Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Chronic kidney disease and associated mortality after liver transplantation – A time-dependent analysis using measured glomerular filtration rate

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Background & Aims: The accuracy of creatinine-based estimated GFR (eGFR) in assessing the prevalence of chronic kidney disease (CKD) and associated mortality after liver transplantation (LTx) is unknown. Using measured GFR (mGFR) by iothalamate clearance, we determined the prevalence of the entire spectrum of renal dysfunction and the impact of CKD on mortality after LTx.

Methods: A database that prospectively tracks all LTx recipients at this academic transplant program from 1985 to 2012 was queried to identify all adult primary LTx recipients. Our post-LTx protocol incorporates GFR measurement by iothalamate clearance at regular intervals. A multistate model was used to assess the prevalence of CKD, kidney transplant, and death after LTx. Time-dependent Cox regression analysis was performed to evaluate the impact of mGFR and eGFR changes on survival.

Results: A total of 1211 transplant recipients were included. At the time of LTx, the median age was 54 years, 60% were male and 86% were Caucasian. At 25 years after LTx, 54% of patients died, 9% underwent kidney transplantation, whereas 7%, 21%, and 18% had mGFR >60, 59–30, and <30 ml/min/1.73 m^2 respectively. The risk of death increased when mGFR decreased below 30 ml/min/1.73 m^2: HR = 2.67 (95% CI = 1.80–3.96) for GFR = 29–15 ml/min/1.73 m^2 and HR = 5.47 (95% CI = 3.10–9.65) for GFR <15 ml/min/1.73 m^2. Compared to mGFR, eGFR underestimated mortality risk in LTx recipients with an eGFR of 30–90 ml/min/1.73 m^2.

Conclusions: An overwhelming majority of LTx recipients develop CKD. The risk of death increases exponentially when GFR <30 ml/min/1.73 m^2. Creatinine-based eGFR underestimates the mortality risk in a large proportion of patients.

Keywords: Renal failure; Iothalamate clearance; Prevalence; Outcomes.
Received 12 October 2013; received in revised form 25 February 2014; accepted 31 March 2014; available online 5 April 2014
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2014.05.011.
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Abbreviations: LTx, liver transplantation; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CKD, chronic kidney disease; MDRD, modified diet in renal disease; KTx, kidney transplantation; MELD, model for end-stage liver disease.

Introduction

Advances in immunosuppression and perioperative management have revolutionized liver transplantation (LTx) outcomes in the past 3 decades [1]. Improved long-term survival has led in turn to increased prevalence of 'late' complications after LTx such as chronic kidney disease (CKD). CKD has become one of the leading causes of morbidity and death after LTx [2]. Although calcineurin inhibitor-toxicity is typically considered a major contributor, other risk factors for CKD include perioperative acute kidney injury, diabetes mellitus, hypertension, and chronic hepatitis C infection [3–5].

The reported prevalence of CKD after LTx ranges between 10% and 45% [6–17]. The wide range is largely attributed to the different criteria used to define CKD and different follow-up lengths, which make the existing literature difficult to compare. Moreover, renal function was assessed using creatinine-based equations, which is influenced by factors other than renal function, namely muscle mass [18] and tends to overestimate GFR in patients after liver transplantation [19]. Studies using measured GFR (mGFR) to assess the prevalence and mortality impact of CKD in these patients are limited [20]. Most of the studies describe the prevalence and mortality risk associated with advanced stages of kidney failure, which affect a relatively small proportion of LTx patients. These studies underestimate the true burden of CKD, because they do not assess the long-term outcomes in liver recipients who do not reach these end stages [21].

In this work, we analyze the prevalence of CKD by its severity and assess its impact on patient survival. We take advantage of the data resources available to this program from protocolized measurement of GFR by iothalamate clearance in liver recipients. Using mGFR, we aimed to determine (a) the prevalence of the entire spectrum of renal dysfunction after LTx and (b) the impact of CKD on patient survival after LTx.

Methods

Patients

Data on all adults undergoing primary LTx at Mayo Clinic, Rochester, MN between 1985 and 2012 were extracted from a prospective database tracking all LTx recipients. We excluded patients who underwent simultaneous multiple organ transplant and those who underwent a repeated LTx. The study was approved by our institutional review board.

Data

All laboratory data, including mGFR, were extracted from the LTx database and the institutional laboratory file. Outcome of follow-up, including patient survival and kidney transplantation (KTx), was also extracted from the LTx database, supplemented by the institutional registration file to determine the vital status of patients who may have been lost to follow-up.

GFR was measured by iothalamate clearance [22,23]. In addition, estimated GFR (eGFR) was calculated using serum creatinine values and the Modified Diet in Renal Disease (MDRD-4) equation [24]. Measured or eGFR were capped at 150 ml/min/1.73 m^2, as some results were implausibly high (e.g., >200 ml/min/1.73 m^2). Serum creatinine results from 1985 to 2006 were re-calibrated by subtracting 0.14 mg/dl from the original value, in concordance with the serum creatinine assay standardization in October 2006. All serum creatinine data were used except those within 30 days prior to death, since those results may be reflective of the multi-organ failure leading to the patient's death, rather than representing CKD predictive of death.

Standard definitions of chronic kidney disease stages were used, as per the Kidney Disease Improving Global Outcomes (KDIGO 2012) guidelines. CKD stage 3a was defined by GFR of 45–59 ml/min/1.73 m^2; CKD stage 3b by GFR of 30–44 ml/min/1.73 m^2, CKD stage 4 by GFR of 15–29 ml/min/1.73 m^2, and CKD stage 5 by GFR <15 ml/min/1.73 m^2. Given the variability of serum creatinine, the mean of the 2 lowest creatinine values over the prior 6 months was used for these definitions when eGFR was analyzed.

Analytical approach

In describing the prevalence of post-LTx CKD, a multistate model was utilized. A multistate model is an extension of a competing risk model, in which patients can go through different intermediate states before reaching the final state. The model allowed patients to move back and forth between CKD stages until reaching the final state of either KTx or death, transition out of which was not allowed. For example if a patient received KTx and then subsequently died, the patient remained in the KTx state. This method appreciates the dynamic transitions between CKD stages, as well as the occurrence of KTx and death over time.

Renal function at LTx, at 4 months, and yearly after LTx was assessed separately by eGFR and, when available, by mGFR. Given the goal of the analysis being long term effect of CKD, we excluded deaths that occurred in the immediate (i.e., <4 months) post-LTx period. Similarly, in light of reversible events that may affect renal function acutely in the immediate post-operative period, data in the first 4 months post-LTx were ignored.

Because of the long study period, we divided the data into two eras – pre-MELD (1985–2001) and MELD (2002–2012). Initial analyses were performed for the entire study period and then each era was considered separately.

In the second part of the analysis, we determined the age and sex-adjusted impact of post-LTx renal function on survival. The time-dependent Cox regression analysis was used to estimate the effect of a GFR result obtained at any time during the follow-up (separately for mGFR and eGFR). Smoothing splines were used to graphically assess the relation between GFR and mortality and to identify any thresholds in GFR at which the relation changes. To evaluate the extent to which eGFR may incorrectly assess mortality risk, we constructed a reclassification table, which compared the proportion of patients in each eGFR category who actually belonged in a different CKD stage when assessed by mGFR. Using Cox regression models, we determined the age and sex adjusted risk of death among subjects who were reclassified to a higher or lower GFR range, in comparison to the subjects who were not reclassified [25]. All statistical analyses were conducted using R software.

Table 1. Patient characteristics at transplantation.

Parameter	Patients n = 1211
Age, yr (median, IQR)	54 (46-60)
Male (%)	724 (60)
Race (%)	
White	1046 (86)
Black	22 (2)
Asian	36 (3)
Other	107 (9)
Liver disease etiology	
Viral	28%
Alcoholic	14%
Cholestatic	26%
Other	32%
Bilirubin, mg/dl (median, IQR)	4.5 (2.4-8.8)
Creatinine, mg/dl (median, IQR)	1.0 (0.8-1.3)
INR (median, IQR)	1.4 (1.2-1.7)
Sodium, mmol/L (median, IQR)	136 (132-139)
MELD (median, IQR)	17 (12-22)
Patients (%) by eGFR ranges	
≥60 ml/min/1.73 m^2	878 (72.9)
59-30 ml/min/1.73 m^2	240 (19.9)
29-15 ml/min/1.73 m^2	60 (5.0)
<15 ml/min/1.73 m^2	26 (2.2)

Results

Patients

A total of 1266 patients met the eligibility criteria. Of these, 1211 (96%) were alive at 4 months after LTx and were included in the analysis. The median age at LTx was 54 (range 19–73) years; the majority of the recipients were male and white (Table 1). The median follow-up time for the overall study period was 6 (range 0–26.4) years, expectedly longer for the pre-MELD era (11 years) than for the MELD era (3 years). GFR was measured at least once at LTx, at 4 months or later post-LTx in 95% of patients (mean of 5 measurements per patient). Over the entire study period, a total of 6246 iothalamate measurements and 34,353 creatinine values for eGFR assessment were available. Approximately 54% of patients died in the study period. The causes of death included malignancy (25%), graft failure (14%), infections (13%), cardiovascular events (7%), renal failure (5%), other (18%) and were unknown in 18% of cases.