



Pretransplant renal function evaluated by serum cystatin C was associated with mortality after liver transplantation: a single-center experience

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Background: In the model for end-stage liver disease (MELD) score, renal function was well thought to be associated with the prognosis of liver recipients. Serum cystatin C (CystC)-based equations were considered more accurate for calculating estimated glomerular filtration rate (eGFR) than creatinine (Pcr) based equations. Thus, we aimed to assess the association between eGFR estimated by chronic kidney disease epidemiology collaboration (CKD-EPI)-CystC equation and post-transplantation mortality.

Methods: From January 2015 to January 2018, prior to liver transplantation (LT) and other clinical parameters, CystC was collected in all 307 consecutive patients who underwent LT at our center. Patients were divided into four groups according to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification.

Results: Based on CKD-EPI-CystC and the KDOQI classification, 117 patients (38.1%) were stage I, 76 (24.8%) were stage II, 85 (27.7%) were stage III, and 29 (9.4%) were stage IV–V. After univariate and multivariate analysis, MELD score [hazard ratio (HR) =1.035; 95% confidence interval (CI), 1.006–1.066; P=0.018], associated HCC (HR =2.314; 95% CI, 1.253–4.273; P=0.007), and KDOQI stage III (HR =1.850; 95% CI, 1.001–3.419; P=0.049), and stage IV–V (HR =3.915; 95% CI, 1.843–8.316; P<0.001) according to CKD-EPI-CystC equation were confirmed to be independent prognostic factors for post-LT survival.

Conclusions: The pretransplant renal function evaluated by serum CystC was associated with mortality after LT and could be used for predicting post-transplant survival.

Keywords: Creatinine; estimated glomerular filtration rate; liver transplantation (LT); prognosis; serum cystatin C

Submitted Dec 25, 2018. Accepted for publication Apr 19, 2019.

doi: 10.21037/atm.2019.05.22

View this article at: <http://dx.doi.org/10.21037/atm.2019.05.22>

Introduction

Liver transplantation (LT) has become the mainstream and only radical therapy for patients with end-stage liver disease (1). Due to the worldwide shortage of liver donors, only a few patients received transplantation in time, and the mortality rate among patients on the waiting list has increased. Therefore, a more reliable pretransplant recipient evaluation system was needed in order to establish a more justifiable allocation system. For achieving such a goal, the model for end-stage liver disease (MELD) score was proposed (2). Compared with the Child-Pugh grading score, MELD score includes renal function, which has been well-established to be associated with the prognosis of liver recipients, as a predictor for patient mortality (3).

In the MELD score, the renal function was reflected by creatinine, which was commonly used for calculating the estimated glomerular filtration rate (eGFR). However, Gonwa *et al.* (4) stated that creatinine-based equations of eGFR, including Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease 4 (MDRD-4) were neither accurate in the pre- nor post-liver transplant population, especially in patients with advanced liver disease, high bilirubin, or refractory ascites. Thus, a substitutive indicator for renal function in such patients was needed.

Serum cystatin C (CystC) was considered as a more consistent and appropriate alternative endogenous filtration marker to furnish more accurate assessments of eGFR than creatinine. The measurement of CystC was not interfered with by muscle mass, age, gender, jaundice, or hemolysis (5). Also, equations based on CystC, including CKD-EPI-CystC and Hoek formulas, were revealed to have lower bias and higher accuracies than creatinine-based ones in a patient with cirrhosis (5).

In the present study, we aimed to assess the association between eGFR estimated by CKD-EPI-CystC equation and post-transplantation mortality.

Methods

Patients and methods

Patients with simultaneous multiple organ transplantation, acute fulminant liver failure, or prior LT were excluded from the present study. In total, from January 2015 to January 2018, 307 consecutive patients with cirrhosis who underwent LT at the First Affiliated Hospital, School

of Medicine, Zhejiang University were included. Data regarding recipient age, sex, presence of hepatocellular carcinoma (HCC), MELD score, body mass index (BMI), Child-Pugh grading score, pretransplant international normalized ratio (INR), albumin, total bilirubin (TB), plasma creatinine (Pcr), blood urea nitrogen (BUN), and serum CystC were retrospectively collected.

Estimated GFR

The eGFRs were commonly estimated by CKD-EPI-Pcr, MDRD-4, MDRD-6, Hoek, CKD-EPI-CystC, and CKD-EPI-Pcr-CystC equations (6-9). All equations are listed in *Table 1*. As the Pcr, CystC, and urea nitrogen were the most frequently encountered parameters for assessing renal function, the CKD-EPI-Pcr, MDRD-6, and CKD-EPI-CystC equations based on those three parameters were selected in the present study for further evaluation.

Based on the eGFR calculated by the CKD-EPI-CystC equation, patients were divided into four groups according to the Kidney Disease Outcomes Quality Initiative (KDOQI) classification (10): stage I (normal renal function, $\text{eGFR} \geq 90 \text{ mL/min/1.73 m}^2$), stage II ($60 \leq \text{eGFR} < 90 \text{ mL/min/1.73 m}^2$), stage III ($30 \leq \text{eGFR} < 60 \text{ mL/min/1.73 m}^2$) and stage IV-V ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$).

Follow-up data

A standardized follow-up protocol was adopted for all patients, in which the end-point was patient death or graft loss. Patients who were lost to follow-up were considered dead. All data were analyzed anonymously and de-identified prior to analysis. The data was updated to October 12th, 2018.

Ethical statement

Written informed consent was obtained from all participants. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, and in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

The variables were expressed as median with interquartile range (IQR) or number (percentage). Survival curves

Table 1 Equations used to calculate GFRs and MELD score

Equation	Full expression (mL/min/1.73 m ²)
MDRD-4	$=175 \times (\text{Pcr})^{-1.154} \times \text{age}(\text{years})^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$
MDRD-6	$=161.5 \times (\text{Pcr})^{-0.999} \times \text{age}(\text{years})^{-0.176} \times (\text{urea nitrogen})^{-0.17} \times (\text{albumin})^{-0.318} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if black)}$
CKD-EPI-Pcr	$=141 \times \min(\text{Pcr}/\kappa, 1)^{\alpha} \times \max(\text{Pcr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}(\text{years})} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$; κ is 0.7 for female and 0.9 for males; α is -0.329 for females and -0.411 for males; “min” is the minimum of Pcr/κ or 1 and “max” the maximum of Pcr/κ or 1
Hoek	$=-4.32 + 80.35 \times 1/\text{Cystatin C}$
CKD-EPI-Cys C	$=133 \times \min(\text{Cystatin C}/0.8, 1)^{-0.499} \times \max(\text{Cystatin C}/0.8, 1)^{-1.328} \times 0.996^{\text{age}(\text{years})} \times 0.932 \text{ (if female)} \times 1.159 \text{ (if black)}$; “min” is the minimum of $\text{Cystatin C}/0.8$ or 1 and “max” the maximum of $\text{Cystatin C}/0.8$ or 1
CKD-EPI-Pcr-Cys C	$=135 \times \min(\text{Pcr}/\kappa, 1)^{\alpha} \times \max(\text{Pcr}/\kappa, 1)^{-0.601} \times \min(\text{CystC}/0.8, 1)^{-0.375} \times \max(\text{CystC}/0.8, 1)^{-0.711} \times 0.995^{\text{age}(\text{years})} \times 0.969 \text{ (if female)} \times 1.08 \text{ (if black)}$; κ is 0.7 for female and 0.9 for males. α is -0.248 for females and -0.207 for males. “min” is the minimum of Pcr/κ or 1, or the minimum of $\text{Cystatin C}/0.8$ or 1. “max” is the maximum of Pcr/κ or 1, or the maximum of $\text{Cystatin C}/0.8$ or 1
MELD score	$=10 \times [0.957 \times \ln(\text{Pcr}) + 0.378 \times \ln(\text{Total Bilirubin}) + 1.12 \times \ln(\text{INR}^3) + 0.643]$

MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; MELD, model for end-stage liver disease; Pcr, creatinine; Cys, serum cystatin C; INR, international normalized ratio.

were analyzed using the Kaplan-Meier method with the log-rank test. Cox regression was carried out to evaluate the risk factors for patient survival. Variables reaching 10% significance in univariate analysis were included in the multivariate analysis. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with statistical software package SPSS19.0 (SPSS Inc, Chicago, IL, USA).

Results

Distribution and clinical characteristics of patients

In total, 307 patients were included in the present study. A total of 265 patients (86.3%) were male, and the median age of the study group was 50 years old (mean 49.7 years old; range, 24–74 years old). A total of 252 recipients (82.1%) were infected with the hepatitis B virus (HBV), and 110 (35.8%) were diagnosed with HCC. The median follow-up time was 15.5 months (mean 17.8 months; range, 0–41.8 months).

The median eGFR according to the CKD-EPI-Pcr, MDRD-6, and CKD-EPI-CystC equations were 103.88 mL/min/1.73 m² (mean 100.43 mL/min/1.73 m²; range 12.17–153.80 mL/min/1.73 m²), 213.71 mL/min/1.73 m² (mean 222.22 mL/min/1.73 m²; range 24.19–534.67 mL/min/1.73 m²), and 77.92 mL/min/1.73 m² (mean 77.59 mL/min/1.73 m²; range 5.66–150.86 mL/min/1.73 m²)

respectively. Distribution and clinical characteristics of patients according to KDOQI classification based on CKD-EPI CystC equation are presented in *Table 2*.

Patient survival

Patients with higher KDOQI stage based on the CKD-EPI-CystC equation were found to have a shorter survival time (*Figure 1*, $P=0.001$). The 3-month, 1- and 3-year survival rates in KDOQI stage I based on CKD-EPI-CystC were 94.8%, 88.5%, and 76.1%, respectively; 86.5%, 80.9%, and 71.6% in stage II, respectively; 84.7%, 76.5%, and 58.7% in stage III, respectively; and 69.0%, 55.6%, and 50.0% in stage IV–V, respectively ($P=0.001$). In univariate analysis for post-transplant mortality, MELD score ($P=0.046$), eGFR according to MDRD6 equation ($P=0.006$), CKD-EPI-Pcr equation ($P=0.004$), and CKD-EPI-CystC equation ($P<0.001$) were found to be associated with increased risk of mortality (*Table 3*). Although associated HCC was not found to be significant for mortality in univariate analysis ($P=0.502$), based on our previous experience, it had significant impact on post-transplant survival and therefore was brought into multivariate analysis. After multivariate analysis, three independent prognostic predictors for patient survival were identified: MELD score [hazard ratio (HR) =1.035; 95% confidence interval (CI), 1.006–1.066; $P=0.018$],

Table 2 Baseline patient characteristics

Variables	All population (N=307)	KDOQI 1 (N=117)	KDOQI 2 (N=76)	KDOQI 3 (N=85)	KDOQI 4–5 (N=29)
Sex (male/female)	265/42	107/10	65/11	71/14	22/7
Age (years)	49.7±10.1	46.9±9.9	50.1±9.9	51.6±9.7	54.0±9.9
BMI (kg/m ²)	23.17±3.20	23.70±3.63	23.00±2.92	22.85±3.02	22.57±2.44
INR	1.96±1.11	1.86±1.04	1.94±1.08	2.02±1.22	2.29±1.06
Albumin (g/L)	34.78±4.80	35.59±4.52	34.58±4.97	34.46±4.76	32.99±5.16
TB (μmol/L)	212.93±223.00	146.54±166.72	171.36±176.44	286.36±264.42	374.48±261.99
Creatinine (μmol/L)	76.04±43.14	60.51±12.74	67.68±22.61	82.04±30.49	143.03±97.74
Cystatin C (mg/L)	1.23±0.73	0.70±0.14	1.08±0.09	1.54±0.20	2.86±1.12
Associated HCC	110 (35.8%)	57 (48.7%)	26 (34.2%)	25 (29.4%)	2 (6.9%)
MELD score	19.58±9.67	17.30±9.17	18.42±9.01	21.21±9.18	27.00±10.65
Child-Pugh score	9.06±2.62	8.45±2.70	8.96±2.68	9.47±2.37	10.52±2.12
CKD-EPI-Cystatin C, mL/min	77.59±36.43	117.59±15.98	73.07±8.09	45.54±7.46	22.03±6.58

KDOQI stage was defined according to the CKD-EPI-Cystatin C equation. Values are mean ± standard deviation or n (%). KDOQI, Kidney Disease Outcomes Quality Initiative; BMI, body mass index; INR, international normalized ratio; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease.

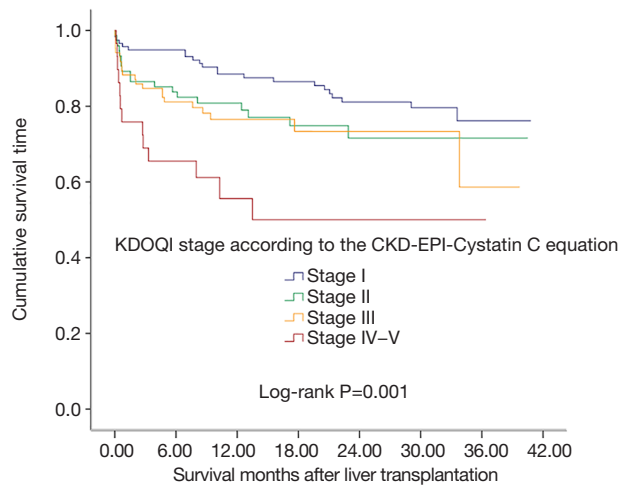


Figure 1 Survival curve of patients underwent liver transplantation according to the KDOQI stage using CKD-EPI-Cys C equation. KDOQI, Kidney Disease Outcomes Quality Initiative; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; Cys C, serum cystatin C.

associated HCC (HR =2.314; 95% CI, 1.253–4.273; P=0.007), and KDOQI stage III–V according to CKD-EPI-CystC equation (Table 3).

Conclusions

To the best of our knowledge, the present study was the first large, single-center study based on a Han population which evaluated the association between preoperative serum CystC with post-transplant mortality. The results confirmed that eGFR prior to transplantation according to CKD-EPI-CystC equation had significant prognostic value for patient survival. Recipients with higher preoperative eGFR were expected to have a higher survival rate. Creatinine-based equations, including MDRD-6 and CKD-EPI-Pcr, were found to have no value for predicting postoperative patient survival.

CystC, known as cysteine protease inhibitor C, was considered an ideal indicator for accurate assessment of renal function. Released into the blood by all nucleated cells at a steady rate, serum CystC is eliminated exclusively by glomerular filtration and then completely reabsorbed and catabolized by the proximal tubular epithelial cells, instead of going back to the blood. In a previous study, the concentration of serum CystC was not influenced by age, sex, muscle volume, serum bilirubin, malignant tumor, drugs, etc. and only affected by renal function (11). The half-life of CystC was shorter than creatinine (1.5 vs. 4–5 hours), which made it more accurate for reflecting rapid changes

Table 3 Cox regression analysis of potential factors associated with mortality

Variables	Hazard ratio	P	95% confidence interval
Univariate analysis			
MELD score	1.023	0.042	1.001–1.047
KDOQI stage according to			
MDRD 6	1.669	0.006	1.160–2.403
CKD-EPI-Pcr	1.499	0.004	1.140–1.970
CKD-EPI-Cyst C	1.495	<0.001	1.197–1.866
Associated HCC	1.173	0.502	0.737–1.866
Multivariate analysis			
MELD score	1.035	0.018	1.006–1.066
Associated HCC	2.314	0.007	1.253–4.273
KDOQI stage according to CKD-EPI-Cyst C			
Stage I	1		
Stage II	1.648	0.119	0.880–3.087
Stage III	1.850	0.049	1.001–3.419
Stage IV–V	3.915	<0.001	1.843–8.316

P<0.05 was considered to be statistical significant. MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; KDOQI, Kidney Disease Outcomes Quality Initiative; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; Pcr, creatinine; Cyst C, serum cystatin C.

in renal function (12). Owing to the implementation of international reference material, present commercial CystC assays were highly concordant, which made the measurement of CystC precise and reproducible (13). In patients with advanced liver disease, studies supported the notion that CystC-based equations were more accurate and reliable than creatinine-based ones (5,14).

Primary or secondary renal dysfunction is prevalent in patients before and after LT. It was proposed that renal function evaluated by CystC-based eGFR had a significant correlation with long-term survival of liver recipients (15,16). Thus, in our study, we divided the patients into four groups according to the KDOQI stage based on the eGFR calculated by CKD-EPI-CystC equation. The results showed that patients in KDOQI stage I had a 1-year survival rate of 83%, while for those patients in the KDOQI stage IV–V only 25% survived more than 1 year. These results are consistent with previous reports and suggest that pretransplant renal function may be a significant predictor for patient mortality after transplantation, and that renal function can be best described by eGFR based on CKD-EPI-CystC equation.

The MELD scoring system, introduced in 2002, incorporated plasma creatinine, TB, and the INR, and has been proven to be a simple and objective tool for quantifying the clinical status of potential liver transplant recipients (17). According to the criterion, LT should be considered when the MELD score is above 15 (18,19). In accordance with previous studies, the multivariate analysis of our study confirmed that MELD score was independently associated with decreased survival. However, Kim *et al.* stated that a few initial variables of the MELD score had not been completely proven to have prognostic values while other effective variables, such as CystC in this study, have not been taken into account for this model (19). With regards to assessing the discrepancy resulting from an excessive proportion of serum creatinine and INR in the MELD score equation (20), it might be plausible to replace creatinine with CystC for calculating MELD score, a measure which is worth further evaluating.

A few limitations of the present study needed to be mentioned. The first is that we did not use a gold standard method to assess the actual value of GFR. Another limitation is that the information for postoperative

complications, such as acute or chronic renal dysfunction, infection, and primary liver graft dysfunction, was not recorded or further analyzed. However, the aim of our study was assessing the prognostic value of CystC for liver recipient's survival, instead of detecting the accuracy of CystC for determining actual GFR. These limitations did not, however, compromise the integrity of the present work.

In conclusion, MELD score and preoperative eGFR based on the CKD-EPI-CystC equation were both independent risk factors for long-term survival after LT. Patients in a higher KDOQI stage determined by pretransplant serum CystC, rather than Pcr, was expected to have a lower survival rate. These findings suggest that CystC might be the better index for replacing creatinine in calculating MELD score.

Acknowledgments

Funding: This work was supported by National Natural Science Foundation of China (No. 81572307, 81773096), Major Project of Medical and Health Technology Development Program in Zhejiang Province (No. 7211902), Medical Health Science and Technology Project of Zhejiang Provincial (No. 2016KYB083), Public Welfare Technology Research Project of Zhejiang Province (No. LGD19C040006), General Research Project of the Zhejiang Provincial Education Department (No. Y201840044), and Clinical Medicine Innovation Center of Precision Diagnosis and Treatment for Hepatobiliary and Pancreatic Disease of Zhejiang University (No. 2017-02-06).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. All participants had signed written informed consent. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University. All data were analyzed anonymously and identified prior to analysis. Written informed consents for publication are obtained from all participants. Detail has been removed from these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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Cite this article as: Ding Y, Wu T, Zhang W, Zhang S, Wang W. Pretransplant renal function evaluated by serum cystatin C was associated with mortality after liver transplantation: a single-center experience. *Ann Transl Med* 2019;7(11):243. doi: 10.21037/atm.2019.05.22