Research Article

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The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation

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Transplantation

Background & Aims: The growing discrepancy between supply and demand for liver transplantation has necessitated a greater use of higher risk grafts. Donation after Circulatory Death (DCD) liver transplant recipients have an increased frequency of acute kidney injury (AKI). We hypothesised that other higher risk grafts might also impact negatively on renal function. Our aim was to examine the effect of the evolving use of higher risk grafts on the incidence of post liver transplant AKI.

Methods: Single-centre study of 1152 patients undergoing first-single-organ liver transplantation for chronic liver disease 01/2000–12/2011. To assess the impact of the evolution of graft quality over time; donor/graft/recipient variables were compared over three 4-year periods.

Results: Pretransplant recipient renal function improved during follow-up (p <0.001), and the median postoperative day-1 (p <0.001), -2 (p <0.001), and -3 (p <0.001) tacrolimus trough levels fell. The proportion of patients receiving a higher risk graft was 31.8% in 2000–2003, 40.9% in 2004–2007, and 59.1% in 2008–2011 (p <0.001). There was a progressive increase in AKI (2000–2003, OR 1.00; 2004–2007, OR 1.43; 2008–2011, OR 2.40, p <0.001). After adjusting for recipient variables increasing recipient warm ischaemic time (p = 0.019), DCD transplantation (p <0.001), donor age ⩾60 years (p = 0.020), and donor body mass index ⩾30 kg/m^2 (p <0.001) were independent predictors of AKI.

Conclusions: The increasing use of higher risk liver grafts is associated with an increased incidence of AKI. These findings support the need for therapies that minimise the hepatic ischaemia-reperfusion injury.

Keywords: Liver transplantation; Acute kidney injury; Higher risk graft; Donor; Chronic kidney disease.

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Abbreviations: AKI, acute kidney injury; AST, aspartate amino-transferase; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVA, cerebrovascular accident; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; DRI, donor risk index; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; HIRI, hepatic ischaemia-reperfusion injury; HR, hazard ratio; ICU, intensive care unit; IDDM, insulin dependent diabetes mellitus; INR, international normalised ratio; IQR, inter-quartile range; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NIDDM, noninsulin dependent diabetes mellitus; OR, odds ratio; RCC, red cell concentrate; RRT, renal replacement therapy; UKELD, UK score for patients with end-stage liver disease.

Introduction

The growing discrepancy between supply and demand for liver transplantation has necessitated the search for measures to expand the donor pool. Driven by a progressive rise in wait-list mortality, transplant programmes have increasingly relied on "extended criteria donor" or "higher risk" grafts [1,2]. National statistics from the USA confirm a steady increase in older donors and Donation after Circulatory Death (DCD), which now comprise 13% and 5% of all deceased donor liver transplants respectively [1,3]. In the UK, where the organ donation rate is comparatively low and wait-list mortality high, 29% of liver donors are aged over 60 years and 19% are DCD [2,4]. Furthermore, the proportion of clinically obese donors has almost doubled in the last ten years [2].

No consensus definition for higher risk grafts has been agreed. In addition to age and body mass index (BMI), donor factors that are frequently considered to mediate greater risk include a prolonged stay in the Intensive Care Unit (ICU), hypernatremia and elevated liver blood tests [5–7]. Split livers are also often labelled as higher risk grafts [5,6]. However, livers that are split are of ideal quality being sourced from optimal donors, and larger volume centres report comparable survival rates to full-size Donation after Brain Death (DBD) controls [8].

The negative implications of higher risk livers for graft and patient survival have been clearly demonstrated [6,9,10]. Yet any increased risk to the individual recipient has been deemed as acceptable by the transplant community given the reduction in wait-list mortality [11,12]. Moreover, when the number of adverse factors per donor is limited, and possibly when such organs are allocated to patients with lower MELD scores, graft survival is not very different to standard donors [10]. Authorities advocate that the utilization of higher risk grafts continues to increase to meet the escalating need for liver transplantation [13]. Therefore,

a better understanding of the consequences of higher risk grafts with regard to recipient morbidity is warranted to maximise benefit.

Acute kidney injury (AKI) is a major cause of morbidity and mortality after liver transplantation [14–17]. Besides the longer recovery period and greater financial cost, AKI is an independent risk factor for death in the ICU [14,15,17,18]. Furthermore, AKI can cause permanent structural damage, with progressive tubulo-interstitial fibrosis and long-term repercussions for renal function [16,19]. Liver transplant recipients with post-operative acute renal failure are twice as likely to develop chronic kidney disease (CKD), resulting in a 5-fold increased risk of death [16].

We have recently shown that DCD liver transplantation is associated with an increased frequency of AKI [17]. In this setting peak peri-operative serum aspartate amino-transferase (AST), a surrogate marker of hepatic ischaemia-reperfusion injury (HIRI), is the only variable related to renal outcomes [17]. HIRI is accompanied by a systemic inflammatory response, which is the common pathway for the multiple organ dysfunction of sepsis and other inflammatory disorders [20–23]. Thus, HIRI, by driving the systemic inflammatory response, may play a critical and potentially modifiable role in the pathogenesis of AKI after DCD liver transplantation [24,25]. Increasing donor age and organ steatosis are known to increase the susceptibility to HIRI [26,27]. It follows that other higher risk grafts may also impact negatively on post liver transplant renal function.

Our aim was to examine the effect of the evolving use of higher risk grafts on the incidence of AKI after liver transplantation.

Patients and methods

This was a single-centre study of consecutive adults who underwent first single-organ liver transplantation for chronic liver disease between January 2000 and December 2011. Exclusion criteria were a previous renal transplant and renal replacement therapy during the pre-operative phase. Twenty patients who died within 7 d of transplantation were also not included. Therefore, the study cohort comprised 1152 patients. To assess the impact of the evolution of graft quality over time; donor/graft/recipient variables were compared over three 4-year periods: 01/2000–12/2003, 01/2004–12/2007, 01/2008–12/2011.

Data was taken from a prospectively completed database. Donor risk index (DRI) was calculated as previously described [6]. A higher risk graft was defined for the purposes of this paper as DCD, donor age $\geqslant$60 years, donor BMI $\geqslant$30 kg/m^2, donor ICU stay >7 d, donor serum sodium >165 mmol/L, and/or donor serum bilirubin >51 μmol/L [7]. An elevated donor serum AST was not used because this parameter was not available in 47% of cases.

Recipient characteristics were documented at time of hospitalisation for transplantation. The MELD (Model for End Stage Liver Disease) score was determined and presented as calculated without exception points [28]. The UK Score for Patients with End-Stage Liver Disease (UKELD), a scoring system now used routinely in the UK to prioritise graft allocation, was also calculated [29].

During the immediate post-operative period patients receiving renal replacement therapy (RRT) were given a peak serum creatinine of 3 times baseline if the actual recorded value was less [30]. Peri-operative acute renal dysfunction (during the first 7 d after transplantation) was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for stage 2 or worse AKI: peak serum creatinine $\geqslant$2 times baseline [31]. The main measure of renal function thereafter was estimated glomerular filtration rate (eGFR), determined using the Modification of Diet in Renal Disease (MDRD) Study 4-variable equation [32]. CKD was defined as eGFR <60 ml/min/1.73 m^2 on at least 2 occasions and sustained from 6 months post-transplant [33].

Standard immunosuppression was tacrolimus aiming for a trough of 8–10 within the first 3 months of transplantation, azathioprine and reducing dose steroid discontinued by 3 months. Renal sparing immunosuppression was used with increasing frequency and in most cases consisted of half dose tacrolimus aiming for a trough of 5–8, mycophenolate and reducing dose steroid discontinued by 3 months. In a minority of patients delayed introduction of calcineurin inhibitor with interleukin-2 receptor antagonist cover was employed. All immunosuppression choices were physician and surgeon dependent.

Statistical analyses

Continuous variables are expressed as median and interquartile range (IQR) and compared using the Kruskal-Wallis test. χ^2 analysis or Fisher's exact test were used for comparison of categorical data. Cumulative incidence of CKD and survival was estimated using Kaplan-Meier, and adjusted hazard ratios were determined using Cox proportional hazards analysis.

The association between time period, and higher risk grafts, and AKI were examined using separate logistic regression analyses. In the models all clinically relevant variables were entered simultaneously. Donor serum sodium >165 mmol/L and donor serum bilirubin >51 μmol/L were not included because of small patient numbers. Post-operative day-2 was selected as the most appropriate time to examine any impact of the calcineurin inhibitor on the frequency of AKI. A tacrolimus trough was not available in 22.0% of patients. When included in the multivariate analyses, day 2 tacrolimus trough was not associated with AKI and did not impact significantly on the models. Consequently, day 2 tacrolimus trough was omitted from the final multivariate analyses presented in the manuscript. To determine whether there was an additive effect of higher risk donor factors, interaction terms if p <0.10 were entered into the model (DCD*donor ICU stay >7 d; donor aged $\geqslant$60 years*donor BMI $\geqslant$30 kg/m^2). Similarly, the interaction terms had no statistically significant effect and were not included in the final model. There was no interaction between recipient MELD and higher risk donor factors or DRI.

A p <0.05 was considered statistically significant unless otherwise stated. Data was analysed using the SPSS 18 package.

Results

Trends in recipient, donor, and graft characteristics

Recipient characteristics at the time of hospitalisation for transplantation are outlined in Table 1. There was no change in median age (p = 0.206), frequency of hepatitis C (p = 0.212) or diabetes mellitus (p = 0.106) between the 3 study periods. Although hepatocellular carcinoma was more common (p = 0.019), there was no clear overall change in the MELD score. Median serum creatinine was lower (p <0.001), and the frequency of renal dysfunction (p <0.001) and hyponatraemia less (p = 0.002) in later years.

Donor and graft characteristics are detailed in Tables 2 and 3. There was a progressive reduction in median cold ischaemic time (p <0.001) and recipient warm ischaemic time (p <0.001). The use of higher risk grafts was observed to increase. DCD liver transplantation was introduced in 2004–2007 (p <0.001), and the frequency of whole DBD grafts from donors age $\geqslant$60 years (p = 0.001), with a BMI of $\geqslant$30 kg/m^2 (p = 0.012), and with an ICU >7 d (p = 0.014) rose. Overall, the proportion of patients receiving a higher risk graft was 31.8% in 2000–2003, 40.9% in 2004–2007, and 59.1% in 2008–2011 (p <0.001). The median DRI increased in parallel from 1.59 to 1.87 (p <0.001). Characteristics of whole DBD and DCD grafts when considered separately are provided in Supplementary Table 1.

Intra-operative red cell concentrate (RCC, p <0.001), fresh frozen plasma (p <0.001) and platelet transfusions (p <0.001) reduced, as well as the use of cryoprecipitate (p <0.001). There was a progressive fall in median post-operative day-1 (p <0.001), day-2 (p <0.001) and day-3 (p <0.001) tacrolimus trough levels (p <0.010 considered statistically significant). The estimated 1-year survival was 84.6%, 88.9%, and 92.3% for 2000–2003, 2004–2007, and 2008–2011, respectively (log rank p = 0.003).