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Evaluation of renal function in patients with cirrhosis

To the Editor:

We read with great interest the excellent review by Francoz et al. [1], recently published in the Journal of Hepatology, regarding the difficulties in the accurate assessment of renal function in patients with cirrhosis. This has become even more important and necessary in the MELD era. The main message is in keeping with our previous review [2], that is that although serum creatinine (Cr) is a routine laboratory test and widely accepted as a measure of renal function, it is only an indirect marker of renal function, i.e. of glomerular filtration rate (GFR). Indeed, a problem, not often recognized by hepatologists, is that measurement of Cr suffers from a variety of interferences [3]. In particular, in patients with cirrhosis, we have shown that the interference of bilirubin on Cr measurement is a major problem leading to differences in MELD scores up to seven points when bilirubin is higher than 23.4 mg/dl, i.e. those with the highest priority for liver transplantation [3]. Francoz et al. [1] mentioned that several methods have been developed in order to overcome this interference, but we have shown that the problem has not been resolved [3]. Furthermore, using different methods of measurement leads to further discrepancy in Cr values [3,4]. Hence, standardisation of laboratory techniques and 'normal' values would have to be undertaken for all liver transplant units to avoid systematic biases in MELD-based allocation systems, or those which incorporate Cr values [4].

Apart from difficulties in measurements, it is well recognized that Cr concentration is influenced by several factors unrelated to renal function, such as total muscle mass. The latter can lead to discrepancies in Cr concentration between individuals with the same renal function but of different age, race, and sex [5]. This important issue was not emphasized in this review [1]. In the UNOS database [6], it has been shown that women were more likely to die on the waiting list in the post-MELD era, compared to the pre-MELD one, although women were listed with lower median MELD scores, compared to men (14 vs. 15, $p < 0.001$) [6]. These findings are likely to be due to the fact that women have lower Cr for the same renal function (GFR), compared to men, as we have published previously [7]. Interestingly, we found that correcting Cr by equalising the GFR between men and women resulted in an increase in MELD score by 2 or 3 points in 65% of female LT candidates [7]. Our findings with gender influences on Cr measurement are also pertinent to ethnicity differences with a lower GFR for the same Cr value in those of Asian ethnicity and conversely a higher GFR for those of African descent. Thus, a correction factor for gender and ethnicity could be introduced.

Alternatively, the use of "true" GFR could be considered in order to eliminate any gender or race bias. Interestingly, Lim et al. [8] in the same Journal found that GFR (estimated by using ^{125}I-iothalamate) was superior to Cr in assessing mortality risk on the waiting list. Its incorporation in the MELD score (in the place of Cr), led to a relatively small, but nevertheless, significant improvement of discriminative ability of MELD. Unfortunately, Lim et al. [8] did not evaluate the prognostic impact of MELD-Cr and MELD-GFR scores in male and female candidates separately. However, directly measured GFR is expensive and impractical for routine use, and thus, identification of more accurate and clinically applicable serum markers for renal function in cirrhosis are necessary and could remove the bias of Cr in the MELD score. Similar to our conclusions in our review [2], Francoz et al. [1] suggested cystatin-C as an alternative marker of renal function. However, cystatin-C has its own limitations and we have found that the available data on cystatin-based formulae have poor agreement with "true" GFR in patients with cirrhosis [9]. The inaccuracy of these mathematical equations may be related to the fact that the original cohorts from which they were derived did not include patients with cirrhosis. We believe that new equations are needed in patients with cirrhosis to reflect "true" GFR as accurately as possible.

Conflict of Interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Evangelos Cholongitas
Elias Xirouchakis
Matteo Garcovich
Andrew K. Burroughs
The Royal Free Sheila Sherlock Liver Centre and University Department of Surgery, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG, UK
Tel.: +44 20 74726229; fax: +44 20 74726226
E-mail address: Andrew.Burroughs@royalfree.nhs.uk (A.K. Burrough)