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INVITED COMMENTARY

Liver transplant and kidney disease: the scope of the problem

Isabelle Binet

Nephrology and Transplantation Medicine, Kantonsspital St Gallen, St Gallen, Switzerland

Correspondence
Dr. med. Isabelle Binet, Nephrologie/ Transplantationsmedizin, Kantonsspital St Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland
Tel.: +41 71 4941031;
fax: +41 71 4942877;
e-mail: isabelle.binet@kssg.ch

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Kidney disease is increasingly recognized as a crucial determinant for outcome in nonrenal solid organ transplant recipients. Severe or end-stage chronic kidney disease (CKD) is expected in 10–30% of nonkidney recipients, but even nonsevere CKD needs to be taken into account and may occur in up to 70%. Acute kidney injury (AKI) episodes as well as CKD contribute directly and indirectly to substantial morbidity and mortality, not the least because CKD is a strong independent cardiovascular risk factor.

The multiple conditions which represent risk factors for CKD are often to be found in liver transplant candidates: pretransplant CKD, diabetes, hypertension, hepatitis C, and age among others. Glomerulonephritis associated with the liver disease may also occur. With access to liver transplantation into higher age and despite larger comorbidities, CKD impacts the post-transplant outcome in an increasing number of recipients. The issue is furthermore of importance for those surviving the longest, that is, in liver recipients who underwent a pediatric transplantation [1].

'Spare the nephron' was a popular concept for liver recipients in the early 2000s. It was mostly directed at calcineurin inhibitor sparring protocols. However, the experience shows that the issue is a lot more complex, goes beyond immunosuppression alone and needs to be addressed at an early stage in the pretransplant phase. In this regard, an approach to try and identify liver candidates with a relevant renal risk is extremely valuable. This is especially true considering the risk of developing CKD stage 4 with an eGFR <30 ml/min/1.73 m^2 reaches 75% for those at highest risk [2].

What are the issues?

The first issue is the correct diagnosis of CKD and of the degree of kidney impairment in liver candidates.

The importance of kidney function in liver candidates is well recognized as illustrated by the MELD score. The MELD score incorporates creatinine as one of its 4 criteria to direct liver allocation and thus acknowledges the importance of kidney function for the urgency of receiving a transplant. Unfortunately, creatinine per se is a poor marker of kidney function and this is especially true in end-stage liver disease. Estimated glomerular filtration rate (eGFR) is a more appropriate way to deal with the degree of kidney function impairment; however, the currently used formula has also been shown to overestimate kidney

function in cirrhotic patients. None of formulas have been validated for end-stage liver disease, and furthermore, liver candidates often display muscle wasting, poor nutritional status with low-protein diet, reduced physical activity, and an expanded extracellular volume which participates to body weight.

As the study by Weismüller rightly points out creatinine based eGFR is far from adequate for liver candidates [2] . Indeed, in the last 10 years, a substantial body of evidence emerged to point at cystatin C as a better marker of kidney function in liver patients [3]. Cystatin is a protein generated at a constant rate by all body cells and freely filtered by the glomeruli and then catabolized by the tubular epithelial cells. There is no indication of hepatic elimination of cystatin C, and its serum concentration is independent of the splanchnic blood flow which makes it an interesting renal marker in end-stage liver disease [4]. In their publication, Weismüller *et al.* [2] chose to use one of the various cystatin C formulas available to compare a cystatin-eGFR to the MDRD-eGFR and correct for the GFR overestimation accordingly. As this is the basis for the risk prediction score developed in the study, a further validation using either different formulas or the increasingly popular combined creatinine–cystatin CKD-EPI formula is needed to confirm the results [5]. Very recently, Allen *et al.* [6] showed that the combined creatinine–cystatin CKD-EPI formula performed best against the gold standard of iothalamate clearance in liver recipients after transplantation; this formula was also predictive of mortality.

The second issue is identifying the liver candidates with such structural or residual damage to their kidney that a combined liver–kidney transplant will be needed.

No kidney should be wasted for a recipient who does not need it or will recover kidney function after a successful liver transplantation. On the other hand and across all solid organs, it is known that nonrenal recipients fare poorly with advanced CKD or on dialysis. The Weismüller publication [2] does not give us a straight answer but provides a tool to identify those most at risk to develop CKD stages 3, 4, and 5 at 3 years post-liver-transplant based on a bedside-friendly score including age, MDRD-eGFR, diabetes, hepatitis C, and primary sclerosing cholangitis. The limit of this model is that it is based on a single-center cohort and that the validation used patients from the same center. If, however, the model could be validated in another cohort, then this would represent a strong point to use the score for interventional studies and decision making, including when to perform a kidney biopsy in liver candidates.

The pretransplant risk evaluation is crucial if a strategy of combined transplantation is considered and if immunosuppression needs to be tailored from the start of transplantation. In contrast, the various publications which correlate risk of advanced CKD from post-transplant factors identify patients a posteriori. Indications for combined liver–kidney transplantation may be straightforward in primary hyperoxaluria type 1 or in certain cases of polycystic liver and kidney disease. However, it becomes urgent to develop an algorithm for decision making 'liver alone' versus 'combined liver–kidney' in the more common situations of liver failure with hepatorenal syndrome and the more and more frequent end-stage liver disease with diabetic, vascular hypertensive nephropathy or in case of chronic glomerulonephritis.

A different attempt to predict post-transplant CKD worsening with noninvasive methods applied to liver transplant candidates such as proteome analysis failed so far to identify a reliable pattern [7].

What lessons did we learn?

The study by Weismüller [2] points out to three important lessons.

Data from transplant recipients gathered in a structured manner in a cohort allow longitudinal analysis and the development of such prediction models. Collaboration with biostatisticians and epidemiologists can amplify the value of cohort data beyond descriptive analysis. This is the basis for strategies and interventions to optimize outcome of the recipient and of the donated organs.

Similar to KDIGO, outcome prediction models can be depicted in a user-friendly manner with color grids which can easily identify patients at risk and be used at the bedside for information and decision making together with the patients.

Considering the prevalence and the impact of CKD on liver transplant outcome, an intensified collaboration between liver transplant specialists and nephrologists is mandatory in liver transplant programs. This collaboration should start before wait-listing of the liver candidate and continue over the long-term post-transplant follow-up.

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