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A pocket guide to identify patients at risk for chronic kidney disease after liver transplantation

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Conflict of interest
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Summary

Chronic kidney disease (CKD) after liver transplantation (LT) has a strong impact on transplant and patient survival. After LT, a significant proportion of patients develop renal dysfunction with a high risk to progress to end-stage renal disease (ESRD). Because of the multifactorial nature of CKD in the post-transplant period, the ability to accurately identify patients at risk and the development of preventative strategies remain unsolved issues. In some patients, the pretransplant kidney function significantly declines within the first year post-LT. Until now, no user-friendly and reliable prediction scores exist to identify these patients early on. Data from 328 consecutive adult patients receiving their first LT between 2004 and 2008 at Hannover Medical School were analyzed to develop a prediction model using ordinal logistic regression. We developed a concise risk score identifying the five most important predictors and performed a temporal validation using a prospectively monitored patient cohort of 120 patients from our transplant center. Based on those five parameters, we developed a pocket guide card for clinical use that could be a useful tool for instant identification of patients at high risk as well as patients more suitable for combined liver and kidney transplantation (CLKT).

Introduction

After liver transplantation (LT), acute kidney injury (AKI), as well as post-transplant CKD (pTxCKD), is highly prevalent. The risk of end-stage renal disease (ESRD) requiring dialysis after LT varies, but reaches up to 5% per year in the post-transplant period [1]. The etiology of both is multifactorial with preoperative (pre-existing kidney-/liver disease), intra-/perioperative and postoperative (e.g. immunosuppression) factors playing a significant role. AKI and CKD are frequently seen in patients with end-stage liver disease and are of great prognostic relevance. As creatinine is one of the three parameters used to calculate the model for end-stage liver diseases (MELD), the main parameter for the urgency-based liver allocation in Germany as well as in many other regions worldwide, many patients that undergo LT start with an acute but frequently underestimated deterioration in renal function. The estimation of renal function before LT remains a major challenge. In case of a decreased liver function and reduced muscle mass, serum creatinine (CREA) can be in the "normal range". Measurements of creatinine clearance can be falsely elevated as tubular secretion of creatinine is increased in patients with liver disease, and ascites can lead to overestimation of GFR as significant amounts of marker substances (such as creatinine) can diffuse into the ascites yielding lowered serum concentrations. In comparison with CREA, cystatin C seems to be a better marker especially in patients with only mild-to-moderate kidney disease as the cystatin C concentration is only minimally affected by decompensated cirrhosis. A iodthalamate clearance is the only valid and clinically applicable method to evaluate true excretory kidney function in patients with severe liver disease [2]; however, this method cannot be used routinely. It is likely that the true prevalence of renal disease is underestimated in patients on the waiting list for a liver transplant as most published studies used CREA levels for diagnosis.

Five years after LT, impaired renal function can be documented in up to 70% of the patients, with a GFR <60 ml/min/1.73 m^2 [3]. So far the identified risk factors include hepatitis C, age of the recipient, female gender, diabetes, hypertension, pre-existing proteinuria, and a reduced GFR prior to or 6–12 months after transplantation. Most of these factors cannot be actively influenced, but in patients with pre-existing CKD, many centers have success by lowering target levels of nephrotoxic immunosuppressive drugs. A switch from calcineurin inhibitors (CNIs) to mTor inhibitors or mycophenolate mofetil (MMF) leads to an improvement of renal function in a variety of patients [4–7]. However, according to histopathological studies, the spectrum of renal lesions after LT is broad and only a subgroup of patients had evidence of CNI toxicity, while diabetic and hypertensive nephropathy seems to be more prevalent. [8–10]. Unfortunately, the referral to a nephrologist is often delayed in this patient population, and nephrologists are only consulted in the late phase, after being on the waiting list, when kidney function has already significantly declined or dialysis is required. At these stages, a clarifying kidney biopsy might put the patients under a too high bleeding risk and can also pose a technical challenge. To improve this situation, we have to identify patients at risk as early as possible. To accomplish this, we aimed to develop a way to determine a risk prediction score in order to categorize patients into high and low risk groups for the development of CKD stages 3, 4, or worse that is easily applied in a consulting situation. We used retrospective data from a patient cohort transplanted at Hannover Medical School between 2004 and 2008 to develop the model and identify the most important factors influencing a likely decline in kidney function after LT. We used a prospectively monitored patient cohort as part of the renal comorbidity after solid organ transplantation (RECAST) program [1] to validate the model and created risk score tables in a pocket guide format to categorize patients according to their risk profile.

Patients and methods

Study population

In the retrospective cohort study, we analyzed all consecutive adult patients who underwent a first LT due to chronic liver disease between January 1, 2004 and May 1, 2008 at Hannover Medical School. Patients with a combined liver–kidney transplantation and patients on chronic hemodialysis before LT as well as high urgency transplantations due to fulminant hepatic failure (without a prior hepatopathy) were excluded from the analysis. The pretransplant GFR assessment in this population was performed at least 4 weeks before transplantation to exclude acute deterioration of kidney function. In the prospective validation cohort, we used adult patients who underwent LT between 2008 and 2012 as part of the RECAST program at Hannover Medical School. Patient demographics are described in Tables 1 and 2.

Outcomes

The outcome for this study was CKD stage according to *Kidney Disease: Improving Global Outcomes* [11]. The selected thresholds were CKD stage 3 (defined as estimated GFR between 60 and 30 ml/min/1.73 m^2) and stage 4 (defined as estimated GFR between 30 and 15 ml/min/1.73 m^2), or worse. For cluster analysis, k-means clustering analyses were performed, and several clusters were combined according to their pattern of GFR course.

Table 1. Recipient and graft characteristics of the study cohort (n = 328).

	230 patients included in analysis for year 1	182 patients included in analysis for year 3
Demographics		
Age (years, mean ±SD)	47.5 ± 11.7	47.3 ± 11.4
Gender, male (%, *n*)	60 (139)	60 (109)
Etiology of liver disease (%, *n*)		
Alcoholic cirrhosis	18 (41)	18 (32)
Primary Sclerosing Cholangitis	18 (41)	18 (33)
Hepatitis C	16 (36)	14 (25)
Hepatitis B	11 (26)	10 (18)
Hepatocellular Carcinoma*	17 (39)	14 (26)
Primary Biliary Cirrhosis	6 (13)	7 (12)
AIH	7 (15)	8 (14)
Liver cysts	4 (9)	4 (7)
others†	17 (40)	19 (35)
Pretransplant renal insufficiency/risk factors		
Diabetes prior LT (%, *n*)	14 (33)	19 (35)
Arterial Hypertension prior LT (%, *n*)	17 (40)	16 (30)
Proteinuria (reagent strip) (%, *n*)	7 (15)	5 (9)
Need for hemodialysis prior LT (%, *n*)	3 (6)	1 (2)
CKD stage ≤4 prior LT (%, *n*)	98 (225)	98 (179)
CKD stage ≤3 prior LT (%, *n*)	90 (207)	92 (167)
Graft/perioperative parameters		
Time on ICU following LT (days, mean ±SD)	19.5 ± 24.5	19.1 ± 23.8
Biochemistry prior transplantation		
Estimated GFR (ml/min/1.73 m²)	71.2 ± 31.9	70.1 ± 30.5
Bilirubin (μmol/l)	76.8 ± 116.2	82.5 ± 124.0
INR (ratio)	1.43 ± 0.44	1.39 ± 0.40
Cholinesterase (kU/l)	3.8 ± 2.1	3.9 ± 2.2
Sodium (mmol/l)	136.9 ± 4.8	136.5 ± 5.0

AIH, autoimmune hepatitis; HCC; hepatocellular carcinoma.
*Primary HCC in nine patients. Secondary HCC in patients with Hepatitis C (19), Hepatitis B (16), alcoholic cirrhosis (11), NASH (3), adenomatosis (2), hemochromatosis (2).
†Others: Wilson disease, amyloidosis, Osler disease, adenomatosis, chronic cholangitis following Kasai operation due to biliary atresia, glycogenosis, Caroli's syndrome, portal vein thrombosis due to prothrombin mutation, focal nodular hyperplasia, porphyria, congenital bile duct hypoplasia, congenital liver fibrosis, alpha1-antitrypsin deficiency, cystic fibrosis, nonalcoholic steatohepatitis, protein-C/S-deficiency, liver metastases from neuroendocrine tumors, hemosiderosis, liver congestion.

Predictors and missing data

The following data were obtained from the patients' medical records:

1. Epidemiological and clinical data: recipient age, recipient sex, etiology of liver disease, diabetes mellitus prior LT, arterial hypertension prior LT (defined as >140/90 mmHg), acute or temporary need for hemodialysis prior LT, time on intensive care unit following transplantation.

2. Pretransplant recipient laboratory data: urine protein (assessed by dip stick positivity as present or absent), serum bilirubine, international normalized ratio (INR), serum choline esterasis, serum sodium.

Creatinine-based formulas to calculate glomerular filtration rate tend to overestimate the renal function in patients with liver disease. In our patient cohort, using a cystatin C-based formula as reference [12], we calculated regression of differences in means from the four variables using modification of diet in renal disease formula [13]. Through this we saw an overestimation of GFR by 30 ml/min/1.73 m² for pretransplant values, by 7 ml/min/1.73 m² at 1 year after transplantation, and by 2 ml/min/1.73 m² at 3 years after transplantation creatinine-based formulas. Therefore, if available, we preferred estimation of glomerular filtration rate applying a cystatin C-based formula.

Otherwise, we adjusted the MDRD-based eGFR values accordingly. In brief, 30 ml/min/1.73 m² was subtracted from the MDRD-based eGFR for the pretransplant values; at 1 year, 7 ml/min/1.73 m² was subtracted; at 3 years, 2 ml/min/1.73 m² was added. GFR estimates above 150 ml/min/1.73 m² got truncated at this threshold. Records with eGFR below zero were dropped. This procedure affected 3 to 11 percent of the data points [for the 1 year cohort, 25 values at baseline (11%), after 1 year 16 values (7%) and for the 3 year cohort at baseline 15 values (9%) and after 3 years 6 values (3%)]. For clinical use of the developed score table, the serum cystatin C levels have to be used.

Stage of CKD was calculated according to KDIGO [11]. GFR and associated CKD at baseline and at the time of evaluation were mandatory for inclusion in the analysis. For the remaining missing variables, multiple imputation was used. At 1 year, 20 from 5980 data points (3%) had to be imputed. 6% of urine protein (13 out of 230) and 2% of sodium (4 out of 230) were the variables with some missing data, INR, add-on MMF, and add on Sirolimus in one case each. At 3 years, imputation was necessary for 12 of 4732 data points (3%), with 10 of 182 (5%) for urine protein, 2 of 182 for sodium (1%).

Model development

At the beginning, we developed four different full models to predict renal function at either 1 or 3 years after LT using predictors available either before transplantation or both before and immediately after transplantation. We performed proportional odds logistic regression

Table 2. Recipient and graft characteristics of the validation (renal comorbidity after solid organ transplantation) cohort (n = 120).

	120 patients
Demographics	
Age (years, mean ±SD)	51.7 ± 10.6
Gender, male (%, *n*)	66 (79)
Etiology of liver disease (%, *n*)	
Primary sclerosing cholangitis	15 (18)
Hepatitis C	18 (21)
Pretransplant renal insufficiency/risk factors	
Diabetes prior LT (%, *n*)	17 (20)
Proteinuria (reagent strip) (%, *n*)	15 (16)
CKD stage ≤4 prior LT (%, *n*)	89 (107)
CKD stage ≤3 prior LT (%, *n*)	75 (90)
Graft/perioperative parameters	
Time on ICU following LT (days, mean ±SD)	19.3 ± 23.6
Biochemistry prior transplantation	
Estimated GFR (ml/min/1.73 m²)	65.4 ± 36.0
Creatinine (μmol/l)	87.4 ± 44.2

analysis separately for all models. The proportionally assumption was reasonable for the considered predictors. Potential nonlinearity in continuous variables and interactions between predictors were carefully assessed. Penalized maximum likelihood estimation was applied to shrink the models' regression parameters for over optimism. We used the R software (version 2.15.2; R Foundation for Statistical Computing, Vienna, Austria) with the packages GGPLOT2, METHCOMP, MFUZZ, PROC, and RMS [14–16]

Assessment of discrimination and internal validation

Overall discrimination was assessed by the c statistic [which is equivalent to the area under the curve (AUC) statistic]. Calibration was assessed by a graph for observations against predictions as well as the intercept and slope of the regression line. For internal validation, we used bootstrapping to correct for over optimism regarding performance measures.

Model simplification and presentation

The full models contained 20–22 predictors which were thought to be too cumbersome to use in clinical practice. For model simplification, the approach by Harrell [17] was applied that included a modified fast backward variable selection and led to a ranking of the variables. We aimed to develop models with a maximum of seven predictors, following closely the ranking mentioned above. As a further attempt for model simplification, we aimed to develop a score chart using a traffic light approach for identification of a patient's risk.

External (temporal) validation

For external validation of the model, we used 120 patients from an independent cohort that was transplanted in our center after 2008 that were prospectively followed as part of the RECAST program. Patient demographics are described in Table 2. Compared to the development cohort, the validation cohort was significantly older, included more patients with proteinuria and less patient with a CKD stage of 3 or less and stage 4 or less.

Results

Development of kidney function after LT is variable over time

During the study period, 328 eligible patients received a first LT in our center. For inclusion in our analysis, the outcome variable CKD stage (derived from GFR) had to be available, thus the number of patients included in our analysis was 230 at year 1 after LT and 182 at year 3 after LT. Patient characteristics are displayed in Table 1. The kidney function of patients before LT and the development of kidney function at year 1 and year 3 after transplantation are depicted according to the CKD stage (Fig. 1a). We observed in the study population a very inhomogeneous course of kidney function development. Before LT, 23% of the study population started with a normal kidney function CKD stage 1, while 37% were in CKD stage 2, 31% CKD stage 3, 7% CKD stage 4, and 2% CKD stage 5 (Fig. 1a). As expected, kidney function declined in year 1 after LT. A decline in kidney function could be documented in 40% of the study population, leading to an increase CKD stage 3 by 11% CKD stage 4 by 3% and CKD stage 5 by 2%. This indicates an incidence of ESRD of 3.6% in the first year after LT (Fig. 1a). This distribution changed to year 3. As expected, the rate of patients requiring renal replacement therapy increased from 3.6% in year 1 to 4.2% in year 3; however, surprisingly there was a decline in CKD stage 4 by 5% and in stage 3 by 11% indicating that between year 1 and year 3 some patients experienced an improvement in kidney function. To analyze this phenomenon in more detail, we performed a k-means clustering analyses and combined several clusters according to their pattern of GFR course. Indeed, when we group patients according to their GFR development over the 3 years, we identified three different patterns: one group experienced a significant decline in their kidney function in year 1 after transplantation followed by a partial improvement at year 3 (Fig. 1b, pattern 1, n = 32); a second group showed an improvement of kidney function over the course of 3 years (Fig. 1b, pattern 2, n = 50); and another group with a V-shaped decline in year 1 and a significant improvement by year 3 (Fig. 1b, pattern 3, n = 78). All patients in the analyzed cohort received a

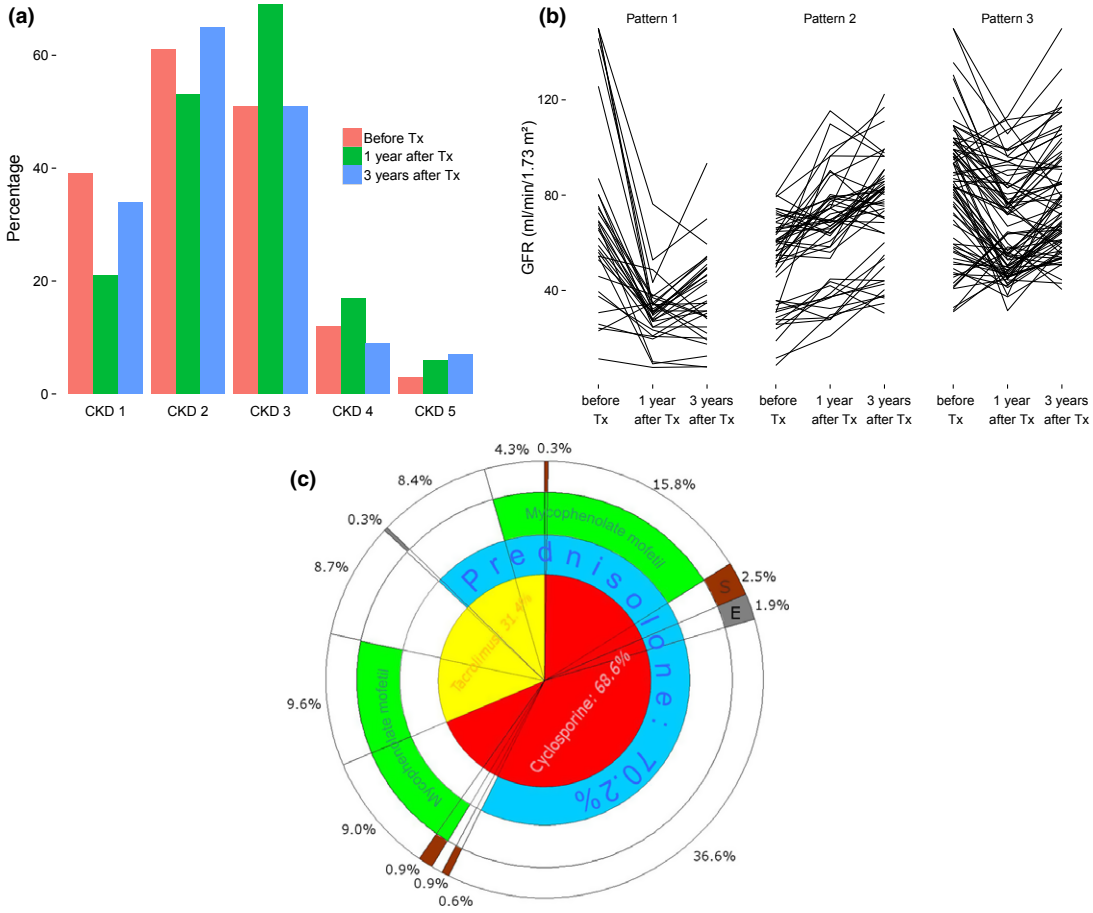

Figure 1 Changes in kidney function in the study population over time. (a) Kidney function in the study cohort according to CKD stage before (red) at 1 year (green) and at 3 years after transplantation (blue). (b) Variety of patterns of kidney function development in the study cohort. (c) Primary immunosuppression in the study cohort. All patients received a CNI, either tacolimus (yellow), or cyclosporine (red). Additionally, they received prednisolone (blue) and/or MMF (green) and/or an mTOR inhibitor [Sirolimus (brown) or Everolimus (gray)]. % refers to patients on the specified regimen. See text for details on target through levels.

CNI-based immunosuppression plus prednisolone and/or MMF and/or an mTOR inhibitor (Fig. 1c). The target trough levels for CNI were 8–10 μg/l for Tacrolimus and 160–200 μg/l for Cyclosporine in year 1, depending on etiology of liver disease, comorbidities and comedications. Levels were reduced to a maintenance level of 5–7 μg/l for Tacrolimus and 100–120 μg/l for Cyclosporinin year 3 after transplantation.

Development of full prediction models

All variables were used for proportional odds logistic regression analysis to identify predictors. We did not detect relevant departures from the linearity assumption for continuous predictors. The impact of potential interactions between predictors was negligible. Depending on the specific multivariable model, we identified several protective predictors (criterion $P < 0.1$): younger age at LT, higher GFR before LT, or primary sclerosing cholangitis as underlying disease. Predictors associated with a negative outcome were diabetes mellitus, hepatitis C, extended stay on ICU post-LT.

Discrimination (as indicated by the C statistic, an equivalent to the area under the curve [AUC] of receiver operator characteristic-[ROC]-curves) was in the range between 0.71 and 0.77 and thus considered as fair. Using variables available before transplantation, the AUCs for CKD stage 3 or worse were 0.77 and for CKD stage 4 or worse were 0.77 and 0.79 at 1 year after LT (Fig. 2a) and 0.79 and 0.84 at 3 years after LT (Fig. 2b). Adding perioperative variables (namely time in ICU and hemodialysis after transplantation), AUC increased to 0.81 (CKD stage 3 or worse) (Fig. 2c) and 0.84 (CKD stage 4 or worse) at 1 year after transplantation and 0.83 and 0.86 at 3 years after LT (Fig. 2d).

The calibration plots indicated an adequate fit for CKD stage 3 or worse with a good concordance of predicted and

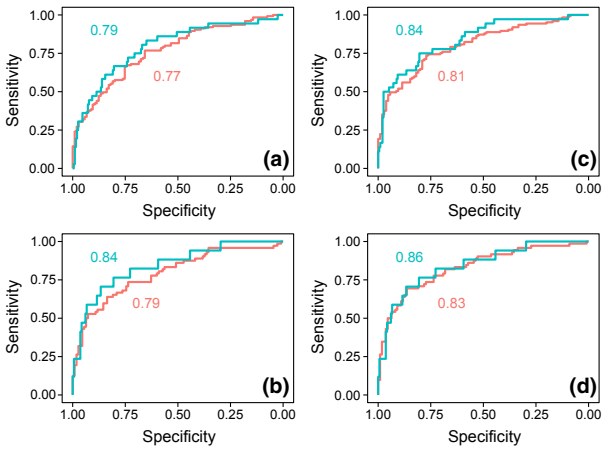

Figure 2 Performance of the full model to predict CKD 3 and 4. (a) Receiver operating characteristic curves for the full model indicate AUCs to predict CKD3 and for CKD 4 using preoperative variables at 1 year (a) (CI: CKD 3 0.7049–0.8258; CKD 4 0.7089–0.879), 3 years (b) (CI: CKD3 0.7247–0.8624; CKD4 0.7391–0.9465) and perioperative variables at 1 year (c) (CI: CKD3 0.7498–0.8609; CKD4 0.7668–0.9137) and 3 year (d) (CI: CKD3 0.7682–0.8932; CKD4 0.7746–0.9467).

Figure 3 Importance plot. Ordinal logistic regression models for CKD at 1 and 3 years after liver transplantation including perioperative variables (peri) or preoperative variables (pre) were developed. Importance was determined by the Wald statistic (chi-squared) minus the degrees of freedom of the respective variable.

observed probabilities (calibration-in-the-large −0.03, calibration slope 1.08); for CKD stage 4 or worse, calibration was less ideal with a trend toward underestimation using the model (calibration-in-the-large 0.17, calibration slope 1.08) (data not shown). As it is not practical for a clinician to consider all variables of the above mentioned full models, we tried to develop a short model. For the short model, we wanted to identify the most important variables. To accomplish this we investigated the importance of each variable in the different models.

The importance of the top predictors in the various models and development of a simplified model

To determine the importance of the variables in the model, we used the Wald statistic (chi-squared) minus the degrees of freedom of the respective variable. Using this approach, we found that the importance of the variables differs between the models. We found that GFR before transplantation is a very important variable in all models. In contrast, ICU time has a significant influence on CKD stage at 1 year after transplantation; however, its impact is less on the CKD stage after 3 years (Fig. 3).

We determined that for the development of a simplified model to predict CKD using only preoperative variables, we would have to use the following variables for prediction of CKD: GFR before transplantation, age and a diagnosis of diabetes, hepatitis C, and primary sclerosing cholangitis (PSC) (Fig. 3). The simplified models yielded a near similar prediction as the full models ($R^2 = 0.93$). As expected, when we used only these five variables, AUCs diminished from 0.765 to 0.739 for prediction of CKD 3 and from 0.794 to 0.774 for CKD4 (Fig. 4a).

To investigate how well our model can predict CKD development, we performed an external validation using an independent set of patients transplanted subsequently at Hannover Medical School between 2008 and 2012 that was prospectively monitored as part of the RECAST program [1] (for patient characteristic of the five used variables see Table 2). As expected, this led to a further decrease in AUCs to 0.716 for CKD3 and more markedly to 0.639 for CKD4 (Fig. 4b).

Development of a risk score table and pocket guide

For practical use by the clinician, we generated a color-coded table that enables us to identify the patients at risk for the development of CKD 3 and 4 by simply inputting the available information at initial assessment. The age of the patient (in years) at the time point of the visit is subtracted from the GFR (in ml/min/1.73 m^2) before LT. It is important to note that the risk score calculation is different in patients without a diagnosis of PSC (Fig. 5, left panel) versus patients transplanted due to PSC (Fig. 5, right panel) and changes with the presence or absence of diabetes mellitus and hepatitis C. Thresholds for the risk score were determined considering the principles that a high sensitivity stands for a low predicted risk, while a high specificity stands for a high predicted risk (sometimes the mnemonics "SnNout" and "SpPin" are used to describe this relationship). We aimed at 80–90% for both sensitivity and specificity. As there is always a trade-off for these related

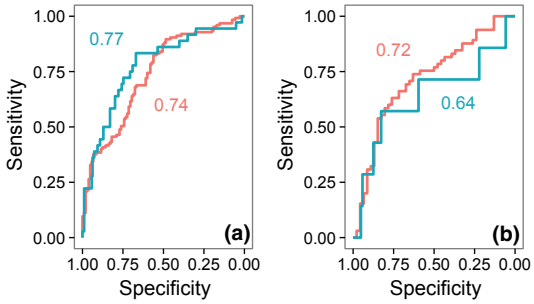

Figure 4 Performance of the simplified model to predict CKD 3 and 4. (a) Receiver operating characteristic curves for the simplified model indicate AUCs to predict CKD3 (red) and for CKD 4 (blue) at 1 year using preoperative variables [CKD 3 = 0.74 (CI: 0.6753–0.8031); CKD 4 = 0.77 (CI: 0.6841–0.8637)]. (b) Receiver operating characteristic curves after temporal validation for the simplified model AUCs to predict CKD3 (red) and for CKD 4 (blue) at 1 year using preoperative variables (CKD 3 0.72 (CI: 0.6173–0.8141); CKD 4 0.64 (CI: 0.3655–0.9119).

measures, different thresholds are necessary. A "green" score means the patient is in the low risk group (risk score −4 or less, sensitivity in the validation cohort 82%. A green patient has a risk of 27% to develop CKD stage 3 or worse at 1 year after transplantation. If a patient scores in the yellow area, the risk is 60%. If a patient scores within the red area, this patient has a 78% risk to develop CKD stage 3 or higher at 1 year after transplantation (risk score 1 or above, specificity in validation cohort 85%). The risk to develop CKD stage 4 in the bright red area is 14%) (Fig. 5). The dark red area represents scores predicting CKD stage 4 or worse with a specificity of 93% (validation cohort). The risk to develop CKD stage 4 is 75%.

Discussion

The long-term survival of the native kidney function in patients after LT is critical, as CKD is a frequent problem

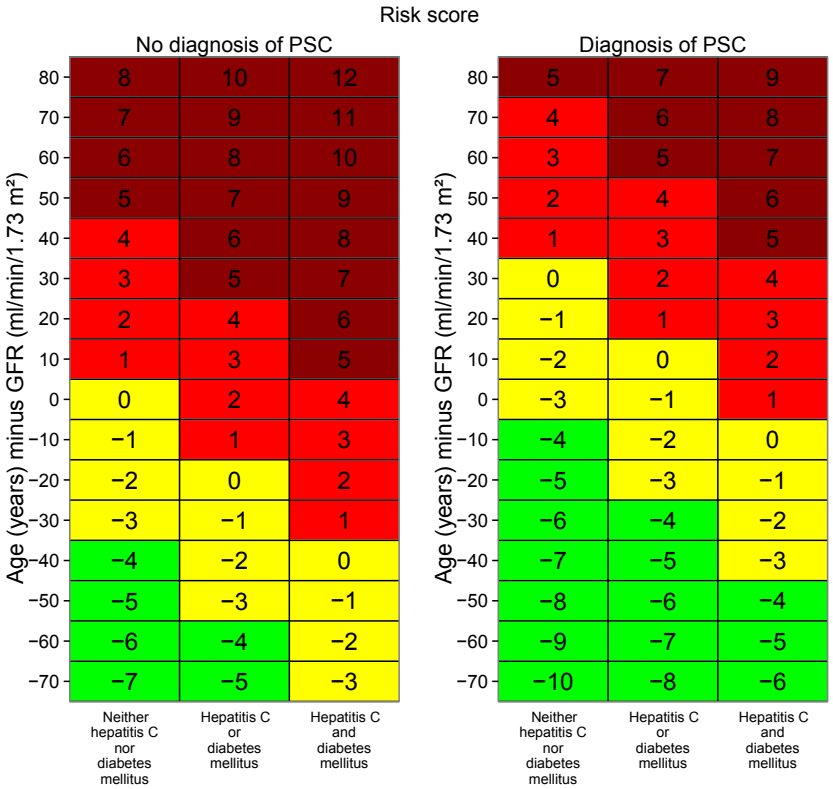

Figure 5 Risk score to predict probability for CKD stage 3 or worse at 1 year after transplantation. Age (in years) at the timepoint of liver transplantation is subtracted from cystatin C-based GFR (ml/min/1.73 m^2) before liver transplantation. Risk score is different in patients without a diagnosis of PSC (left panel) versus the group that was transplanted due to PSC (right panel) and changes with the presence or absence of diabetes mellitus and hepatitis C. If a patient has a score within the red area (score: 1–4), this patient has a high risk (78%) to develop CKD stage 3 or higher after 1 year after transplantation (Specificity in validation cohort 85%). A "green" score (−4 to −10) means the patient is in the low risk group (27%) to develop CKD stage 3 or higher after 1 year after transplantation (Sensitivity in the validation cohort 85%). A "dark red" score (5 and above) means the patient has a high risk (75%) to develop CKD Stage 4 or higher 1 year after transplantation.

after transplantation and has a significant impact on morbidity and mortality, especially in the MELD-era [18]. Nephrologists are frequently asked to consult with patients awaiting a liver transplant, and sometimes decisions are currently derived more by the clinician's experience rather than from scientific data. Importantly, the need for a valid prediction system is reinforced as the option for a combined kidney–liver transplantation has to be evaluated before LT.

The purpose of this study was to identify preoperative risk factors for advanced CKD following LT and to develop a simple clinically useful risk determination system that helps to identify patients at risk during the consult visit. To accomplish this, we analyzed first a cohort that was transplanted in our center between 2004 and 2008. The first surprising finding was that the number of patients developing CKD stage 3 went up in the first year after transplantation but then significantly declined in the third year after transplantation, which was not explained by the numbers of patients progressing to more advanced stages. Instead, we detected a higher number of patients in CKD stage 1 and 2 in the third year after transplantation indicating that in some patients the kidney function had recovered. Nevertheless, we detected an increasing rate of patients reaching CKD stage 5 after 3 year post-liver transplantation (Fig. 1a). Based on this finding, we used a pattern recognition algorithm and indeed we could detect three different patient groups. One group with a significant decline in their kidney function in year 1 after transplantation followed by a partial improvement at year 3 one group with a V-shaped course and a group that started with bad kidney function and showed an improvement of kidney function over the course of 3 years (Fig. 1b). This unusual course of CKD stage development already indicates how difficult it can be to predict CKD stage 3 or 4 one or 3 years after LT. To develop a prediction model, we first used all available variables for proportional odds logistic regression analysis. The model performance was fair for the 1 year and the 3 year prediction models with AUC of 0.71 and 0.74, respectively. This is, considering the above mentioned population, already very promising, however, it would not be of practical use by physician as not all of these parameters would be available immediately at the time of consult. This is similar to other prognostic models that were recently published [19] but would require computational analysis. Therefore, we were trying to identify the most important preoperative factors to develop a simplified model. We found in our cohort that GFR before transplantation, age and a diagnosis of diabetes, hepatitis C, and PSC are the most important variables for prediction of CKD. While GFR at baseline, age, diabetes, and hepatitis C have been identified previously as important risk factors that influence the prognosis, we identified the diagnosis of PSC as the primary indication for LT as an independent protective factor for the development of CKD after LT. This cannot only be due to the younger age or higher pretransplant GFR of these patients as in multivariate analysis age, GFR, and PSC all turned out as independent risk factors. However, in contrast to most of the other large indication groups for LT (viral hepatitis, alcoholic cirrhosis), PSC is not a parenchymatous but a cholestatic disease. Hence, the pathophysiological mechanisms that lead to renal failure in end-stage liver disease (hepatorenal syndrome) are usually milder or even absent in PSC. Most patients with PSC are not transplanted because of cirrhosis with portal hypertension or chronic liver failure but for biliary complications such as recurrent septic cholangitis, untreatable pruritus or hilar or intrahepatic dominant strictures that are suspicious of malignancy. They only rarely develop biliary cirrhosis with its typical complications and are therefore transplanted with much lower MELD scores, when they qualify for a standard exceptional MELD [20,21].

When we compared the full models to the simplified model, we found that it made very little difference to the AUCs (prediction of CKD 3 declined from 0.765 to 0.739 for CKD4 from 0.794 to 0.774). To validate this, we used a different cohort that we had prospectively monitored between 2008 and 2012. As expected, this led to a further decrease in AUCs to 0.716 for CKD3 and 0.639 for CKD4. Nevertheless, considering that all we imputed into the model were only five clinical parameters we still consider this a very solid result. The pocket guide score table that we developed will enable the clinician to identify patients at risk immediately at the time of consult. We are convinced that this simplified prediction system is a helpful tool in developing preventative strategies, as the patients at risk are the population that would benefit most from perioperative renal protection measures and early CNI dose adjustments or withdrawal and conversion to non-nephrotoxic immunosuppressants such as mTor inhibitors. As mTor inhibition is now an accepted treatment regimen, this pocket guide could assist in decision-making and further improve the treatment outcomes in terms of native kidney function [22,23].

We recommend a mandatory nephrologist's consult for all patients that score in the yellow and red areas of the score card. In those patients, a kidney biopsy might lead to important additional information. In addition, the option for a combined kidney–liver transplantation has to be evaluated and discussed with the nephrologists before LT. So far the only clear definition to list a patient for a combined transplantation is a prolonged dialysis period in the pretransplant setting. This is a disadvantage as kidney replacement therapy might be necessary immediately after, within the first year after transplantation or both. If kidney func-

tion does not recover, the patient has to be listed for a kidney transplant later. Those patients are especially at risk as they now have to use other renal replacement therapy options until they receive a kidney transplant and waiting times can be many years, if no living donor is available. Therefore, we suggest to consider patients in the dark red area of the score card for the option for a combined kidney–liver transplantation. The transplantations should be performed sequentially with the option for a kidney transplantation offered in the year after the successful LT. Eurotransplant gives the option to list patients for both and delay the kidney transplant. These patients receive 500 bonus points between 87 and 365 days after LT. This option has several advantages compared to the simultaneous procedure. The patient's hemodynamics and coagulopathy have stabilized, the procedure is less complex and physicians can observe the course of kidney disease over time, and re-evaluate if the patient is still a candidate for kidney transplantation after liver function has recovered. Our study has two limitations: We used for validation a prospective unrelated patient population which is a valid approach for external (temporal) validation, but it is still a single center study and GFR was estimated based on cystatin C rather than measured. Therefore, a multicenter study is in preparation to validate the score card precision.

Authorship

TJW, CL, CPS, HS, JK, MPM, HH and MS: designed the study. TJW, MS, CL, EE and FL: collected data. TJW, CL and MS: analyzed the data and wrote the paper.

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