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TITLE PAGE

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/liv.12989

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Abbreviations

LT, liver transplantation; Pcr, plasma creatinine; CystC, cystatin C; MDRD4, four variable Modification of Diet in Renal Disease equation**;** MDRD-6, six-variable Modification of Diet in Renal Disease equation; CKD-EPI**,** Chronic Kidney Disease Epidemiology Collaboration equation; KDOQI, Kidney Disease Outcomes Quality Initiative; GFR, glomerular filtration rate; eGFR, estimated GFR; MELD, Model for End-Stage Liver Disease**;** CKD, chronic kidney disease; BMI, Body Mass Index; HCC, hepatocellular carcinoma

Conflict of interest

The authors declare that they have not conflict of interest related to this manuscript.

Financial support

None

Abstract

Backgrounds: In patients with cirrhosis, cystatin C (CystC) based equations may be more accurate indicators of glomerular filtration rate (GFR) than creatinine (Pcr) based equations. Renal function before liver transplantation (LT) is thought to impact survival after LT. We

aimed at assessing pretransplant creatinine and CystC based equations with respect to their predictive value on long-term survival after LT.

Methods: From 2001 to 2011, CystC was determined at pre-LT evaluation in 682 patients together with GFR assessed using MDRD-4, MDRD-6, CKD-EPI-cystatin C, CKD-EPI-creatinine, and CKD-EPI-creatinine-cystatin C equations. Patients were classified according to the Kidney Disease Outcomes Quality Initiative classification (KDOQI).

Results: Median age at LT was 55[49-60] years with a median MELD score of 13.5[8.3-19.2] and a median post-transplant follow-up of 60[26-89] months. Using CKD-EPI Cystatin C and the KDOQI classification, 21.1% of patients were stage 1, 43.1% stage 2, 29.1% stage 3 and 6.5% stage 4. Kaplan Meier survival estimates was significantly different between KDOQI stages when determined using the CKD-EPI-CystatinC equation. This was not the case when using the other equations. At multivariate analysis, GFR and KDOQI estimated using the CKD-EPI-CystatinC equation were significantly associated with death (HR:0.992;CI95%:0.986-0.999 and 1.24;CI95%:1.02-1.50, respectively). When assessed using the MDRD-4, MDRD-6, CKD-EPI-Creatinine-CystatinC and CKD-EPI-Creatinine equations GFR was not significantly associated with death.

Conclusions: Estimated pre-LT renal function is predictive of post-LT survival only when assessed using the CKD-EPI cystatin C equation. This supports the use of Cystatine C and of its related equation for the assessment of renal function before liver transplantation.

Keyword: Cystatin C, creatinine, liver transplantation, glomerular filtration rate

Key Point Box

- **Long term survival after liver transplantation is significantly different between KDOQI stages when determined using the CKD-EPI-Cystatin C equation**
- **Glomerular filtration rate estimated by the CKD-EPI-Cystatin C equation is associated to long term survival**
- **Other equations used to estimate glomerular filtration rate are not associated with long term survival**
- **Estimating pretransplant glomerular filtration rate using the CKD-EPI-Cystatin C equation should improve the management of candidates for liver transplantation**

INTRODUCTION

Renal function plays a critical role in the prognosis of patients with cirrhosis. [1] During the last decade, Child-Pugh score was challenged by the more efficient and objective MELD (Model for End-stage Liver Disease) score. [2, 3] This brought renal function, estimated by serum creatinine, at the foreground in the management of patients with cirrhosis, due to its weight in MELD score. [4]

Studies showed that creatinine and creatinine-based equations are inaccurate in patients with cirrhosis, notably because of low muscular mass, edemas and interference of serum bilirubin levels with creatinine measurement. [5, 6] Recently, Francoz *et al.* showed that MDRD4 and CKD-EPI creatinine formulas significantly overestimated true GFR,[7] especially in patients with severe ascites. [8]

Serum cystatin C (CystC) synthesis is constant even in the setting of inflammation or neoplasm. [9, 10] Its concentration is independent of muscle mass, age and gender, and can be reliably determined even in case of hyperbilirubinemia. [11]

In patient with cirrhosis, CystC based equations had better performance than creatinine-based equations to assess GFR. [12, 13] Recently, new equations to evaluate GFR based on standardized assays of serum creatinine and CystC (CKD-EPI creatinine and CKD-EPI cystatin C), or a combination of both, were reported to have improved performance in the estimation of GFR in patients with no liver disease. [14, 15] In cirrhotics, De Souza *et al.* showed that the CKD-EPI cystatin C equation was more accurate than other cystatin and creatinine-based equations in the measurement of GFR. [16]

The assessment of renal function in candidates for LT has two goals: selecting patients with renal failure who could benefit from simultaneous liver-kidney transplantation, [7, 17] and determining the mortality risk of patients after LT. [18] Post-LT chronic kidney disease (CKD) is frequent and associated with increased mortality. [19, 20] Its main determinant is the presence of pretransplant CKD which may lead to post-transplant kidney failure, mainly when associated to the nephrotoxicity of anticalcineurin drugs and/or to other morbidities. [20-22] Using serum creatinine in a very large population, Nair *et al.* showed that pretransplant renal dysfunction was associated with a decrease in 2-year survival after liver transplantation (LT). [23]

A precise estimation of renal function in LT candidates should result in unveiling those requiring an optimized management to prevent renal failure, and identifying the long-term impact of renal function on post-transplant survival.

The aim of the study was to assess the predictive value of GFR for long-term survival after liver transplantation when measured by reference to the new CKD-EPI equations.

Patients and Methods

Patients

All patients who underwent LT in our center from 01/2001 to 12/2011 were included except in case of previous LT, multiple organ transplantation or emergency LT (lack of pretransplant evaluation). Cystatin C measurement is part of routine pre-LT workup in our center since 2001.

Combined kidney-liver transplantation was discussed in patients with estimated GFR≤30 mL/min/1.73 m2 based on MDRD4. Patients with kidney-liver transplantation were not included in the study.

The study protocol conformed to the guidelines of the declaration of Helsinki and was approved by the ethics committee of the University Hospital of Rennes.

The following data were recorded: age, Body Mass Index (BMI), cause of cirrhosis, presence of hepatocellular carcinoma (HCC), ascites (stage 1-2-3, according to Child-Pugh score) and encephalopathy (stage 1-2-3, according to Child-Pugh score), routine biochemical and liver tests and Child-Pugh score. MELD score was available in all patients after March 2007 and retrospectively calculated in others when INR was available. Age and BMI of donors were recorded.

Biochemistry

Cystatin C was prospectively assessed – at the same time and on the same blood sample as serum creatinine - using the Siemens N-latex-Cystatin C kit with BNII-systems. Values obtained before the use of the international reference material for cystatin C (ERM-DA471/IFCC) were recalculated according to manufacturer's recommendations (correction factor of 1.11).

GFR was assessed according to MDRD4, MDRD-6, CKD-EPI cystatin C, CKD-EPI-creatinine, and CKD-EPI cystatin C-creatinine equations. [15, 24, 25]

French policies precluding the record of ethnic background, GFR was determined assuming all patients were non Blacks. However evaluation of patient currently on the waiting list (N=87) and patient who underwent LT in 2013 (N=117), showed that lower than 1% of patient were black. Therefore we think that it would not significantly alter estimated GFR.

According to estimated GFR (eGFR) obtained from CKD-EPI-cystatin equation, patients were divided into the four groups of the Kidney Disease Outcomes Quality Initiative classification (KDOQI)[26] : stage I (normal renal function, eGFR $\geq$ 90 mL/min/1.73 m2), stage II (60$\leq$eGFR <90mL/min/1.73 m2), stage III (30$\leq$eGFR<60 mL/min/1.73 m2) and stage IV-V (eGFR<30 mL/min/1.73 m2).

Follow up data

Follow up data were obtained from the local database and the National Biomedicine Agency (which conducts a mandatory follow-up for all transplanted patients at least once a year). According to French law, the corresponding database was declared to the "national committee of Informatics and Freedom" (CNIL, n°96-025).

Patients lost to follow-up were considered dead. The main endpoint was death from any cause after LT. Causes of death were prospectively recorded as infections, cardio vascular events, cancers (including recurrence of HCC), liver-related (rejection, recurrence of initial liver disease), others causes, and undetermined.

Statistical analysis

Continuous data were expressed as median [first-third quartile]. Univariate analysis was performed using Chi square or Mann Whitney test as applicable.

Patient survival was determined for each KDOQI-group using univariate Kaplan-Meier analysis. Because of the low number of KDOQI stage 4 patients (N=8 using MDRD-4), stage 3 and 4 were merged for the Kaplan-Meier analysis. Differences between groups were compared using the Log Rank test.

Cox regression analysis was performed to assess the independent effects of pre-LT parameters on survival.

Data were analyzed using 22^{d} version of SPSS (SPSS Inc., Chicago, USA). $P < 0.05$ was considered significant with a two-tailed test.

RESULTS

Patients

During the study period, 1049 patients underwent LT, of whom 104 had previous LT, 46 multiple-organ transplantation, and 113 emergency transplantation. Among the 786 eligible patients, the 682 who had cystatin C measurement available at pretransplant assessment constituted the study population.

Clinical characteristics of the population are presented in Table 1. Median follow-up was 60[26-89] months.

The cause of cirrhosis was alcohol in 415 patients, chronic hepatitis C in 108, chronic hepatitis B in 27, chronic hepatitis D in 1, and other causes in 131. LT was performed because of HCC in 255 patients whose the underlying liver disease was related to alcohol (n=169), hepatitis C (n=45), hepatitis B (n=15), hepatitis D (n=1), non-alcoholic steato-hepatitis (n=5), hemochromatosis (n=7) and other causes (n=13).

MELD was available in 442(65%) patients. Median MELD was 13.5[8.3-19.2] in the whole population, 9.2[6.7-13.1] in patients with cirrhosis and associated HCC and 18.5[13.5-23.8] in patients without HCC. Ninety nine patients (14.5%) had a MELD score higher than 20. Median donor age was 49[36-62] years, median donor BMI was 24.3[21.9-27.4]kg/m2. Median time between evaluation and liver transplantation was 17[6-35] weeks.

At pretransplant assessment, median serum creatinine was 74[63-85.2]µmol/l and median serum cystatin C 0.99[0.85-1.20]mg/L. Median eGFR was 68.8[53.1-85.3] ml/min/1.73m² according to the CKD-EPI-cystatin C equation, 95.8[81-105.3]ml/min/1.73m² according to the CKD-EPI creatinine equation, 80.9[65.7-94.5]ml/min/1.73m² according to the CKD-EPI creatinine-cystatin C equation, 90.5[74.4-108.5]ml/min/1.73m² according to the MDRD-4 equation, and106.3[85-125.9] ml/min/1.73m² according to MDRD-6. The median difference between eGFR according to CKD-EPI cystatin C and MDRD6 was -35.7[-50.6- -20.9]ml/min/1.73m²

Of the 682 patients, eight patients were lost to follow-up and 173 died during follow up. Causes of death were cancer in 57 (8.3%), infection in 35 (5.1%), cardio vascular disease in 23 (3.4%), liver-related disorder in 18 (2.6%), others in 14 (2.1%), and undetermined in 26 (3.8%).

KDOQI groups according to estimated GFR

Distribution and clinical characteristics of patients according to KDOQI classification using CKD-EPI cystatin C are presented in Table 1.

Factors associated with mortality

At univariate analysis, including all the clinical and biological variables from the donor and the recipient and the estimated GFR according to the different equations, serum cystatin C (p=0.001), donor age (p=0.005) and eGFR according to CKD-EPI cystatin C (p=0.003) and

CKD-EPI creatinine cystatin C (p=0.009), and the type of the underlying liver disease (p=0.018) were associated with an increased risk of death.

Cox regression analysis with stratification on the causes of liver disease and adjusted for donor and recipient age, total bilirubin, prothrombin index, ascites stage, hepatocellular carcinoma and serum albumin showed that eGFR based on CKD-EPI cystatin C was the only variable significantly associated with death (p=0.029; HR 0.992; CI95%: 0.986-0.999) when introduced as a continuous variable into the model (Table 2). Similarly KDOQI stage based on CKD-EPI cystatin C was significantly associated with death (p = 0.025; HR 1.24; CI95% 1.02-1.50).

By contrast, eGFR was not significantly associated with death when calculated according to MDRD-4, MDRD-6, CKD-EPI creatinine-cystatin C and CKD-EPI-creatinine equations.

Long term survival

Kaplan-Meier survival estimates in the overall population at 1, 3 and 5 year were 89.6%, 80.9% and 76% respectively.

Figure 1 depicts survival curves of patients according to KDOQI stage using the different equations.

Survival significantly differed according to KDOQI stages determined using CKD-EPI cystatin C (p=0.015). Pairwise comparison showed that survival of KDOQI stage 1 patients was significantly higher than KDOQI stage 2 (p=0.027) and 3-4 (p=0.003) patients. There was no significant difference between KDOQI stage 2 and 3-4 patients (p=0.29).

By contrast, survival did not significantly differed according to KDOQI stages determined using MDRD-4 (p=0.77), MDRD-6 (p=0.3), CKD-EPI creatinine (p=0.49), or CKD-EPI creatinine- cystatin C (p=0.071) equations.

Regarding causes of death, using CKD EPI cystatin C equation, KDOQI stage 2 and stage 3-4 patients had significantly higher infection related death than KDOQI stage 1 patients (p=0.02 and 0.03 respectively). Deaths of undetermined origin were higher in KDOQI stage 3-4 patients (p=0.02). Others causes of deaths were not significantly different.

DISCUSSION

For the first time, the present study, based on a large number of patients with a wide range of liver and renal dysfunction, showed that renal function estimated using the CKD-EPI cystatin C equation is a prognostic factor of death after liver transplantation. By contrast creatinine-based equations failed to be associated with long-term outcome.

Mindikoglu *et al.* and De Souza *et al.* showed that cystatin C is a better marker of renal function in patient with cirrhosis, but they found conflicting results with respect to the more accurate equation to be used [16, 27]. Differences in the populations studied may explain these conflicting results. Mindikoglu *et al.* studied patients with hepatitis C-related cirrhosis without criteria for LT whilst De Souza *et al.* studied patients with end-stage alcoholic cirrhosis and with lower weight. Moreover sex ratios (male/female) differed markedly, which renders the comparison difficult, serum creatinine being lower in females than in males for a given GFR value. [28] However both studies concluded that cystatin C-based equations were more accurate than creatinine-based equations.

Our population was similar to that of De Souza *et al.*[16] with respect to age, weight, sex ratio (2.87 versus 2.54) and causes of liver disease, most of our patients having alcoholic cirrhosis (60.9%). The proportion of patients with ascites was lower when considering mild ascites (24% versus 42%) but similar when considering refractory ascites (22.8% versus 17.8%). For these reasons, we extrapolated the results from De Souza *et al.* to our population, and we chose eGFR determined with CKD-EPI cystatin C equation as the reference. In agreement with these authors, our study shows that eGFR, is a prognostic factor of death when estimated using the CKD-EPI cystatin C but not the CKD-EPI creatinine cystatin C equation.

Of note, graft allocation policy changed during the study period (March 2007) due to the introduction of the MELD score, which has resulted in a higher proportion of patients transplanted with severe liver disease. The discrepancy between estimated GFR and true GFR determined by gold standard is significantly correlated to the severity of liver disease and the presence of ascites [16, 27]. However introducing the status regarding the allocation policy (before or after) in our multivariate analysis did not significantly change results regarding the prognostic value of any of the eGFR equations (data not shown).

One limitation of our study is the lack of a gold standard method to assess the true value of GFR. However our study aimed at assessing the clinical relevance of cystatin C as a prognosis tool for candidates to LT, but not the accuracy for GFR determination. Our study did not address the question of the most accurate method to assess renal function but it clearly showed that discrepancies in the prognostic value of creatinine-based and cystatin C-based equations were relevant. Another limitation of the study is the lack of post LT information regarding other disease that could influence long terme survival irrespectively of pre LT

GFR. The strength of our study is the large and homogenous population with a long follow-up of patients selected for LT.

With regard to the Cystatin C measurement technique, in order to reduce the variability between laboratories, the International Federation for Clinical Chemistry (IFCC) produced the reference material ERM-DA471/IFCC. [29] This certified material promoted to reduce concerns generated by different calibrators, is available to manufacturers of cystatin C reagents since 2010. However, a recent study showed that the variability in cystatin C determination persisted between manufacturers of *in vitro* diagnosis reagents [30]. These variations did not have any impact on the results of our study but for future studies, special attention should be paid to the technique used and to the calibration traceability to the ERM-DA471/IFCC reference material. Moreover this variability must be taken into account before cystatin C could be used to compare, or prioritize on the LT waiting list, patients from different centers.

The direct correlation between pretransplant renal function and long-term mortality was debated for a long time. Using the sole serum creatinine, several studies concluded to decreased post-LT survival in case of pre-LT renal failure [31-34]. On the contrary, Brown *et al.*, in a large number of patients, failed to find any impact of pre-LT renal function. [35] Similarly, Gonwa *et al*. showed that pre LT renal function has no effect on patient survival after LT when using creatinine-based eGFR. [36] This likely testifies of the low accuracy of serum creatinine determination to assess renal function.

The benchmark study by Nair *et al.* was able to demonstrate, using serum creatinine-based equations, that patients with impaired renal function had shorter long-term survival. [23] The very large population studied may have afforded the statistical power that was lacking to previous negative studies, and allowed for these conclusive results. It is noteworthy that our results based on a smaller population show that CKD-EPI-cystatin C eGFR is significantly associated with long term survival, suggesting a more accurate assessment of the impact of pretransplant renal function on survival after LT. Moreover, whereas calculated creatinine clearance was described as a categorical variable only in the study by Nair *et al.,[23],* our results show that CKD-EPI cystatin C eGFR is significantly associated with survival, whether it is considered as a categorical variable (KDOQI stage) or not. Referring to a continuous variable is likely to be more efficient when assessing a prognosis factor related to a physiological function. In their multivariate analysis, Nair *et al.* could assess the immediate and 2-year mortality, but not the 5-year mortality due to incomplete data for up to 47% of patient. [23] Thanks to the mandatory national follow-up in France, we had only 5 patients lost to follow-up and thus we were able to assess the impact of pretransplant renal function over the whole study period.

Accordingly to previous studies of similar sample size, [35, 36] we did not found significant correlation between creatinine-based eGFR and long-term survival. Although it was recently shown to be the more accurate eGFR equation in patients with cirrhosis, [7] MDRD-6 equation failed to show the impact of pretransplant renal function on survival after LT in our population.

Another major point is to identify the GFR threshold above which renal impairment is associated with increased mortality. Nair *et al.* considered 70mL/min/1.73 m² as normal renal function, and showed that patients with calculated creatinine clearance lower than 40mL/min/1.73 m² had higher mortality. [23] More recent guidelines suggested a different classification and consider 90mL/min/1.73m² as the initial threshold. [37] Following these criteria, our results showed that even patients with mild renal impairment (KDOQI stage2: 60 ≤ eGFR < 90 mL/min/1.73 m²) had decreased long-term survival, thus emphasizing the need for definite evaluation of renal function. Improved identification of patient with mild renal impairment before LT could provide guidance for the choice of immunosuppressive regimen to further prevent CKD after LT. It is noteworthy that our results are based on eGFR at the time of evaluation for liver transplantation, therefore tailored regimen could be conveniently proposed at the time of evaluation. Calcineurin inhibitors sparing regimen, [38-40] and intensive management of CKD risks factors, [41] could be initiated earlier and be more efficient to reduce the prevalence of long-term chronic kidney disease. [42]

The use of CKD-EPI cystatin C equation in patients with cirrhosis may lead to overestimate the severity of renal disease in patients with normal renal function. [16] However, we think that, until better marker of GFR is routinely available, overestimation of renal disease is less harmful than its underestimation in candidates for LT.

In conclusion, we demonstrated that discrepancies between CKD-EPI cystatin C and creatinine - based equation are clinically relevant in patients with end-stage liver disease and that eGFR is predictive of long-term survival after liver transplantation if determined using the CKD-EPI cystatin C equation. This suggests that using cystatin C instead of creatinine to

assess renal function in LT candidates may allow for a more reliable detection of patients at risk who need optimized management before and after LT.

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Table 1 Characteristics of study population.

KDOQI stage was defined according to the CKD-EPI-Cystatin C equation. Ascites and encephalopathy stage were determined according to Child-Pugh score. Values are median (interquartile range) or n (%).

KDOQI, Kidney Disease Outcomes Quality Initiative; BMI, body mass index; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease.

	All population (N=682)	KDOQI 1 (N=144)	KDOQI 2 (N=294)	KDOQI 3 (N=199)	KDOQI 4-5 (N=45)
Sex (M/F)	506/176	111/33	231/63	135/64	29/16
Age (years)	55 [49-60]	54 [47-59]	54 [48-60]	56 [51-61]	56 [48-62]
Associated HCC	255(37.4%)	68(47.2%)	123(41.8%)	54(27.1%)	10[22.2%)
BMI	26.2[23.4-29.7]	25.9[23.2-29.3]	26.5[23.5-29.9]	25.9[23.4-29.7]	23.2[25.8-28.9]
Donor age (years)	49[36-62]	48[35-63]	50[37-63]	49[34-61]	48[39-62]
Donor BMI	24.3[21.9-27.5]	24.3[21.8-27.3]	24.2[21.9-27.1]	24.2[22.5-27.9]	24.9[21.9-27.6]
MELD score	13.5[8.3-19.2]	9.5[6-13.3]	12.9[7.9-17.7]	15.8[11.9-21.3]	20.5[16.6-24.4]
Meld score > 15	198(29%)	19(13.2%)	76(25.9%)	78(39.2%)	25(55.6%)
Encephalopathy					
Stage 1	562(83%)	121(84%)	256(86%)	152(76%)	33(73%)

Stage 2	103(15%)	20(14%)	33(11%)	41(21%)	9(20%)
Stage 3	16(2%)	3(2%)	5(2%)	5(3%)	3(7%)
Ascites					
Stage 1	361(53%)	96(67%)	185(63%)	75(38%)	5(11%)
Stage 2	164(24%)	26(18%)	67(23%)	56(28%)	15(33%)
Stage 3	156(23%)	22(15%)	42(14%)	67(34%)	25(55%)
Child score	8[5-10]	6[5-10]	7[5-10]	9[7-11]	9[8.8-11]
INR	1.57[1.26-2.03]	1.37[1.17-1.79]	1.53[1.26-2]	1.72[1.36-2.21]	1.83[1.36-2.08]
Creatinine (µmol/L)	74[63-85]	61[53-72]	71.5[63-79]	83[72-97]	142[112-165]
Cystatin C (mg/L)	0.99[0.85-1.20]	0.73[0.68-0.78]	0.95[0.9-1.02]	1.28[1.16-1.44]	2.31[2.04-2.62]
CKD-EPI-Cystatin C (ml/min)	68.9[53.1-85.3]	103.1[90.9-110.2]	73.6[67.3-80]	49.4[41.2-55.6]	23[18.4-26.8]
Na (mmol/L)	138[134-140]	138[135-140]	138[135-140]	137[133-140]	135 [132-137]
Cirrhosis etiology					
Alcohol	415(60.9%)	85(59%)	167(56.8%)	131(65.8%)	32(71.1%)
B hepatitis	27(4%)	11(7.6%)	11(3.7%)	4(2%)	1(2.2%)
C hepatitis	108(15.8%)	11(7.6%)	65(22.1%)	25(12.6%)	7(15.6%)
Others	132(19.3%)	37(25.8%)	51(17.4%)	39(19.6%)	5(11.1%)

Table 2 Cox regression analysis.

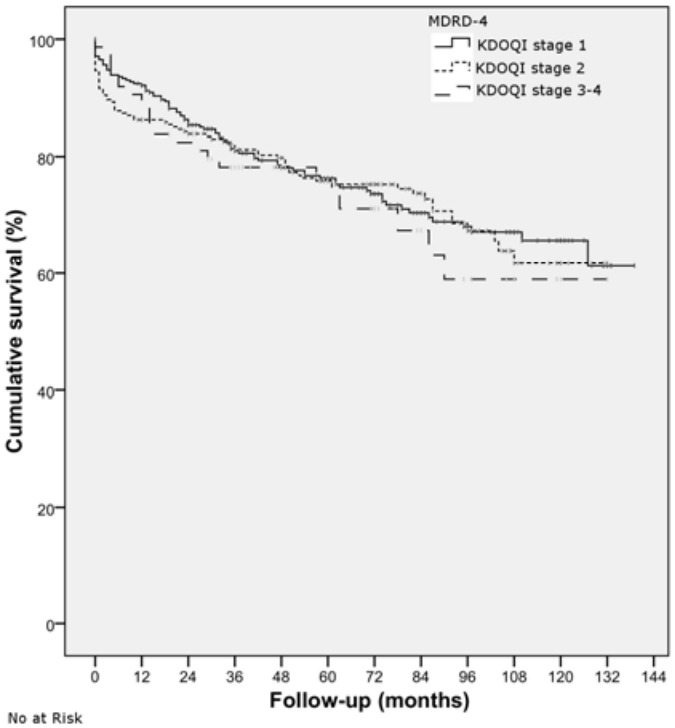
Cox regression analysis was performed with stratification according to the underlying liver disease. Ascites was quoted 1-2-3 according to Child-Pugh classification. Hepatocellular carcinoma was used as a nominal categorical variable. Hazard Ratio is in bold when significant.

	Hazard Ratio	*p*	*95 % Confidence Interval*
Recipient Age (years)	0.998	p=0.829	0.980-1.016
Donor Age (years)	0.994	p=0.158	0.985-1.002
Ascites	1.020	p=0.860	0.816-1.275
Albumin (g/L)	1.000	p=0.991	0.972-1.029
Prothrombin Index (%)	0.994	p=0.268	0.983-1.005
Serum Bilirubin (µmol/g)	1.000	p=0.886	0.998-1.002
Hepatocellular Carcinoma	0.738	p=0.101	0.514-1.061
CKD-EPI-CystC (ml/min/1.73m²)	**0.992**	**p=0.029**	**0.986-0.999**

FIGURE LEGENDS

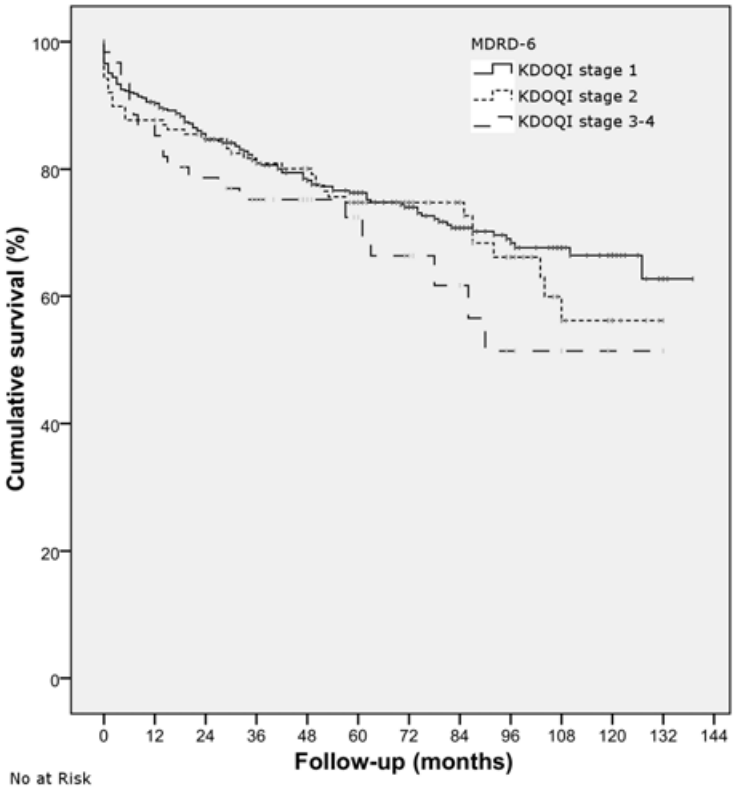
Figure 1: Kaplan-Meier survival curves of patients with liver transplantation according to their respective KDOQI stage. Panel (A): KDOQI stage using MDRD-4. **Panel (B):** KDOQI stage using MDRD-6 **Panel (C):** KDOQI stage using CKD-EPI creatinine-cystatin C **Panel (D):** KDOQI stage using CKD-EPI cystatin C.

KDOQI: Kidney Disease Outcomes Quality Initiative. CKD-EPI: chronic kidney disease epidemiology collaboration equation; MDRD-4: four-variable Modification of Diet in Renal Disease equation; MDRD-6: six-variable Modification of Diet in Renal Disease equation.



No at Risk

Stage 1	:342	314	271	214	184	158	129	98	79	61	38
Stage 2	:260	223	206	183	165	147	117	87	53	29	13
Stage 3-4	:73	66	59	49	39	33	26	16	12	8	2



No at Risk

Stage 1	:465	418	363	294	255	224	183	138	107	76	45
Stage 2	:137	120	114	102	93	79	61	44	25	15	7
Stage 3-4	:60	52	47	39	29	24	19	12	9	6	2