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Is estimated glomerular filtration rate superior to serum creatinine in predicting mortality on the waiting list for liver transplantation?

Joanna A. Leithead,[1] Suzanne M. MacKenzie,[2] James W. Ferguson[1] and Peter C. Hayes[1]

1 Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, Edinburgh, UK
2 Department of Clinical Biochemistry, Royal Infirmary of Edinburgh, Edinburgh, UK

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Correspondence
Joanna Agnes Leithead, Clinical Research Fellow, Scottish Liver Transplant Unit, Royal Infirmary of Edinburgh, 51, Little France Crescent, Edinburgh EH16 4SA, UK. Tel.: +44 787 026 4110; fax: +44 131 242 1633; e-mail: jleithea@staffmail.ed.ac.uk

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Summary

Serum creatinine is an important prognostic indicator in patients on the liver transplant waiting-list, being a component of the Model for End Stage Liver Disease (MELD) score. However, creatinine is influenced by age, gender and race, and in this role may disadvantage some individuals. The Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) takes into account these variables and may be a superior measure of renal function. Our aim was to examine whether the MDRD 4-variable, 5-variable and 6-variable eGFRs are superior to serum creatinine in predicting 3-month waiting-list mortality in patients with end-stage liver disease. This was a retrospective single-centre study of 427 adults listed for first liver transplantation. The median listing MDRD 4-variable, 5-variable and 6-variable eGFR was 69, 71 and 73 ml/min/1.73 m^2, respectively. The median listing serum creatinine was 89 μM. MDRD 4-variable ($P = 0.002$), 5-variable ($P < 0.001$) and 6-variable eGFR ($P < 0.001$), and serum creatinine ($P < 0.001$), were all predictors of mortality on the transplant waiting-list. Of the three MDRD equations, the 6-variable eGFR was the better prognostic indicator. The substitution of 6-variable eGFR for serum creatinine did not improve the prognostic accuracy of the MELD ($P = 0.825$) and UK score for Patients with End-Stage Liver Disease ($P = 0.781$) scores. In conclusion the MDRD eGFR is comparable, but not superior to serum creatinine, in predicting death within 3 months of listing for liver transplantation.

Cirrhosis is associated with a progressive functional renal impairment characterised by increased tubular sodium reabsorption, impaired free water clearance and prerenal azotemia [1]. This spectrum of renal dysfunction evolves in parallel with advancing disease and consequently the clinical manifestations of renal dysfunction, ascites, hyponatraemia and hepatorenal syndrome, are important prognostic markers [2–5]. Serum creatinine as a continuous variable is an independent predictor of mortality following the transjugular intrahepatic portosystemic shunt procedure and in those on the liver transplant waiting list [6,7]. It is a component of the Model For End-Stage Liver Disease (MELD) score, which is used to prioritise graft allocation.

However, serum creatinine is not solely influenced by glomerular filtration and is not an accurate estimator of renal function [8]. Creatinine production is proportional to muscle mass, and is greater in men than in women, in younger than older individuals and in black people than in white people, despite similar glomerular filtration rate [9]. In addition, in cirrhosis reduced creatine production by the liver, muscle wasting and increased renal tubular secretion of creatinine may result in a falsely low serum creatinine level [10,11].

The effect of gender, age and race on serum creatinine is of particular concern in the MELD era of organ allocation. United Network for Organ Sharing (UNOS) data has demonstrated that women listed for liver transplantation are less likely to survive to transplantation than men, supporting a systematic bias of the scoring system [12–14]. Similarly, an inherent discrimination against older patients could explain the independent association of increasing age with waiting-list mortality [15]. It follows that a scoring system with an alternative measure of renal function may be preferable to MELD.

The gold standard measure of glomerular filtration rate, inulin clearance, has recently been shown to be superior to serum creatinine in predicting liver transplant waiting-list mortality [16]. Unfortunately, inulin clearance is time consuming, impractical and costly and is not a useful test if repeated measures are required [10,11]. Calculated glomerular filtration rate is a possible alternative and has been evaluated as an absolute measure of renal function, although not as a prognostic marker, in this setting [17].

The most accurate calculated glomerular filtration rate for cirrhotic patients is provided by the Modification of Diet in Renal Disease study (MDRD) equations, which are creatinine-based estimates modified for age, gender and race [17–19]. The MDRD 4-variable calculated glomerular filtration rate is readily available, at minimal cost, with routine reporting advocated in several countries, and is an attractive measure of renal function [20,21]. The MDRD 5-variable and 6-variable calculated glomerular filtration rates, in addition, adjust for blood urea nitrogen, and blood urea nitrogen and serum albumin, respectively, and could be superior prognostic indicators.

The aim of our study was to examine whether the MDRD calculated glomerular filtration rate is superior to serum creatinine in predicting prognosis on the liver transplant waiting list. In a subgroup of patients measured creatinine clearance (CrCl) was also available and was examined as a prognostic indicator.

Methods

This was a single-centre retrospective study of consecutive adults listed for first liver transplantation between November 1992 and June 2007. Patients listed for acute liver failure, hepatocellular carcinoma, or joint liver/kidney transplantation, or who had documented intrinsic renal disease were not assessed. Those removed from or still active on the waiting list were also not included.

The following variables at time of liver transplant assessment were recorded: gender, age, race, aetiology of liver disease, presence of ascites or hepatic encephalopathy and laboratory data (serum sodium, creatinine, bilirubin, albumin and international normalised ratio). Estimated glomerular filtration rate was calculated from the relevant parameters using the MDRD 4-variable [eGFR (MDRD4) = $186 \times \text{creatinine (mg/dl)}^{-1.154} \times \text{age (years)}^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$], MDRD 5-variable [eGFR (MDRD5) = $270 \times \text{creatinine (mg/dl)}^{-1.007} \times \text{age (years)}^{-0.180} \times \text{blood urea nitrogen (mg/dl)}^{-0.169} \times (0.755 \text{ if female}) \times (1.178 \text{ if black})$] and MDRD 6-variable [eGFR (MDRD6) = $170 \times \text{creatinine (mg/dl)}^{-0.999} \times \text{age (years)}^{-0.176} \times \text{blood urea nitrogen (mg/dl)}^{-0.170} \times \text{albumin (g/dl)}^{+0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$] equations [18,19]. The MELD score was determined as previously described [22]. The UK Score for Patients with End-Stage Liver Disease (UKELD), a recently devised scoring system that incorporates serum sodium in addition to the MELD variables, was also calculated [23].

In a subgroup of patients transplanted between May 2000 and June 2007 CrCl was available. This was determined from a 24-h urinary collection performed routinely during the in-patient assessment period. Failure to obtain a CrCl was, in most cases, secondary to poor patient compliance.

Statistical analyses

Normally distributed continuous variables and nonparametric continuous variables were compared using the Student's *t*-test and Mann–Whitney test, respectively. Chi-square analysis was used for the comparison of categorical variables. Survival modelling was performed using Cox proportional hazards regression. Data was censored at the time of liver transplantation and to lessen the influence of extreme values all continuous laboratory variables were transformed into their natural logarithms. To allow the comparison of MELD or UKELD with a similar model with logeGFR or logeCrCl substituted for logecreatinine the regression coefficients of MELD or UKELD were initially adjusted for our patient population. Regression coefficients were then recalculated in the presence of logeGFR instead of logecreatinine. Receiver-operating characteristic (ROC) curves were generated to assess the accuracy of models in predicting 3-month waiting-list mortality. Concordance statistics were compared using the method described by Hanley and McNeil [24]. All patients censored prior to the specified time point were excluded from these analyses. A value of $P < 0.05$ was considered statistically significant at all times. Data were analysed using the SPSS 15 package (SPSS Inc., Chicago, IL, USA).

Values are expressed as mean and standard deviation (SD), and median and inter-quartile range (IQR) as appropriate.

Results

Patient characteristics

The mean age of the patients (n = 427) at time of listing for liver transplantation was 55.3 (SD 11.6) years and the male to female ratio was 1:1. The main indications for transplantation were primary biliary cirrhosis (119 patients, 27.9%), alcoholic liver disease (103 patients, 24.1%), sclerosing cholangitis (62 patients, 14.5%), hepatitis C cirrhosis (37 patients, 8.9%) cryptogenic cirrhosis (36 patients, 8.4%) and autoimmune hepatitis (33 patients, 7.7%). The median listing MELD score was 16 (IQR 13–20) and the median listing UKELD score was 56 (IQR 54–60).

Sixty patients (14.1%) died prior to liver transplantation. The median time from listing to death was 50 (IQR 26–101) days. For patients who were transplanted the median waiting-time was 68 (IQR 27–142) days. Two hundred and twelve patients (49.6%) were transplanted and 44 patients (10.3%) died within 3 months of listing.

The median listing serum creatinine was 89 (IQR 77–107) μM, the median listing serum sodium was 136 (IQR 132–139) mM, and 60.6% of patients had ascites. The median eGFR (MDRD4), eGFR (MDRD5) and eGFR (MDRD6) was 69 (IQR 57–83) ml/min/1.73 m^2, 71 (IQR 56–86) ml/min/1.73 m^2, and 73 (IQR 57–89) ml/min/1.73 m^2, respectively.

Comparison of MDRD equations as predictors of waiting list mortality

Logecreatinine (OR 14.12; 95% CI 3.76–53.13, $P < 0.001$), logeGFR (MDRD4) (OR 0.18; 95% CI 0.06–0.53, $P = 0.002$), logeGFR (MDRD5) (OR 0.16; 95% CI 0.06–0.44, $P < 0.001$), and logeGFR (MDRD6) (OR 0.14; 95% CI 0.05–0.39, $P < 0.001$) demonstrated an association with 3-month waiting-list mortality.

Receiver-operating characteristic curves for logecreatinine, logeGFR (MDRD4), logeGFR (MDRD5) and logeGFR (MDRD6) as predictors of 3-month waiting list mortality are shown in Fig. 1. When all eGFR equations were compared logeGFR (MDRD6) had the greatest concordance statistic [logeGFR (MDRD4) 0.648; 0.548–0.749: logeGFR (MDRD5) 0.683; 0.587–0.780: logeGFR (MDRD6) 0.695; 0.601–0.789, logecreatinine 0.696; 0.598–0.793, c-statistic and 95% confidence interval]. LogeGFR (MDRD6) statistically outperformed logeGFR (MDRD4) ($P = 0.054$), and was comparable to logeGFR (MDRD5) ($P = 0.614$) and logecreatinine ($P = 0.981$). Following on from this, all further analyses comparing eGFR with serum creatinine were performed using the eGFR MDRD 6-variable equation.

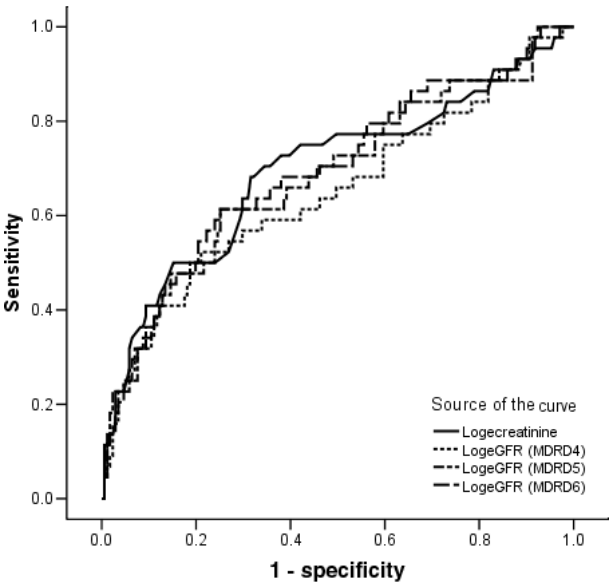

Figure 1 Receiver-operating characteristic curves of log serum creatinine (logecreatinine), log eGFR calculated using the Modification of Diet in Renal Disease (MDRD) 4-variable equation [logeGFR (MDRD4)], log eGFR calculated using the MDRD 5-variable equation [logeGFR (MDRD5)] and log eGFR calculated using the MDRD 6-variable equation [logeGFR (MDRD6)] for predicting 3-month liver transplant waiting list mortality.

Does substitution of eGFR (MDRD6) for serum creatinine improve the prognostic accuracy of MELD and UKELD?

ROC analysis was used to determine whether the substitution of logeGFR (MDRD6) for logecreatinine improved the accuracy of the existing prognostic models, MELD and UKELD (Table 1). The regression coefficients for

Table 1. AUC for receiver-operating characteristic curves for prediction of 3-month liver transplant waiting-list mortality in all patients.

Model	c-statistic	95% CI
MELD (adj)	0.841	0.773–0.909
MELD (eGFR)	0.846	0.777–0.915
UKELD (adj)	0.859	0.790–0.928
UKELD (eGFR)	0.864	0.795–0.933

eGFR, estimated glomerular filtration rate; MELD, Model for End-Stage Liver Disease; MELD (adj), MELD score with regression coefficients adjusted for our model; UKELD, UK score for Patients with End-Stage Liver Disease; UKELD (adj), UKELD score with regression coefficients adjusted for our model; MELD (eGFR), MELD score with logeGFR substituted for logecreatinine; UKELD (eGFR), UKELD score with logeGFR substituted for logecreatinine; c-statistic, concordance statistic.

each model were initially adjusted for our study population [MELD (adj)/UKELD (adj)], and thereafter recalculated in the presence of logeGFR (MDRD6) instead of logecreatinine [MELD (eGFR)/UKELD (eGFR)].

The LogeGFR (MDRD6) substituted for logecreatinine did not change the concordance statistic for MELD as a predictor of 3-month waiting-list mortality [MELD (adj) versus MELD (eGFR), $P = 0.825$). Furthermore, logeGFR (MDRD6) substituted for logecreatinine did not alter the concordance statistic for UKELD as a predictor of death by 3 months [UKELD (adj) versus UKELD (eGFR), $P = 0.781$].

In view of the concern that the MELD and UKELD scoring systems are systemically biased and may discriminate against female and older patients the concordance statistics of individual patient groups were also determined (Table 2). There was no statistically significant difference in the concordance statistics of the MELD score or UKELD score between genders (MELD, $P = 0.718$; UKELD, $P = 0.645$) and age groups (MELD, $P = 0.099$; UKELD, $P = 0.216$). LogeGFR (MDRD6) substituted for logecreatinine did not change the concordance statistic for MELD or UKELD as predictors of 3-month waiting-list mortality in female, male, older or younger patients (P values not shown).

Does substitution of CrCl for serum creatinine improve the prognostic accuracy of MELD and UKELD?

Measured creatinine clearance was available in 139 of the 256 patients (54.3%) listed for liver transplantation between May 2000 and June 2007. The CrCl patients were comparable to patients who did not have a recorded CrCl (Table 3). In this cohort of 139, 31 patients (22.3%) died prior to transplantation. The median time from listing to death was 49 (IQR 19–88) days. The median waiting-time to transplantation was 85 (IQR 35–179) days. Fifty-five patients (39.6%) were transplanted and 25 patients (18.0%) died within 3 months of listing.

The median listing serum creatinine, serum sodium, eGFR (MDRD6) and CrCl was 91 (IQR 79–110) μM, 136 (IQR 131–139) mM, 75 (60–87) ml/min/1.73 m^2, and 72 (51–95) ml/min, respectively. CrCl demonstrated a greater correlation with eGFR (MDRD6) (0.615, $P < 0.001$) than with serum creatinine (−0.452, $P < 0.001$).

Logecreatinine (OR 7.77, 95% CI 1.33–45.51, $P = 0.023$) and logeCrCl (OR 0.22, 95% CI 0.07–0.67,

Table 3. Comparison of listing variables in patients listed for liver transplantation between May 2000 and June 2007 who did and did not have measured creatinine clearance available.

Variable	No CrCl (n = 117)	CrCl (n = 139)	P-value
Age (years)	54.0 (12.3)	55.3 (11.4)	0.374
Male gender	62 (53.0)	85 (61.2)	0.188
Noncholestatic disease	71 (60.7)	83 (59.7)	0.874
INR	1.4 (1.2–1.6)	1.3 (1.1–1.6)	0.553
Bilirubin (μM)	76 (42–139)	84 (46–156)	0.526
Albumin (g/l)	28.9 (5.4)	29.0 (5.4)	0.876
Encephalopathy	36 (43.9)	35 (42.7)	0.875
Ascites	60 (60.6)	70 (60.3)	0.969
Sodium (mM)	135 (132–138)	136 (131–139)	0.591
Creatinine (μM)	91 (78–106)	91 (79–106)	0.795
eGFR (MDRD6)	73 (58–90)	76 (60–87)	0.997
MELD	17 (14–20)	16 (14–21)	0.771
UKELD	57 (54–61)	57 (54–61)	0.936

Values expressed as mean (standard deviation), median (inter-quartile range) and number (percentage) where appropriate.
Units for eGFR (MDRD6) = ml/min/1.73 m^2.
CrCl, measured creatinine clearance; INR, international normalised ratio; MDRD, Modification of Diet in Renal Disease; MELD, Model for End-Stage Liver Disease; eGFR (MDRD6), estimated glomerular filtration rate derived from 6-variable MDRD equation.

Table 2. AUC for receiver-operating characteristic curves for prediction of 3-month liver transplant waiting-list mortality in different patient groups.

	Females		Males		Older		Younger	
Model	c-statistic	95% CI	c-statistic	95% CI	c-statistic	95% CI	c-statistic	95% CI
MELD	0.807	0.677–0.938	0.775	0.660–0.890	0.734	0.612–0.857	0.872	0.764–0.981
MELD (adj)	0.847	0.740–0.955	0.820	0.723–0.917	0.810	0.703–0.916	0.882	0.797–0.967
MELD (eGFR)	0.848	0.733–0.962	0.843	0.752–0.933	0.791	0.677–0.906	0.880	0.788–0.971
UKELD	0.794	0.664–0.924	0.833	0.729–0.936	0.771	0.659–0.884	0.876	0.755–0.988
UKELD (adj)	0.826	0.712–0.940	0.874	0.784–0.963	0.833	0.731–0.936	0.891	0.794–0.989
UKELD (eGFR)	0.828	0.715–0.941	0.879	0.790–0.967	0.825	0.719–0.931	0.891	0.788–0.993

Older defined as age ≥60 years, younger defined as age <60 years.
eGFR, estimated glomerular filtration rate; MELD, standard Model for End-Stage Liver Disease score; UKELD, standard UK score for Patients with End-Stage Liver Disease score; MELD (adj), MELD score with regression coefficients adjusted for our model; UKELD (adj), UKELD score with regression coefficients adjusted for our model; MELD (eGFR), MELD score with logeGFR substituted for logecreatinine; UKELD (eGFR), UKELD score with logeGFR substituted for logecreatinine; c-statistic, concordance statistic.

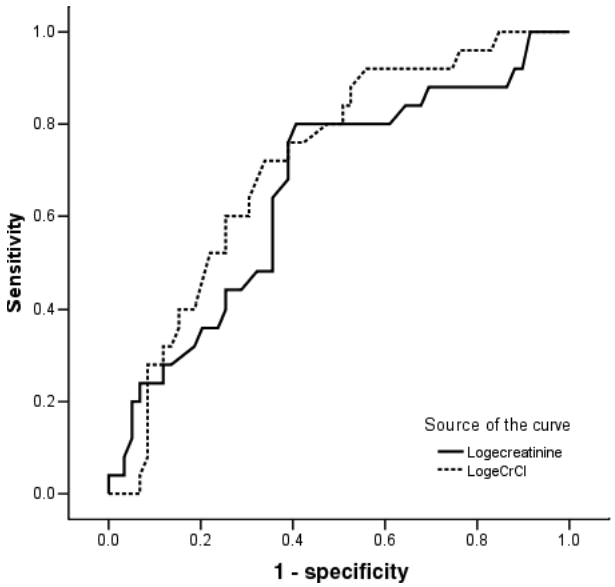

Figure 2 Receiver-operating characteristic curves of log serum creatinine (logecreatinine) and log creatinine clearance (logeCrCl) for predicting 3-month liver transplant waiting list mortality.

$P = 0.008$) were associated with 3-month waiting-list mortality. The ROC curves for logecreatinine and logeCrCl are shown in Fig. 2. Logecreatinine and logeCrCl had similar concordance statistics for the prediction of death by 3 months (logecreatinine 0.660; 0.532–0.788: logeCrCl 0.718; 0.604–0.831, c-statistic and 95% confidence interval, $P = 0.353$).

As before, ROC analysis was used to determine whether the substitution of logeCrCl for logecreatinine improved the accuracy of the existing prognostic models, MELD and UKELD (Table 4). LogeCrCl substituted for logecreatinine did not change the concordance statistic for MELD [MELD (adj) versus MELD (CrCl), $P = 0.249$] or UKELD [UKELD (adj) versus UKELD (CrCl), $P = 0.198$] as a predictor of 3-month waiting-list mortality.

Table 4. AUC for receiver-operating characteristic curves for prediction of 3-month liver transplant waiting-list mortality.

Model	c-statistic	95% CI
MELD (adj)	0.809	0.708–0.910
MELD (CrCl)	0.845	0.765–0.926
UKELD (adj)	0.849	0.756–0.942
UKELD (CrCl)	0.881	0.808–0.954

CrCl, measured creatinine clearance; MELD, Model for End-Stage Liver Disease; MELD (adj), MELD score with regression coefficients adjusted for our model; UKELD, UK score for Patients with End-Stage Liver Disease; UKELD (adj), UKELD score with regression coefficients adjusted for our model; MELD (CrCl), MELD score with logeCrCl substituted for logecreatinine; UKELD (CrCl), UKELD score with logeCrCl substituted for logecreatinine; c-statistic, concordance statistic.

Discussion

Our study has examined for the first time eGFR, calculated using the MDRD equations, in the prediction of mortality on the liver transplant waiting list. We have demonstrated that decreasing eGFR, as a continuous variable, was associated with an increased risk of death within 3 months of listing. This reiterates the well recognised spectrum of renal dysfunction that occurs in the setting of cirrhosis and reflects the underlying circulatory derangement of advanced disease. Of the three MDRD equations, the eGFR derived from the 6-variable equation was the better prognostic indicator. On univariate analysis, eGFR (MDRD6) was comparable, but not superior, to listing serum creatinine for prediction of 3-month waiting-list mortality. When substituted for serum creatinine eGFR (MDRD6) did not improve the prognostic accuracy of the existing MELD and UKELD models.

Although a negative study, the finding that eGFR (MDRD6) is not superior to serum creatinine in the prediction of waiting-list mortality is an important observation. Several studies have previously highlighted the prognostic inadequacies of serum creatinine in patients with end-stage liver disease [12,13]. Concerns have been raised that scoring systems for graft allocation that incorporate serum creatinine may disadvantage some individuals. In searching for alternative measures of renal function the next step is to use creatinine-based estimates of glomerular filtration rate that adjust for patient factors potentially conferring systemic bias. The MDRD eGFR is well validated in the nonliver setting, is calculated from readily available variables including age, gender and race, and has been shown to be the most accurate eGFR in cirrhotic patients [9,17–19]. Our negative results support the need for further research to identify more precise noncreatinine-based measures of renal function in these patients.

An explanation for the failure of eGFR (MDRD6) to improve the MELD and UKELD scoring systems is that the equation does not take into account disease-related factors such as nutritional status. Consequently, eGFR (MDRD6) is not an accurate measure of absolute renal function with one-third of patients demonstrating an MDRD estimate outwith 30% of the measured glomerular filtration rate [17]. The Cockcroft–Gault eGFR adjusts for body weight and, although a less precise estimator of glomerular filtration rate in this population, its ability to predict survival remains unknown [17,25]. Notably, the difficulty in obtaining an accurate dry weight in patients with significant ascites and peripheral oedema makes the Cockcroft–Gault eGFR a less attractive option [10,11].

Other possible weaknesses of eGFR for predicting mortality on the liver transplant waiting list are as follows: similar to ascites and serum sodium concentration, eGFR may be influenced by diuretic use and could theoretically be subject to manipulation [2]. Furthermore, a reduced eGFR may reflect intrinsic renal disease, which may not confer the same prognostic significance. All patients with evidence of renal impairment should have renal pathology excluded with urinalysis and renal imaging [4]. Creatinine assays are not currently standardised and there is significant variability in serum creatinine levels using different methods [26]. Therefore, the prognostic significance of eGFR may not be echoed in all centres.

The association of CrCl with mortality in patients listed for liver transplantation was a further novel finding of this study. Decreasing CrCl, as a continuous variable, was associated with an increased risk of death within 3 months of listing. Mirroring the findings of eGFR (MDRD6) CrCl was a comparable, but not superior prognostic indicator to serum creatinine. When substituted for serum creatinine CrCl increased the accuracy of MELD and UKELD by 3.6% and 3.2%, respectively, although statistical significance was not achieved. The negative result may reflect a relatively small patient subgroup, but probably reflects the inaccuracy of CrCl as a measure of absolute renal function [27].

Despite the large population assessed in this single-centre study, we recognise some potential limitations. Firstly, because of the retrospective nature we cannot ensure that all patients with intrinsic renal disease were excluded from the analysis. In our unit, patients assessed for liver transplantation routinely undergo urine testing and renal ultrasonography, and those with significant renal impairment are considered for renal biopsy. As a result, most patients with intrinsic renal disease should have been identified. Secondly, biochemical values were based on a single measurement and may not have been a true representation of the steady state in all. However, during the 5-day liver transplant assessment our patients are relatively stable and less likely to be subject to diuretic-induced or sepsis-related acute renal impairment. Thirdly, the patients included in the study were listed over a 15-year period during which advances have been made in the management of chronic liver disease, such as the widespread use of terlipressin and albumin for hepatorenal syndrome. Therefore, there may be a small time effect that could not be factored into the statistical analysis. Finally, the indications for transplantation in this cohort differ somewhat from the typical transplant centre with a greater proportion of patients listed for primary biliary cirrhosis and less for viral hepatitis. The MELD score has been shown to have comparable 3-month mortality risk prediction in a diverse range of liver diseases, both cholestatic and noncholestatic [7]. Consequently, we do not believe that the somewhat atypical spread of aetiologies should have influenced our findings.

Clinically applicable, precise measures of renal function are not currently available in cirrhotic patients. Serum creatinine remains the most widely used parameter and despite its limitations has some clinical relevance. A change in serum creatinine may indicate haemodynamic decompensation or intrinsic renal disease, and serum creatinine is an important prognostic indicator [6,7]. In this study we have demonstrated that listing eGFR (MDRD6) was comparable, but not superior, to listing serum creatinine for prediction of 3-month waiting-list mortality, and when substituted for serum creatinine eGFR (MDRD6) did not improve the prognostic accuracy of the existing MELD and UKELD models. Our findings support the need for further research to identify more precise noncreatinine-based measures of renal function.

Authorship

JAL: research design, data collection, data analysis and paper writing. SMMK: data collection. JWF and PCH: research design and paper writing.

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