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The progression of hepatorenal syndrome–acute kidney injury in acute alcohol-associated hepatitis: renal outcomes after liver transplant

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Abstract

Background: Hepatorenal syndrome–acute kidney injury (HRS-AKI) is a complication of advanced liver disease in patients with ascites and circulatory dysfunction. Little data remain on the relationship between HRS-AKI outcomes and different etiologies of liver disease post-liver transplant (LT).

Objectives: The primary aim was to evaluate the effect of HRS-AKI on renal outcomes in patients with acute alcohol-associated hepatitis (AAH) compared to chronic liver disease (CLD) after LT. The secondary aim was to evaluate the impact of acuity and chronicity of alcohol-associated liver disease in patients with HRS-AKI post-LT renal outcomes.

Design: A retrospective observational study of patients undergoing urgent inpatient liver transplant evaluation (LTE) for cirrhosis and AAH at single academic LT center between October 2017 and July 2021 was conducted.

Methods: Patients with HRS-AKI were selected based on indication for LTE: acute AAH_{HRS} or CLD_{HRS}. CLD_{HRS} was categorized by disease etiology: cirrhosis due to alcohol (A-CLD_{HRS}) *versus* cirrhosis from other causes (O-CLD_{HRS}). CLD patients without HRS-AKI were labeled $CLD_{no\ HRS}$.

Results: A total of 210 subjects underwent LTE; 25% were evaluated for AAH and 75% were evaluated for CLD. Hepatorenal syndrome was more common in subjects evaluated for AAH (37/47) than CLD (104/163) (78.7 *versus* 63.8%, $p = 0.04$). For the primary outcome, AAH_{HRS} subjects required ⩾30 days post-LT renal replacement therapy (RRT) more often than subjects with CLD_{HRS} ($p = 0.02$) and $CLD_{no\ HRS}$ ($p < 0.01$). There was no significant difference in other forms of long-term renal outcomes including kidney transplant referral and kidney transplant among cohorts. In subgroup analysis, 30-days post-LT RRT was more common in AAH_{HRS} than in A-CLD_{HRS} ($p = 0.08$). Logistic regression showed that AAH_{HRS} conferred a 20× and 3.3× odds of requiring ⩾30 days post-LT RRT compared to $CLD_{no\ HRS}$ and CLD_{HRS}, respectively. Postoperative complications were similar across cohorts, but had a significant effect on 30-day renal outcome post-LT.

Conclusions: Patients with AAH were more likely to develop HRS and require RRT pre- and post-LT at our center. The etiology of hepatic decompensation and postoperative complications affect renal recovery post-LT. The systemic inflammation of AAH in addition to conditions favoring renal hypoperfusion may contribute to the unfavorable outcomes of HRS-AKI after LT in this patient population.

Keywords: acute alcohol-associated hepatitis, chronic liver disease, hepatorenal syndrome–acute kidney injury, inflammation, liver transplantation, patient outcomes, renal replacement therapy

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Introduction

Hepatorenal syndrome (HRS) is a functional renal disorder secondary to end-stage liver disease. It is thought to be the result of hemodynamic changes in the splanchnic arterial circulation and increased synthesis of vasoactive mediators that cause renal vasoconstriction and mesangial cell contraction and ultimately reduction in renal blood flow and filtration fraction.[1] In addition to circulatory dysfunction, systemic inflammation and oxidative stress also play a role in precipitating kidney injury in HRS. For example, increased levels of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) have been associated with impaired renal function in cirrhosis and liver failure.[2–4]

HRS can present as rapid deterioration of renal function or slowly worsening renal dysfunction in the setting of refractory ascites. Previously, HRS was classified as either type 1 (HRS-1) or type 2 (HRS-2) where a serum creatinine (sCr) cutoff value >2.5 mg/dL was required for diagnosis. However, this recommendation limited treatment efficacy due to initiation of therapy in advanced stages.[5] In 2015, this definition was updated to HRS–acute kidney injury (AKI) and defined by changes in sCr greater than 0.3 mg/dL within 48 h or ⩾50% from baseline value or urine output ⩽0.5 mL/kg body weight for ⩾6 h.[5] Left untreated, HRS-AKI carries a poor prognosis with a median survival of 7–10 days. Although terlipressin with albumin is the most effective pharmacological option in the reversal of HRS-AKI, liver transplantation (LT) remains the ultimate treatment.[6] The rate of reversal of kidney function in cirrhotic patients with HRS-AKI after LT is between 60% and 75%.[7] However, increased duration of pretransplant dialysis sensibly decreases the odds of renal function recovery after LT.

It was once thought that there was no association between the development of HRS and liver disease etiology.[8] However, more recent research suggests that HRS is more likely to develop in patients with cirrhosis due to alcohol-associated liver disease.[7] While there are data supporting the relationship between chronic alcohol liver disease and HRS-AKI, there is a paucity of data on HRS-AKI in patients with acute alcohol-associated hepatitis (AAH), a syndrome defined by jaundice and impaired synthetic dysfunction in the setting of recent, yet prolonged alcohol use.

AAH is associated with systemic inflammation affecting multiple organs and characterized by the rapid progression of portal hypertension mediated by brisk hepatocyte dysfunction. Moreover, alcohol and its breakdown products dysregulate immune signaling, leading to the activation of downstream inflammatory pathways.[9] We hypothesize that this inflammatory milieu together with quick hemodynamic changes may favor the development of HRS-AKI relative to other causes of liver disease. Similarly, in the setting of severe inflammation and rapid progression, it is reasonable to think that the renal recovery may be more difficult to obtain in AAH even after LT.

There is a paucity of literature exploring the relationship between HRS-AKI outcomes and etiology of liver disease in the context of LT. We compared the prevalence of HRS-AKI in three patient cohorts and the effect of HRS-AKI on long-term renal outcomes in patients requiring inpatient LT evaluation (LTE). The primary aim of this study was to assess the impact of HRS-AKI on renal outcomes in patients with AAH compared to chronic liver disease (CLD) after completion of LT. The secondary aim was to evaluate the effect of acuity and chronicity of alcohol-associated liver disease in patients with HRS-AKI post-LT renal outcomes.

Methods

Patient selection

We performed a retrospective observational study of patients undergoing LTE for cirrhosis and AAH during inpatient hospitalization at a large, academic hospital and liver transplant center between October 2017 and July 2021. Patients with fulminant liver failure or prior history of LT were excluded. Patients with HRS-AKI were selected and categorized by indication for LTE: acute AAH_{HRS} or CLD_{HRS}. The presence or absence of HRS was determined using a combination of International Classification of Diseases, Tenth Revision codes and clinical documentation by primary transplant hepatology and consulting nephrology providers. The CLD_{HRS} group was further categorized by disease etiology: cirrhosis due to alcohol ($A\text{-}CLD_{HRS}$) *versus* cirrhosis from other causes ($O\text{-}CLD_{HRS}$). Patients with CLD without a diagnosis of HRS-AKI comprised the control group ($CLD_{no\ HRS}$). Of note, subjects evaluated *via* the institutions AAH protocol had

previously failed conservative medical treatments with prednisolone as tolerated by sCr. Furthermore, patients with HRS-AKI had all failed 48-h albumin challenge prior to diagnosis with HRS-AKI. Ultimately, we defined three subject cohorts: (1) AAH_{HRS}, (2) CLD_{HRS} (subgroups: A-CLD_{HRS} and O-CLD_{HRS}), and (3) $CLD_{no\ HRS}$.

Transplant evaluation was only initiated at the time of admission for every patient. This study involves a patient cohort who underwent urgent inpatient evaluations. All patients were consented for the transplant evaluation and listing and also for the transplant surgery itself.

Data collection and definitions

Demographic, clinical, laboratory, and outcome data were extracted from subjects' medical records and managed using REDCap electronic data capture tools at our institution. The hospitalization at which transplant evaluation occurred will be referred to as the 'Index Admission'. Demographic data included age, biologic sex, race, ethnicity (Hispanic, non-Hispanic, other). Laboratory data included Model for End-Stage Liver Disease (MELD) laboratories including serum sodium, bilirubin, creatinine, and international normalized ratio (INR), and white blood cell count (WBC). Length of evaluation was defined by number of days between evaluation date and listing date. Waitlist time was defined by date of listing until transplant when applicable.

Subjects who died or did not receive a committee decision during index admission were considered to have incomplete index evaluation. For those who completed evaluation during index admission, index outcomes included the following: (1) dead, (2) not approved, (3) approved and waitlisted, (4) transplanted. The percentage of subjects requiring management in the intensive care unit (ICU) was also recorded. Overall transplant outcomes were collected for all subjects; subjects were dichotomized as 'transplanted' or 'not transplanted' and further as 'dead' or 'not dead' if no transplant had occurred. Figure 1 was generated to provide a clear scheme of the evaluation process. The diagram illustrates the number of patients who were initially evaluated, approved, waitlisted to transplant, and ultimately received transplant. Reasons whether patients were not approved and or not listed (psychosocial, medical comorbidities, patient's choice, death) were recorded as well.

Intraoperative blood loss, blood transfusions, and vascular complications are described in the literature as risk factors of many complications after LT and for surgical reintervention after LT.[10,11] Thus, amount of blood transfused in milliliters (mL) was recorded as continuous variable [packed red blood cell (pRBC)]. Perioperative and postoperative complications were collected and included: hepatic artery thrombosis, stenosis of hepatic artery, celiac artery stenosis, hepatic artery pseudoaneurysm formation, portal vein thrombosis or stenosis, hepatic vein stenosis or thrombosis, inferior vena cava thrombosis or stenosis, biliary duct leaks, and large hepatic or perihepatic hematomas that required operating room take back. As the number of complications was small, perioperative and postoperative complications have been collapsed for statistical analysis. Post-LT renal outcomes were evaluated using three dichotomous (yes/no) variables: (1) subject required >30 days post-LT renal replacement therapy (RRT); (2) subject received a post-LT referral for kidney transplant evaluation (KTE); and (3) subject underwent post-LT kidney transplantation.

Study end points and analysis

The primary aim of this study was to evaluate the result of HRS in subjects with acute alcohol-associated liver disease *versus* CLD using post-LT renal outcomes as surrogate for degree of renal dysfunction. Post-LT renal outcomes were reported as proportions and compared between AAH_{HRS} and CLD_{HRS}. Subsequent three-group comparison between AAH_{HRS}, CLD_{HRS}, and $CLD_{no\ HRS}$ was made to account for any general underlying effect of decompensated liver disease and LT on renal outcomes. The secondary aim of this study was to evaluate how acuity and chronicity of alcohol-associated liver disease onset in subjects with HRS-AKI affect post-LT renal outcomes. We compared post-LT renal outcomes in subjects with HRS-AKI in the setting of acute AAH_{HRS} with subjects with HRS-AKI due to A-CLD_{HRS} or O-CLD_{HRS}. Tertiary aims of this study included determining the effect of HRS-AKI on disease severity [MELD-Na, acute-on-chronic liver failure (ACLF)], LT metrics, and LT outcomes in subjects with AAH and CLD.

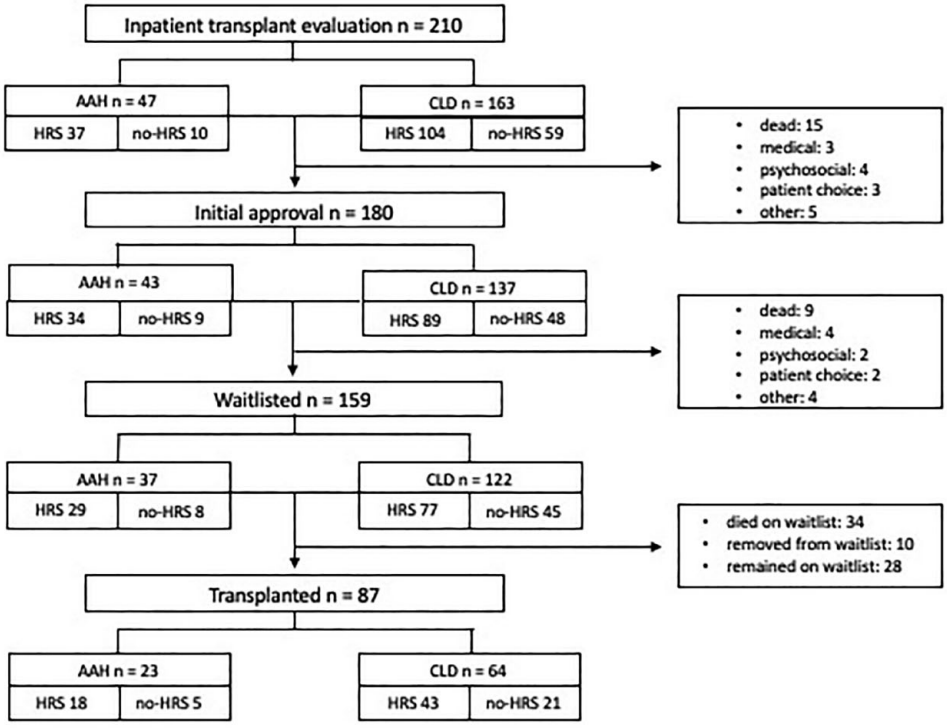

Figure 1. Schematics of transplant evaluation algorithm.
The figure illustrates the number of patients who were initially evaluated, approved, waitlisted to transplant, and ultimately received transplant. The reasons (psychosocial, medical comorbidities, patient's choice, death) which led patients to not being approved, not being waitlisted or transplanted are also included.

Categorical data were compared using Fisher's exact and chi-squared tests depending on sample size. Nonparametric continuous data were reported as median (interquartile range) and compared using Mann Whitney *U* test and Kruskal–Wallis for two-group and three-group comparisons, respectively. Normally distributed data were reported as mean (SD) and compared using student's *t* tests and analysis of variance tests for two- and three-group comparisons, respectively. Odds ratios were derived using univariate logistic regression.

Multivariate logistic regression was used to compare the relationship between study cohort and post-LT renal outcomes when accounting for pertinent covariates including intraoperative transfusion needs, operative complications, and serum bilirubin, which increases the risk of cholemic nephropathy.[10–13] The Hosmer–Lemeshow test was utilized to calculate the goodness of fit. Data were assessed at $p = 0.05$ for significance and 0.15 was considered a trend. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[14]

Results

Demographics

A total of 210 subjects underwent LTE during the study period; 25% were evaluated for AAH and 75% were evaluated for CLD. HRS was more common in subjects evaluated for AAH ($n = 37$) than for CLD_{HRS} ($n = 104$) at the time of LTE (78.7% *versus* 63.8%, $p = 0.04$). Of the CLD_{HRS} cohort, 45% of subjects were diagnosed with CLD secondary to alcohol use disorder (A-CLD_{HRS}; $n = 47$). The mean age in the AAH_{HRS} cohort was significantly younger than in CLD_{HRS} ($p < 0.01$), but there were no differences in sex, education level, BMI, or distance from transplant center. Patients with AAH_{HRS} were more likely to be non-Hispanic and white. Of note, on subgroup analysis, male sex was more common in A-CLD_{HRS} than in AAH_{HRS} ($p = 0.04$).

Evaluation data

MELD-Na score at the time of evaluation differed across groups and was significantly higher in AAH_{HRS} compared to CLD_{HRS} and $CLD_{no\ HRS}$ ($p < 0.01$). SCr, bilirubin, and INR were higher in AAH_{HRS} than in both CLD_{HRS} and $CLD_{no\ HRS}$, while serum sodium did not differ between groups. Higher grade of ACLF (grade 3 ACLF) was observed more often in AAH_{HRS} than in CLD_{HRS} and $CLD_{no\ HRS}$. AAH_{HRS} subjects had increased WBC count compared to CLD_{HRS} ($p < 0.01$) and $CLD_{no\ HRS}$ ($p < 0.01$).

Bacterial infection and spontaneous bacterial peritonitis (SBP) were diagnosed in similar proportions across all groups. History of large volume paracentesis was more common in the CLD_{HRS} cohort compared to the AAH_{HRS} cohort (57.7% *versus* 16.2%, $p = < 0.01$). Over 50% of subjects with HRS required admission to the ICU during their index admission compared to ~25% of the $CLD_{no\ HRS}$ group. However, there were no differences in ICU admissions between AAH_{HRS} and CLD_{HRS} ($p = 0.93$) or AAH_{HRS} and A-CLD_{HRS} ($p = 0.85$). There were also no differences in length of evaluation between AAH_{HRS} and CLD_{HRS} ($p = 0.80$) or AAH_{HRS} and $CLD_{no\ HRS\text{-}AKI}$ ($p = 0.33$). Baseline demographics and evaluation data are summarized in Tables 1 and 2.

Transplant evaluation outcomes

Patients were accepted and waitlisted for transplant at similar rates (Table 1). The most common reasons for not being approved or waitlisted were death and medical contraindication (Figure 1). Duration and frequency of pre-LT RRT did not differ between AAH_{HRS} and CLD_{HRS}. Subjects with AAH_{HRS} received more often LT than CLD_{HRS} (48.6% *versus* 41.3%) and $CLD_{no\ HRS}$ (48.6% *versus* 35%), but this relationship was not statistically significant. SCr and MELD-Na at the time of transplant were higher in the AAH_{HRS} cohort. Patients with CLD_{HRS} died overall more often than AAH_{HRS} ($p = 0.08$) and $CLD_{no\ HRS}$ ($p = 0.03$). Conversely, overall death rate was similar among AAH_{HRS} and $CLD_{no\ HRS}$ ($p = 0.85$) (Table 1). There was no difference in death frequency across the three cohorts after being waitlisted. In subgroup analysis, subjects with AAH_{HRS} and A-CLD_{HRS} experienced death at similar rates ($p = 0.43$).

Study outcomes

The primary outcome measure of this study was observed more frequently in subjects with concomitant AAH and HRS. Specifically, 50% of subjects in the AAH_{HRS} cohort required RRT for 30 or more days after LT compared to 23% of CLD_{HRS} cohort and 5% $CLD_{no\ HRS}$. Overall, patients with AAH_{HRS} required $\geqslant$30 days post-LT RRT significantly more often than subjects with CLD_{HRS} ($p = 0.04$) and $CLD_{no\ HRS}$ ($p = 0.02$). Post-LT RRT occurred at different rates in subjects with CLD_{HRS} and $CLD_{no\ HRS}$, but it did not meet the threshold for significance (Table 1). Furthermore, of the patients who did not require pre-LT RRT, $\geqslant$30 days post-LT RRT was most common in patients with AAH_{HRS}. A total of 2/6 (33%) AAH_{HRS} patients developed new renal dysfunction requiring $\geqslant$30-day RRT post-LT compared to 2/23 (8.7%) CLD_{HRS} patients and 0/19 (0%) $CLD_{no\ HRS}$ patients ($p = 0.04$). When specifically comparing AAH_{HRS} to CLD_{HRS} patients who did not undergo pre-LT RRT, the difference in new postoperative RRT requirement among the two groups approached significance (2/6, 33% *versus* 2/23, 8.7%, $p = 0.12$). Long-term renal outcomes including referral for KTE and undergoing kidney transplant were more common in the AAH_{HRS} subjects, although they did not meet statistical significance (Table 1). In the subgroup analysis, AAH_{HRS} required $\geqslant$30 days post-LT more often than A-CLD_{HRS} ($p = 0.08$) and O-CLD_{HRS} ($p = 0.06$, Table 2).

On univariate logistic regression, AAH_{HRS} was associated with a 3.3× and 20× odds of requiring $\geqslant$30 days post-LT RRR compared to CLD_{HRS} ($p = 0.04$) and $CLD_{no\ HRS}$ ($p < 0.01$), respectively (Table 4). In terms of confounding factors, post-LT RRT requirements did not differ between patients with serum bilirubin $\geqslant$15 and serum bilirubin <15 (40% *versus* 57%, $p = 0.20$, Table 3). Postoperative complications occurred more frequently in patients who required $\geqslant$30 days post-LT RRT than those who did not (45% *versus* 17.7%, $p = 0.01$, see Table 3). Volume of blood transfusion was higher in patients who required $\geqslant$30 days post-LT RRT than those who did not (4200 mL *versus* 3283 mL, $p = 0.03$, see Table 3). In a model adjusted for covariates including age, sex, MELD-Na at transplant, operative complications, and pRBC requirement, the study cohort remained predictive of requiring $\geqslant$30 days post-LT RRT (Table 4). Goodness of fit for the final

Table 1. Demographics, clinical characteristics, and study outcomes.

Characteristics	$AAH_{HRS\ (1)}$	$CLD_{HRS\ (2)}$	$CLD_{no\ HRS\ (3)}$	1 *versus* 2	1 *versus* 3	2 *versus* 3
Subject number	37	104	59	–	–	–
Age (years)	44 (11)	58 (10)	56 (9)	<0.01	<0.01	0.21
BMI (kg/m^2)	31 (8)	32 (9)	30 (8)	0.68	0.53	0.20
MELD-$Na_{eval.}$ (points)	36 (6)	30 (7)	23 (8)	<0.01	<0.01	<0.01
$Creatinine_{eval.}$ (mg/dL)	3.1 (2)	2.6 (1)	1.2 (0.6)	0.03	<0.01	<0.01
MELD-Na_{Tx} (points)	39 (6)	33 (6)	27 (9)	<0.01	<0.01	<0.01
$Creatinine_{Tx}$ (mg/dL)	4.1 (1)	2.5 (1)	1.5 (0.7)	<0.01	<0.01	0.03
Biologic sex						
Male (%)	46.0	58.7	52.8	0.19	0.43	0.59
Female (%)	54.0	41.3	47.8			
Ethnicity						
Hispanic (%)	5.0	10.6	18.7	0.41	0.05	0.13
Non-Hispanic (%)	95.0	89.4	81.3			
Race						
White (%)	95.0	80.0	83.0	0.04	0.14	0.59
Non-white (%)	5.0	20.0	17.0			
Distance to transplant center						
0–50 mi (%)	46.0	61.5	59.3	0.29	0.32	0.98
51–100 mi (%)	40.5	24.0	28.8			
>100 mi (%)	13.5	14.5	11.9			
Acute-on-chronic liver failure grade						
Grade 1 (%)	2.7	32.4	45.8	<0.01	<0.01	0.13
Grade 2 (%)	46.0	54.0	40.7			
Grade 3 (%)	51.0	17.3	13.5			
Transplant evaluation laboratories						
White blood cells (10^3/μL)	18.7 (9)	10.1 (6)	7.9 (4)	<0.01	<0.01	0.27
Hematocrit (%)	28.3 (5)	27.0 (6)	26.7 (6)	0.25	0.19	0.74
Platelets (10^3/μL)	149 (98)	109 (69)	60 (108)	0.01	0.01	0.94
Albumin (g/dL)	3.0 (0.6)	3.2 (0.7)	2.9 (0.5)	0.11	0.17	<0.01

(Continued)

Table 1. (Continued)

Characteristics	$AAH_{HRS\ (1)}$	$CLD_{HRS\ (2)}$	$CLD_{no\ HRS\ (3)}$	1 *versus* 2	1 *versus* 3	2 *versus* 3
Sodium (mmol/L)	133(8)	132 (8)	132 (8)	0.69	0.72	0.99
Bilirubin (mg/dL)	27.0 (11)	10.4(11)	8.1 (7)	<0.01	<0.01	0.16
INR	2.1 (0.8)	1.86 (0.76)	1.7 (1.0)	0.02	<0.01	0.04
Clinical metrics and outcomes						
Required ICU stay (%)	59.4	58.6	25.4	0.93	<0.01	<0.01
Length of evaluation (days)	23 (52)	26 (50)	35 (58)	0.80	0.33	0.35
Listing to transplant time (days)	11 (2)	44 (11)	83 (43)	0.3	0.05	0.20
Listed (%)	78.3	75.0	76.3	0.68	0.82	0.86
Transplanted (%)	48.6	41.3	35.6	0.62	0.18	0.25
Total deaths (%)	21.6	36.5	20.3	0.08	0.85	0.03
Listed deaths (%)	5.0	31.1	30.0	0.25	0.35	0.91
Blood volume intraoperative (mL)	3699 (1408)	3646 (1857)	3058 (1468)	0.91	0.24	0.19
Post-LT complications (%)	33.3	20.9	23.8	0.31	0.51	0.79
Pretransplant RRT requirements						
⩾1 session RRT before Tx (%)	66.7	46.5	9.5	0.45	<0.01	0.01
⩾1 week RRT before Tx (%)	61.1	34.9	9.5	0.18	<0.01	0.09
Posttransplant kidney outcomes						
>30 days post-LT RRT (%)	50.0	23.0	5.0	0.02	<0.01	0.09
Post-LT KTE (%)	22.0	14.0	5.0	0.41	0.27	0.64
Post-LT KTx (%)	11.0	2.0	5.0	0.15	0.36	0.67
Posttransplant ⩾30-day RRT need for patients without RRT need before LT						
New ⩾ 30-day RRT post-LT (%)	33.3	8.7	0.0	0.12	–	–

Demographics, clinical characteristics, and outcomes of the study for the three cohorts, AAH_{HRS}, CLD_{HRS}, and $CLD_{no\ HRS}$, are shown above. Continuous variables are reported as mean (SD) and compared using student's *t* tests and analysis of variance tests for two- and three-group comparisons, respectively. Categorical variables are reported as percentages, and compared using Pearson's χ^2 test. Data were assessed at $p = 0.05$ for significance.
AAH, alcohol-associated hepatitis; CLD, chronic liver disease; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; KTE, kidney transplant evaluation; KTx, kidney transplantation; Tx, transplant; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; RRT, renal replacement therapy.

Table 2. Subgroup analysis: effect of etiology and chronicity of liver disease on HRS outcomes.

Characteristics	AAH_{HRS} (1)	$A\text{-}CLD_{HRS}$ (2)	$O\text{-}CLD_{HRS}$ (3)	1 *versus* 2	1 *versus* 3	2 *versus* 3
Subject number	37	47	57	–	–	–
Age (years)	44 (11)	58 (10)	56 (9)	<0.01	<0.01	0.21
BMI (kg/m^2)	31 (8)	32 (9)	30 (8)	0.68	0.53	0.20
Sex (%Male)	46.0	68.0	51.0	0.04	0.64	0.10
Evaluation laboratories						
MELD-Na_{eval}. (points)	36 (6)	30 (7)	23 (8)	<0.01	<0.01	<0.01
Creatinine (mg/dL)	3.1 (2)	2.6 (1)	2.5 (1)	0.11	0.07	0.86
MELD-Na_{txp} (points)	39 (6)	33 (6)	27 (9)	<0.01	<0.01	<0.01
$Creatinine_{txp}$ (mg/dL)	4.1 (2)	2.4 (1)	2.5 (1)	<0.01	<0.01	0.71
Clinical metrics and outcomes						
Required ICU stay (%)	59.4	57.4	59.6	0.85	0.99	0.82
Length of evaluation (days)	23 (52)	15 (24)	35 (64)	0.55	0.31	0.08
Listing to transplant time (days)	11 (2)	34 (13)	53 (18)	0.27	0.04	0.31
Listed (%)	78.4	81.0	70.0	0.79	0.37	0.21
Total deaths (%)	21.6	29.8	42.1	0.43	0.03	0.18
Listed deaths (%)	18.0	26.0	35.0	55.1	16.9	42.2
Transplanted (%)	48.6	44.7	38.6	0.72	0.34	0.54
Blood volume intraoperative (mL)	3699 (1408)	3737 (1940)	3559 (1816)	0.95	0.80	0.74
Postoperative LT complications (%)	33.3	28.6	13.6	0.73	0.16	0.26
Posttransplant kidney outcomes						
⩾30 days post-LT RRT (%)	50.0	23.8	22.7	0.08	0.06	0.94
Post-LT KTE (%)	22.0	19.0	9.1	0.79	0.28	0.39
Post-LT KTx (%)	11.0	0.0	4.7	0.12	0.34	0.50

Clinical characteristics and outcomes of the study for AAH_{HRS} and CLD_{HRS} subgroups ($A\text{-}CLD_{HRS}$ and $O\text{-}CLD_{HRS}$) are shown above. Continuous variables are reported as mean (SD) and compared using student's *t* tests and analysis of variance tests for two- and three-group comparisons, respectively. Categorical variables are reported as percentages, and compared using Pearson's χ^2 test. Data were assessed at $p = 0.05$ for significance.
AAH, alcohol-associated hepatitis; A-CLD, cirrhosis due to alcohol; CLD, chronic liver disease; HRS, hepatorenal syndrome; ICU, intensive care unit; KTE, kidney transplant evaluation; KTx, kidney transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; O-CLD, cirrhosis from other causes; RRT, renal replacement therapy.

model was 0.88, indicating a good model fit. The logistic regression model also showed that while postoperative complications have a significant effect on 30-day renal outcomes post-LT, intraoperative pRBC transfusion volume did not. Inclusion of bilirubin in this model, to account for the effect of cholemic nephropathy, did not affect the relationship between cohort and RRT need,

Table 3. Effect of confounding factors on ⩾30 days post-LT RRT needs.

Confounding factors	<30 days post-LT RRT	⩾30 days post-LT RRT	*p* Value
Bilirubin > 15 (%)	43.5	60	0.2
Intraoperative pRBC volume (mL)	3324 (1563)	4201 (2057)	0.04
Postoperative complications (%)	17.7	45	0.01

Confounding factors (bilirubin ⩾ 15, postoperative complications occurrence, volume of intraoperative blood transfusion required) were compared across patients who required ⩾30 days post-LT RRT and those who did not.
LT, liver transplantation; pRBC, packed red blood cell; RRT, renal replacement therapy.

Table 4. Multivariate logistic regression predictive of post-LT renal outcomes.

Independent variables	Unadjusted				Adjusted			
	Wald	*Df*	OR	*p*	Wald	*Df*	aOR	*p*
Cohort	8.49	2	–	0.01	5.40	2	–	0.06
AAH_{HRS}	7.05	1	20.00	0.01	5.01	1	19.17	0.02
Age	0.05	1	1.05	0.82	3.17	1	1.08	0.08
Sex	0.07	1	1.15	0.79	0.01	1	1.06	0.91
$MELD_{tpx}$	6.31	1	1.11	0.01	1.86	1	1.08	0.17
pRBC (mL)	4.21	1	1.00	0.04	2.50	1	0.11	1.00
Postoperative complications	5.69	1	3.79	0.02	4.26	1	4.07	0.04
Constant	–	–	–	–	7.00	1	0.00	0.01

Unadjusted model includes binomial logistic regression with one independent variable present (row) and the dependent variable 30-day RRT posttransplant (left side of table); the adjusted model is a single entry logistic regression with all independent variables present and the dependent variable: 30-day RRT posttransplant (right side of table). Reference variable for cohort = $CLD_{no\ HRS}$. When referenced to CLD_{HRS}, AAH_{HRS} aOR = 4.1 ($p = 0.09$). Goodness of fit for the adjusted model which includes the covariates age, sex, MELD-Na at transplant, operative complications, and pRBC requirement was 0.88, indicating a good model fit.
AAH, alcohol-associated hepatitis; aOR, adjusted odds ratio; CLD, chronic liver disease; Df, degrees of freedom; HRS, hepatorenal syndrome; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OR, odds ratio; RRT, renal replacement therapy.

but did reduce the goodness of fit. Ultimately, AAH_{HRS} was associated with a 19× odds of requiring ⩾30 days post-LT RRT compared to $CLD_{no\ HRS}$ and 4× odds of requiring ⩾30 days post-LT RRT compared to CLD_{HRS} (Table 4).

Discussion

We evaluated differences in transplant outcomes and post-LT renal outcomes in patients with AAH and CLD who were diagnosed with HRS. First, we observed high incidence of HRS in each cohort. The prevalence of HRS in AAH is not well studied. Previous literature on HRS in CLD suggests that HRS-AKI affects up to 40% of patients with CLD; however, the proportion is reported to increase with disease progression.[8,15] We found HRS to be present in 63.8% of patients with CLD, which can be attributed to the critical illness of the cohort studied.

Our results show that subjects with AAH_{HRS} were more likely to be approved and transplanted compared to subjects with CLD_{HRS}; yet, this difference was not statistically significant. Furthermore, subjects with AAH_{HRS} were less likely to die than

patients within the CLD_{HRS} cohort despite higher MELD-Na and ACLF scores. Possible reasons for favorable survival outcomes in patients with AAH include younger age and shorter waitlist time[16–18]; however, the frequency of concomitant HRS with AAH was not reported in the referenced studies.

While AAH_{HRS} was associated with improved outcomes in the LTE process, it was associated with worse post-LT renal outcomes. Approximately half the AAH_{HRS} cohort required RRT for ⩾30 days after LT compared to a quarter for the CLD_{HRS} cohort and one out of 20 for the $CLD_{no\ HRS}$ cohort. The relationship between post-LT renal outcomes remained when controlling for pertinent confounders through multivariate regression as shown in Table 4. Although not statistically significant, those with AAH were more likely to both be referred for and undergo kidney transplant.

Renal recovery is estimated to occur in 60–75% of cirrhotic patients with HRS within 30 days after LT,[7] while data on long-term requirement of RRT post-LT showed that less than 10% of surviving patients required RRT at 3 months.[19] We observed a lower rate of HRS reversal in the AAH_{HRS} cohort compared to previously reported in patients with cirrhosis, while the rate of reversal in the CLD_{HRS} cohort was consistent with previous studies.[7,20] In our study new RRT requirement post liver transplant was more common in AAH_{HRS} than in CLD_{HRS}; this further supports that the renal injury experienced by patients with AAH prior to LT persists longer than in CLD patients. These results pose the question of whether the etiology of liver disease plays an important aspect in the pathophysiology of HRS and whether HRS in AAH may occur in a unique physiological milieu that complicates reversal.

The understanding of the underlying mechanism of HRS is evolving with research that suggests systemic inflammation plays a substantial role beyond the well-established model of circulatory dysfunction.[21] Systemic inflammation in decompensated liver disease is secondary to bacterial translocation due to increased intestinal permeability, changes in the quality of the microbiome, and also a result of portal hypertension-associated immune dysfunction.[22] This milieu, even in the absence of active infection, is characterized by increased levels of pathogen-associated molecular patterns and damage-associated molecular patterns, leading to an increase in proinflammatory cytokines.[9,23] Interestingly, Sole *et al.* have showed different cytokine profiles in patients with HRS compared with patients with prerenal AKI and patients with acute decompensation but without AKI. Patients with HRS had higher levels of IL-6, TNFa, IL-8, and VCAM-1 in their plasma, and there was no difference in these cytokine levels between patients with and without infection.[24]

Alcohol-associated cirrhosis with ongoing alcohol use has been associated with increased nonspecific inflammatory markers, such as WBC count and C-reactive protein.[25] Consistent with this finding, the AAH_{HRS} cohort in this study had a significantly higher WBC compared to CLD_{HRS} and $CLD_{no\ HRS}$, despite no difference in infection and SBP rates. We postulate that acute onset of HRS in AAH, and its associated post-LT renal dysfunction, is in part related to the persistent inflammatory state of AAH in conjunction with rapid onset of circulatory dysfunction. As previously discussed, HRS treatment can be less effective in patients with high serum bilirubin levels due to the effects of cholemic nephropathy.[12] Although patients with AAH and HRS in our study did have higher levels of bilirubin relative to other cohorts, the proportion of patients with bilirubin >15 was similar in those who required dialysis after LT and those who did not. Furthermore, controlling for bilirubin levels with binomial logistic regression did not affect post-LT renal outcomes in our study.

Intraoperative blood loss and blood transfusions are also described in the literature as risk factors for many complications after LT and for surgical reintervention after LT[10,11] Vascular and biliary post-LT complications have been shown to cause significant changes in patients' hemodynamics and also contribute to post-LT renal complication.[13] We did not find significant difference in the rate of perioperative and postoperative complications across different patient cohorts. Although logistic regression showed that postoperative complications have a significant effect on 30-day renal outcomes post-LT, the study cohort remained predictive of post-LT renal outcomes. Although intraoperative pRBC transfusion did not differ across different cohorts, patients with >30 days post-LT RRT received higher intraoperative pRBC transfusion volume. However,

controlling for intraoperative pRBC transfusion volumes with binomial logistic regression did not affect the relationship between the cohort and RRT need. This indicates that renal function recovery post-LT is impacted both by extrinsic factors that may cause significant hemodynamic changes and by the etiology of liver disease.

There is limited research assessing whether patients with AAH would benefit from early evaluation for kidney transplantation at the time of or after LT. Simultaneous liver kidney transplant (SLKT) eligibility criteria include patients with chronic kidney disease, sustained AKI, and specific metabolic diseases.[26] Sustained AKI has been defined as the requirement for acute dialysis for 6 weeks or longer; yet, only few studies assessed the need of pre-LT RRT and use of vasopressors for HRS as predictors of renal outcomes post-LT, and whether these variables should be part of the eligibility criteria for SLKT.[27] Interestingly, our study shows that there were no differences in the duration and frequency of RRT requirement prior to LT between the AAH_{HRS} and CLD_{HRS} cohorts.

Conclusion

Although our study is limited by its retrospective design and small sample size, this is one of the first studies to address the differences in renal outcomes post-LT in patients with concomitant HRS and AAH compared to patients with CLD. It should also be noted that our study had an approximately equal representation of the two genders, thus strengthening its external validity; this is relevant as the vast majority of studies on CLD have a male predominant population.

Overall, these results at our transplant center suggest that patients with AAH are more likely to develop HRS and subsequent RRT requirement, and that this difference persists even after LT. Our findings suggest that the etiology of acute hepatic decompensation as well as postoperative complications that result in hemodynamic changes can affect the probability of renal recovery post-LT. Specifically, AAH_{HRS} patients without a RRT need prior to transplant were more likely to develop a new ⩾30-day RRT requirement after LT relative to CLD_{HRS} patients who did not undergo RRT prior to LT. This hints to a possible pretransplant kidney injury experienced by AAH patients, which persists longer compared to CLD patients. Furthermore, when controlling for surgical complications and intraoperative transfusion needs, AAH as etiology of liver disease remained predictive of requiring ⩾30 days of RRT after LT. Future studies are necessary to better delineate the mechanism of HRS in patients with AAH and to determine whether this population would benefit from early evaluation for kidney transplantation.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Institutional review board at our medical center. The IRB ID is STUDY00000016, and it was approved on 11/10/2021. This is an IRB-approved retrospective study, all patient information was de-identified and patient consent was not required.

Consent for publication

All patients were consented for the transplant evaluation and listing and also for the transplant surgery itself. Informed consent for publication was not obtained from each participant as this would have not been feasible given the retrospective nature of the study. As part of the IRB approved by our medical center, it was declared that data may be utilized for publications, and that no patient identifying information would be included.

Author contributions

Alessandro Colletta: Conceptualization; Data curation; Formal analysis; Investigation; Software; Visualization; Writing – original draft; Writing – review & editing.

Katherine M. Cooper: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Deepika Devuni: Conceptualization; Investigation; Project administration; Resources; Supervision; Writing – review & editing.

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Competing interests

Dr. Alessandro Colletta and Dr. Katherine Cooper do not have any competing interests. Dr. Deepika Devuni is an associate professor of medicine at UMass Chan Medical School. She has received grant funding from Sequana Medical for a clinical trial which is unrelated to the present work. She also has a grant from National Institute on Alcohol Abuse and Alcoholism (NIAAA-AA017986-11), which is not related to this research.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author. Demographic, clinical, laboratory, and outcome data were extracted from subjects' medical records and managed using REDCap electronic data capture tools at our institution. All patients' information was fully de-identified.

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