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Early Persistent Progressive Acute Kidney Injury and Graft Failure Post Liver Transplantation

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Background. Acute kidney injury (AKI) in the setting of liver transplantation is a common and multifaceted complication. Studies in the general population have demonstrated worse prognosis with AKI episodes that persist for a longer duration. Our primary objective was to evaluate the impact of early AKI episodes that are persistent or progressive in nature, on patient outcomes and graft survival. **Methods.** This was a retrospective cohort study including all patients who received a liver transplant between 2011 and 2015 at our center. Moderate to severe AKI episodes (AKIN II or III) were recorded immediately before transplantation and after surgery until hospital discharge. We evaluated the incidence density rate (IDR) of graft failure and the time to graft failure in patients with persistent or progressive AKI (*pp*AKI) as compared to controls. **Results.** Two hundred seventy-nine patients received 301 deceased donor liver allografts. Progressive or persistent AKI was documented in more than half of transplant cases (152/301). The rate of graft loss was 3 times higher in the *pp*AKI group (25%) versus the controls (8.7%). The IDR of graft failure was 13.79 per 100 case-years in the *pp*AKI group as compared with 3.79 per 100 case-years in the controls (IDR ratio, 3.64; 95 % confidence interval, 1.88–7.50). After adjusting for hepatic artery thrombosis, ischemic cholangiopathy, infectious complications and Model for End-stage Liver Disease, *pp*AKI was associated with a decreased graft survival time. **Conclusions.** Persistent or progressive AKI after liver transplantation is associated with an increased incidence rate of graft failure and is an independent predictor of decreased graft survival time.

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Acute kidney injury (AKI) is a common complication both before and after liver transplantation (LT) with a reported incidence ranging from 10% to 20% in the pretransplant setting and up to 64% after transplantation.[1-7] AKI in this setting influences postoperative morbidity and mortality.[7-10] Many earlier studies had demonstrated a direct relationship between preoperative AKI and patient survival after LT.[4,11-13] These early findings coupled with the adaptation of the Model for End-stage Liver Disease (MELD) system as an organ allocation tool, which prioritizes patients with renal dysfunction for liver transplants, raised concerns about a potential trend for lower overall survival after LT. However, the adaptation of MELD score did not lead

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to worsened liver transplant outcomes.[11] This is likely explained by the fact that AKI episodes encompass a range of renal insults that differ in terms of etiology, ongoing kidney damage and prognosis. Pretransplant AKI episodes due to hepatorenal syndrome normally resolve post-LT without any untoward effects on patient outcomes while renal insults causing acute tubular necrosis may not resolve fully, leading to chronic kidney disease (CKD), end-stage renal disease, and ultimately decreased patient survival.[14,15]

Similarly, postoperative renal dysfunction is an independent predictor of morbidity and mortality in liver transplant recipients.[3,5,9,10] However, the available data lacks granularity in terms of etiology of AKI, severity, and reversibility of each episode. It is clear that not all AKI episodes are the same and that AKI encompasses a heterogenous group of etiologies with differing likelihoods for reversibility and/or progression. Although determining the exact etiology for each episode of AKI may not be possible or feasible, capturing their severity and reversibility, as harbingers of prognosis can be reliably accomplished. Interestingly, studies in the general population, have documented that regardless of disease severity, an episode of AKI that resolves rapidly is associated with better outcomes than one which persists for a longer duration.[16] However such data are lacking in the liver transplant population. In this study, we attempted to determine the impact of an episode of AKI that is persistent or progressive in course, on patient outcomes and liver allograft survival posttransplantation.

METHODS

This was a retrospective cohort study, including all patients who received a deceased donor liver transplant between January 1, 2011. and December 31, 2015, at a single Canadian transplant center. Our study protocol was approved by The University of British Columbia's Clinical Ethics Review Board.

Medical charts of LT recipients were reviewed for baseline characteristics including: Age, sex, BMI, underlying liver disease, the MELD and Child-Pugh Scores, inpatient status at the time of transplantation, medical comorbidities, including history of diabetes mellitus, hypertension, and CKD.

The following data were collected on donor and graft variables: age, sex, BMI, cause of death, donor origin (local, provincial, national, or international), donor warm ischemic time (defined as the period between systolic blood pressure <60 mm Hg, mean arterial pressure <50 mm Hg or oxygen saturations <60% and cold reperfusion with preservation solution), and cold ischemic time.

Intraoperative variables collected included Operative time, surgical technique (classic or piggyback), total estimated blood loss, intraoperative transfusion requirements (packed red cell concentrate, fresh frozen plasma, and platelet transfusions), autologous red cell transfusions, and recipient warm ischemic time.

Infectious complications postoperatively were defined as an episode of bacterial or fungal sterile site infections (for example, blood stream, deep incisional or organ space infections) as defined by Centers for Disease Control and National Healthcare Safety Network criteria[17] during the first hospital admission for LT.

Episodes of moderate to severe AKI were defined according to the AKI Network (AKIN) classification as peak serum creatinine (SCr) 2.0 to 2.9 times (stage II) or ≥3.0 times (Stage III) the baseline SCr levels.[18] Patients who required renal replacement therapy were also classified as AKIN stage III. Baseline serum creatinine before transplant was defined as the lowest creatinine available within 3 months before transplantation. Patients who did not have a history of CKD or a documented episode of moderate to severe AKI pretransplant, were assumed to have had normal renal function before LT. Moderate to severe AKI episodes (stage II or III) were recorded immediately before transplantation and after surgery until hospital discharge. Only AKI episodes during the initial hospital admission for LT were captured and designated as "early" posttransplant AKI. Persistent or progressive AKI (*pp*AKI) was defined as either a preoperative episode of moderate or severe AKI that failed to improve (normalization of SCr to baseline value or a decrease in SCr sufficient enough for downstaging of AKIN stage), or worsened (AKIN stage II progressing to III) by the time of hospital discharge, or the development of a new episode of moderate or severe AKI postoperatively in patients with normal renal function before transplantation. Patients who never developed AKI (either preoperatively or postoperatively), or had their AKI episode improve (downstaging of AKIN classification) or completely resolved post-LT, served as the comparator control group. All patients were followed up until either the administrative censoring at the end of the follow-up period on March 31, 2017, or until their death, or re-transplantation.

In our center, standard immunosuppression protocol consists of tacrolimus aiming for trough levels of 4 to 8 ng/mL, mycophenolate mofetil 1 g twice daily, and tapering corticosteroids for the first 4 months post-LT. In patients with a history of kidney dysfunction, a renal sparing immunosuppression protocol can be initiated at the discretion of the treating physician. This protocol includes induction with interleukin-2 receptor antagonist, basiliximab, and delayed introduction of calcineurin inhibitors in addition to mycophenolate and steroids.

Statistical Analysis

Numerical data is presented as mean with standard error when normally distributed and nonparametric data as median with the interquartile range (IQR). Categorical data are presented with their corresponding percentages. Continuous numerical data are compared using the Student *t* test; categorical data is compared using the χ^2 test or Fisher exact test when applicable. Nonparametric data were compared using the Kruskal-Wallis test.

Our primary outcome was the rate of graft loss that included a composite of death or retransplantation due to graft failure. We reported the incidence density rate (IDR) that accounts for variable lengths of follow-up for each patient. Incidence density rate for graft failure and the time to graft failure was compared in patients with *pp*AKI against controls. Patients that had graft loss as a result of recurrent hepatocellular cancer or death from reasons unrelated to their graft function were included in the IDR analysis, but their deaths were not counted as part of the composite outcome. We also performed a time to event analysis. As some patients could have been transplanted multiple times, we used a time to recurrent event analysis using a counting process. In a counting process, when a subject experiences multiple events, their follow-up time is reset at the time of the recurrence as opposed to be continued from the time of inclusion into the

study. The analysis time started at the time of transplantation and ended when a patient died or was retransplanted as a consequence of graft dysfunction. Patients who died for reasons unrelated to graft function or from recurrent hepatocellular carcinoma were censored at the time of death. Administrative censoring occurred on the last day of follow-up set for this cohort (March 31, 2017). Survival curves were estimated with the Kaplan-Meier method and the Cox proportional regression model was used to estimate the effect of *pp*AKI on graft survival adjusted with variables that have been associated with increased risk of graft loss, including development of ischemic cholangiopathy (IC), hepatic artery thrombosis and MELD score at the time of transplant. Analyses were performed using STATA 14 (StataCorp, College Station, TX).

RESULTS

Two hundred seventy-nine patients received 301 deceased donor liver allografts. Before transplantation, 23% (70/301) developed moderate to severe AKI and 9% (28/301) required renal replacement therapy, while posttransplantation, more than half developed AKI (157/301) with 15% (46/301) requiring dialysis. Progressive or persistent AKI was documented in approximately 50% of transplant cases (152/301). A number of patient, donor and intraoperative variables were associated with *pp*AKI (Table 1). Recipients' age, BMI, and etiology of liver disease were similar between *pp*AKI group and the controls. However, patients in the *pp*AKI group had higher MELD scores, higher baseline SCr and more frequently had a history of CKD before LT. A significantly higher proportion of patients in the *pp*AKI group were inpatients just before transplantation as compared to the controls (54% vs 29.5%; $P < 0.001$). The majority of donor variables collected were similar between the 2 groups, except donor origin and cold ischemic time. More grafts were procured from out of country or out of province donors in the *pp*AKI group as compared with the controls (17.8% vs 9.4%) but this was not statistically significant ($P = 0.14$). The cold ischemic time was significantly longer in the *pp*AKI group (429.5 vs 378 min, $P = 0.0018$). Total estimated blood loss, intraoperative transfusions and transfusions during the first 24 hours in intensive care unit (ICU) were significantly higher in *pp*AKI group as compared to the controls ($P < 0.001$) (Table 1).

More patients in the ppAKI group (20.4%) also had infectious complications postoperatively as compared with the controls (6.7%; $P < 0.001$). Renal sparing immunosuppression regimen with basiliximab induction and delayed tacrolimus initiation was utilized in 65% (98/152) of *pp*AKI group and 25% of controls. Patients with *pp*AKI had a prolonged length of ICU stay (mean, 17.4 days; 95% confidence interval [95% CI], 12.0-22.8) as compared with the controls (mean, 4.3 days; 95% CI, 3.3-5.2) ($P < 0.0001$). Length of hospital stay was also significantly prolonged in *pp*AKI group (mean, 37.9 days; 95% CI, 31.4-44.3) when compared to the controls (mean, 20.8 days; 95% CI, 18.2-23.4) ($P < 0.001$).

Over a median follow-up of 23.9 months (IQR 8.9, 41.2), a significantly higher proportion of grafts were lost in the *pp*AKI group (38/152) as compared with the controls (13/149)—the IDR of graft failure was 13.78 and 3.79 per 100 case-years in the *pp*AKI group and the controls respectively (IDR ratio, 3.64; 95% CI, 1.88-7.50). There was

TABLE 1.

Recipient, donor, and intraoperative variables

	*pp*AKI (n = 152)	Controls (n = 149)	*P*
Recipient characteristics			
Age, y	56 (49-61)	57 (45.5-62)	0.71
Male sex	64.4	65.1	0.9
BMI	26.2 (23.1-29.5)	24.7 (21.45-28.85)	0.051
Etiology of liver disease			
Hepatitis C	30.3	34.9	
Hepatitis B	8.6	5.4	
Alcohol	14.5	16.1	
NASH	6.6	8.1	
PBC	2	4.7	
PSC	8.6	11.4	0.06
AIH	4.0	10.1	
α-1 ATD	0.7	1.3	
Amyloidosis	2	1.3	
Budd-Chiari	2.6	0	
Cryptogenic	5.3	2	
Polycystic	2.6	0	
Wilson's	0.7	0.7	
Fulminant	3.3	1.3	
Hemochromatosis	2.6	0	
Other	5.9	2.7	
HCC	17.8	21.5	0.41
MELD score	21.55 (14.8-31)	17 (14-21.4)	<0.001
Retransplant	13.8	4.0	0.003
Inpatient at the time of transplant	54	29.5	<0.001
Creatinine, μmol/L	125 (88.3-183.3)	85 (64.5-119)	<0.001
eGFR, mL/min	50 (35-77)	79.5 (54-104)	<0.001
HD before transplant	15.6	2	<0.001
CKD	17.1	8.1	0.018
Hypertension	27.6	15.4	0.1
Diabetes	27.6	22.8	0.34
Ascites			
None	45.7	47.0	
Small	14.6	22.8	0.16
Moderate	25.5	22.2	
Large	13.3	8.1	
Donor variables			
Donor type			
DCD, % (n)	19.1 (29)	14.1 (21)	0.245
NDD, % (N)	80.9 (123)	85.9 (128)	
Age, y	48.3 (34.5-58.5)	46.7 (30.4-58.7)	0.3
Weight, kg	76.8 (65-87)	73 (65-82.7)	0.20
Male sex	59.9	57.8	0.7
Origin			
Local	42.7	42.3	
Provincial	39.5	48.3	0.14
OOP/OOC	17.8	9.4	
Cold ischemia time, min	429.5 (352.5-607)	378 (281-490)	0.0018
Donor warm ischemia time, min	17 (14.5-21)	15 (13-21.5)	0.35

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TABLE 1. (Continued)

	*pp*AKI (n = 152)	Controls (n = 149)	*P*
Intraoperative variables			
Surgical technique			
Classic	27	37.2	0.059
Piggy back	73	62.8	
Rewarm time, min	55 (47-73.5)	54.5 (45-69.25)	0.41
Surgery time, min	332.5 (270-400.5)	325.5 (265-381.5)	0.57
Estimated TBL, L	3.67 (2.2-7.2)	2.85 (1.7-5.2)	0.01
Autologous blood transfusion, mL	1200 (700-2717)	894 (500-1789.3)	0.0071
Transfusions—intraoperative, units			
PRBC	7.45 (5.97)	4.8 (4.5)	<0.001
Platelet	3.27 (3.8)	2.45 (2.1)	0.2
FFP	8.2 (7.1)	6.02 (4.1)	0.001
Cryoglobulins	5.7 (7.9)	3.78 (9.7)	0.06
Transfusions—first 24 h in ICU, units			
PRBC	5.5 (6.5)	2.19 (3.8)	<0.001
Platelet	2.43 (3.4)	1.08 (1.8)	<0.001
FFP	3.94 (6.7)	1.50 (2.96)	<0.001
Cryoglobulins	6.22 (12.3)	1.95 (5.02)	<0.001

Values expressed as mean (standard deviation), median (IQR), and percent where appropriate.

α-1 ATD, alpha-1 antitrypsin deficiency; AIH, autoimmune hepatitis; CKD, chronic kidney disease; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; FFP, fresh frozen plasma; HCC, hepatocellular carcinoma; HD, hemodialysis; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; NDD, donation after neurological death; OOP/OOC, out of province/out of country; PBC, primary biliary cirrhosis; ppAKI, persistent or progressive acute kidney injury; PRBC, packed red blood cells; PSC, primary sclerosing cholangitis; TBL, total blood loss.

also a significant difference in the time to graft loss between the ppAKI group and the controls. Figure 1 shows the Kaplan-Meier curves of graft loss for the 2 groups. Multiorgan failure (MOF), primary graft nonfunction (PNF), hepatic artery thrombosis (HAT), and IC were the major causes of graft loss in the *pp*AKI group, accounting for more than 90% of graft loss in this cohort (Table 2). In multivariate Cox analysis, after adjusting for hepatic artery thrombosis, IC, infectious complications, and MELD score, *pp*AKI was independently associated with a decreased graft survival time (hazard ratio, 3.13; 95% CI, 1.67-5.86) (Table 3).

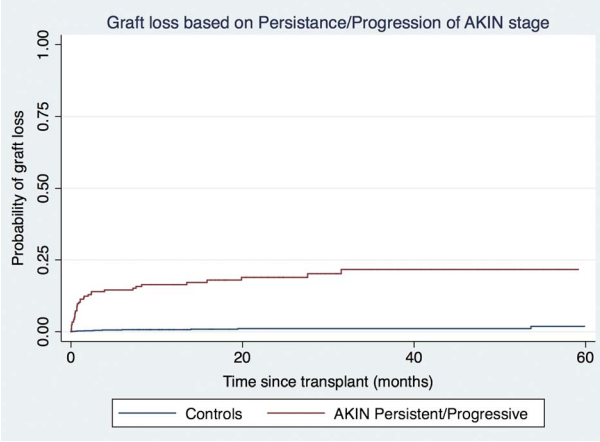

FIGURE 1. Kaplan-Meier plot of graft loss based on presence or absence of persistent or progressive acute kidney injury. AKIN, Acute Kidney Injury Network.

TABLE 2.

Reasons for graft failure

	*pp*AKI n = 38/152	Controls n = 13/149	Total N = 51/301
Hepatic artery thrombosis	7	2	9
IC	8	3	11
MOF	13	5	18
Primary nonfunction	7	0	7
Recurrent disease	2	2	4
Vascular complications	0	1	1
Chronic rejection	1	0	1

IC, ischemic cholangiopathy; MOF, multiorgan failure; ppAKI, persistent or progressive acute kidney injury.

DISCUSSION

In this large, single-center retrospective study, we have demonstrated that acute kidney injury is a dynamic process and a harbinger of poor graft survival. Based on our results, lack of resolution of pretransplant AKI episodes or development of moderate to severe AKI episodes after LT is an independent predictor of graft loss, with an impact only surpassed by hepatic artery thrombosis and IC.

Acute kidney injury was a common complication in our cohort both before and after LT with an incidence of 23% and 52%, respectively. Although the incidence of AKI in our study is congruent with the literature, we found that in nearly 50% of our patients, the AKI episode either failed to resolve or worsened by the time of hospital discharge or death. Patients with such progressive or persistent AKI, not only had an extended length of ICU and hospital stay, but also suffered a significantly higher graft loss. In our study, 25% of the grafts were lost in the *pp*AKI group versus only 8.7% in the controls.

The impact of AKI on posttransplant morbidity and mortality is well documented.[1,5,9,10,14] However, to our knowledge, no study has addressed AKI as a dynamic process in this setting. It is increasingly accepted that a diagnosis of AKI represents a heterogenous group of etiologies with widely differing clinical course, propensity for resolution and patient outcomes.[16] Nadim and colleagues[14] elegantly showed that pretransplant patients with severe AKI due to hepatorenal syndrome had much improved 1- and 5-year survivals posttransplant, as compared with those with pre-LT acute tubular necrosis. This again highlights that the reversibility of AKI, rather than its occurrence, determines its impact on patient outcomes. Similarly, post-LT AKI has been linked to poor patient and graft survival; however, the literature lacks granularity in terms of whether the AKI's "phenotype" and its duration or reversibility would influence patient outcomes. Here, we were able to show that persistent

TABLE 3.

Multivariate analysis of variables associated with graft loss

	HR (95% CI)
*pp*AKI	3.13 (1.67-5.86)
IC	5.20 (2.72-9.97)
HAT	6.20 (3.05-12.57)
Infectious complications	1.72 (0.90-3.29)
MELD	1.02 (0.98-1.05)

CI, confidence interval; HAT, hepatic artery thrombosis; HR, hazard ratio; IC, ischemic cholangiopathy; MELD, Model for End-stage Liver Disease; ppAKI, persistent or progressive acute kideny injury.

or progressive AKI predicts a high rate of graft loss post-LT rather than the occurrence of an AKI episode itself.

Although we have demonstrated a significant association between *pp*AKI and graft loss, our study was not designed to determine a possible pathophysiologic mechanism whereby *pp*AKI negatively impacts graft survival. It is interesting to speculate that *pp*AKI could result in a physiologic "milieu" that may result in prolonged and more difficult transplant surgery, delayed surgical recovery, coagulopathy at the microvascular level that may result in microvascular organ ischemia, an increased predisposition for postoperative infections that may not be clinically obvious and general impaired recovery. These subtle factors may become exaggerated when the donor organ is less than optimal, creating a complex multifactorial pathophysiologic situation that results in graft loss. Alternatively, the kidney could be simply a bystander that serves as a surrogate marker, during the acute events surrounding and leading to graft loss, such as delayed graft function, sepsis, and MOF. Recent studies have linked AKI to high risk allografts, donation after circulatory death (DCD) organs, or donation after neurological death (NDD) organs with prolonged cold ischemic time.[6,19-21] It is thought that the kidney is affected by hepatic ischemia reperfusion injury, which is associated with a systemic inflammatory response that can cause AKI through hemodynamic alteration and direct renal tubular damage.[19] Certainly in our cohort, the cold ischemic time was significantly longer in the *pp*AKI group versus the controls, signaling perhaps a more severe ischemic reperfusion injury in high risk allografts. In addition, more than 50% (20/38) of graft loss in the *pp*AKI group were due to MOF and PNF, again supporting a relationship between high risk allografts and AKI.

Just as important are identifying risk factors for the development of AKI, especially because there are no effective treatments to modify the course of AKI once renal insult occurs. Identifying risk factors will allow the clinician to anticipate AKI and to resume a kidney centric therapeutic approach, such as avoiding nephrotoxic agents, if possible, and close monitoring of patients' volumes status, in an attempt to halt the progression of AKI. We were able to identify recipient (high MELD score, high medical acuity at the time of transplant, and history of CKD), donor (longer cold ischemic times), and intraoperative (high transfusion requirements) factors for *pp*AKI in our population. Previous studies had also demonstrated that DCD LT is associated with an increased risk of AKI.[19] In our study, we did not find such association although there was a trend toward higher incidence of *pp*AKI with DCD versus NDD donors (20% vs 14%), but this difference did not reach statistical significance, likely due to small number of DCD transplant in our cohort (50 vs 251).

Our study is limited by its retrospective design, and our results should be confirmed with a prospective study that attempts to explore physiologic variables that are associated with renal dysfunction in LT. In particular, the interaction between these variables and the organ procurement/surgical implantation process should be explored. Furthermore, elucidating the long-term renal outcomes and their impact on graft survival would be of interest. It is increasingly known that AKI and CKD are interconnected syndromes rather than separate entities, with one being a risk factor for the other.[22] Although the relationship between AKI and CKD is well documented, it would be interesting to delineate the impact of AKI and CKD on patient and graft survival in future studies.

In summary, we have demonstrated that acute kidney injury, especially early persistent/progressive kidney injury is associated with decreased graft survival time and could serve as a marker for potential graft loss post-LT.

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