, Tang SCW, Jha V, Kang DH, et al. Glomerular filtration rates in asians. Adv Chronic Kidney Dis 2018;25:41–48.
[18] Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc 2014;15:95–101.
[19] He W, Zhang S, Song A, Yang M, Jiao J, Allison DB, et al. Greater abdominal fat accumulation is associated with higher metabolic risk in Chinese than in white people: an ethnicity study. PLoS ONE 2013;8 e58688.
[20] Markwardt D, Holdt L, Steib C, Benesic A, Bendtsen F, Bernardi M, et al. Plasma cystatin C is a predictor of renal dysfunction, acute-on-chronic liver failure, and mortality in patients with acutely decompensated liver cirrhosis. Hepatology 2017;66:1232–1241.
[21] Kottgen A, Pattaro C, Boger CA, Fuchsberger C, Olden M, Glazer NL, et al. New loci associated with kidney function and chronic kidney disease. Nat Genet 2010;42:376–384.
[22] O'Seaghdha CM, Tin A, Yang Q, Katz R, Liu Y, Harris T, et al. Association of a cystatin C gene variant with cystatin C levels, CKD, and risk of incident cardiovascular disease and mortality. Am J Kidney Dis 2014;63:16–22.