Prognosis of Patients with Cirrhosis and AKI Who Initiate RRT

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Abstract

Background and objectives Literature on the prognosis of patients with cirrhosis who require RRT for AKI is sparse and is confounded by liver transplant eligibility. An update on outcomes in the nonlisted subgroup is needed. Our objective was to compare outcomes in this group between those diagnosed with hepatorenal syndrome and acute tubular necrosis, stratifying by liver transplant listing status.

Design, setting, participants, & measurements Retrospective cohort study of patients with cirrhosis acutely initiated on hemodialysis or continuous RRT at five hospitals, including one liver transplant center. Multivariable regression and survival analysis were performed.

Results Four hundred seventy-two subjects were analyzed (341 not listed and 131 listed for liver transplant). Among nonlisted subjects, 15% (51 of 341) were alive at 6 months after initiating RRT. Median survival was 21 (interquartile range [IQR], 8, 70) days for those diagnosed with hepatorenal syndrome and 12 (IQR, 3, 43) days for those diagnosed with acute tubular necrosis (P=0.25). Among listed subjects, 48% (63 of 131) received a liver transplant. Median transplant-free survival was 15 (IQR, 5, 37) days for those diagnosed with hepatorenal syndrome and 14 (IQR, 4, 31) days for those diagnosed with acute tubular necrosis (P=0.60). When stratified by transplant listing, with adjusted Cox models we did not detect a difference in the risk of death between hepatorenal syndrome and acute tubular necrosis (hazard ratio [HR], 0.81; 95% confidence interval [95% CI], 0.59 to 1.11, among those not listed; HR, 0.73; 95% CI, 0.44 to 1.19, among those listed).

Conclusions Cause of AKI was not significantly associated with mortality in patients with cirrhosis who required RRT. Among those not listed for liver transplant, mortality rates were extremely high in patients both with hepatorenal syndrome and acute tubular necrosis.

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Introduction

AKI is a common and morbid complication of cirrhosis, occurring in up to 50% of those with decompensated cirrhosis (1,2). About one-third of this AKI improves with administration of albumin or crystalloid, leaving two-thirds of these patients with persistent AKI, such as hepatorenal syndrome (HRS) or acute tubular necrosis (ATN) (1–4). These AKI subtypes carry a dismal prognosis, with 40% requiring RRT and 60% dying by 90 days (3,4). Not unexpectedly, health care costs in this setting are high (5–7).

Those who require RRT represent the most morbid subgroup of the cirrhotic population (8). In addition to the typical acute complications of RRT, such as intradialytic hypotension (9–12), increased risk of cardiac events (13–15), and complications related to venous access (16,17), there are additional physiologic challenges inherent in those with cirrhosis (18). Portal hypertension and splanchnic vasodilation result in decreased effective circulating volume, ascites formation, and low mean arterial pressure (19–21), all of which are barriers to adequate volume management and often necessitate transfer to the intensive care unit for support with intravenous vasopressors and continuous RRT (CRRT) (18).

Currently, there are few studies to guide clinical judgment of which patients with severe cirrhosis are optimal candidates for RRT. The available literature is limited by small sample sizes (22–24), older studies that do not reflect modern practice patterns (25–27), or inclusion of only liver transplantation candidates/recipients (23,24,28–35). Although RRT usually serves as a bridge to liver transplantation among those listed, literature is sparse regarding the use of RRT in those not listed for transplantation, particularly in HRS. Over time, advancements in the medical management of cirrhosis have led to allograft allocation at higher Model for End-Stage Liver Disease (MELD) scores, thus creating a larger population of noncandidates with indications for RRT (36). To provide an update in this growing group, we aimed to compare outcomes after initiation of RRT in cirrhosis, while stratifying by transplant listing status and adjusting for cause of AKI.

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Materials and Methods

Patient Population and Data Collection

We performed a retrospective cohort study of all inpatients with cirrhosis and AKI requiring RRT for either HRS or ATN between 2005 and 2015 in a network of five acute care hospitals (Partners Healthcare, Massachusetts), including one liver transplant center (Massachusetts General Hospital, Boston, MA), where all transplant listing evaluation was done for this population. Data were identified using a centralized clinical data collection warehouse designed for research and quality improvement purposes (37–39). All subjects were treated using local standard of care without intervention from the study team. Follow-up data were obtained *via* electronic medical record and database review and, if needed, by search of online obituaries and Social Security Death Index. Data were complete for each variable, except as noted in table/figure footnotes.

Hemodialysis (HD), CRRT treatments, and clinical diagnoses were identified using the Current Procedural Terminology, 4th Edition and International Classification of Diseases-9/10 codes (see Supplemental Table 1). All potential subjects underwent review of the electronic medical record to confirm accuracy of diagnostic codes and medical history (see Definitions). MELD score and Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure (CLIF-C ACLF) score were calculated at the time of RRT initiation (40,41). Subjects were excluded if they were lost to follow-up after discharge (n=3).

Definitions

Definitions and causes of cirrhosis were on the basis of clinical determination by the treating hepatologist. Subjects were classified as "not listed" if they were evaluated and rejected for liver transplant listing, or if they were felt not to be appropriate for transplant evaluation by treating clinicians (due to critical illness, ongoing alcohol use, *etc.*). Subjects were classified as "listed" for liver transplant if they were registered on the United Network for Organ Sharing waiting list (before or after the start of RRT) at the study's liver transplant center.

All subjects received either intermittent HD or continuous veno-venous hemofiltration (CVVH) as their modality of RRT. CVVH was performed in lieu of intermittent HD when subjects required intravenous vasopressor support and/or were considered hemodynamically unstable by the treating nephrologist. Cause of AKI was on the basis of the clinical evaluation by the treating nephrologist at the time of initiation of RRT. HRS was diagnosed after exclusion of other potential causes of AKI on the basis of diagnostic criteria at the time (42,43). ATN was diagnosed when kidney parameters did not respond to volume administration and clinical history was consistent with ischemic or nephrotoxic AKI. One author confirmed HRS versus ATN status *via* chart review. If the treating nephrologist identified a mixed type of HRS and ATN, the cause was considered ATN, given HRS is a diagnosis of exclusion. If there was discordance between the treating clinician and author review, a second author provided the tie-breaking diagnosis.

Outcomes and Statistical Analyses

The primary outcome for this study was 6-month survival. Transplant-free survival was also assessed among those listed for liver transplant. Secondary outcomes assessed included rates of solitary liver or dual liver-kidney transplantation, and dialysis dependence at 6 months. A multivariable Cox model was created using a univariate screen and stepwise selection algorithm to identify significant factors associated with 6-month mortality (covariates were entered into the model if $P<0.1$ and were retained in the final model if $P<0.05$). Differences in the primary outcome between HRS and ATN subgroups were visualized using a Kaplan–Meier curve and compared using a log-rank test. Prespecified Cox proportional hazard models were performed to determine the effect of HRS versus ATN on mortality after adjusting for age, MELD score, and initial RRT modality. Results of Cox proportional hazard models were summarized with hazard ratios (HRs) and Wald asymptotic 95% confidence intervals (95% CIs) and given a normal distribution of deviance residuals; continuous variables were presented as means and 95% CIs, except for median survival time, which was presented as median and interquartile range (IQR). SAS version 9.4 (Gary, NC) and R version 3.2.2 were used for analysis (44). Two tailed P values <0.05 were considered statistically significant.

Ethics Statement

The Partners Institutional Review Board approved this study. All procedures and practices abide by the guidelines set forth by the Declarations of Helsinki and Istanbul. The need for informed consent was waived for this study.

Results

General Demographics

Figure 1 describes the selection of the cohort used in final analysis. Four hundred seventy-two subjects were included in the final analysis. Three hundred forty-one were not listed for liver transplant and 131 were listed for liver transplant. Eighty-five percent of subjects were either initially evaluated at Massachusetts General Hospital or were transferred there after initiating RRT for expedited transplant evaluation. Of those not listed, 16% (56 of 341) were diagnosed with HRS and 84% (285 of 341) were diagnosed with ATN. Of those listed, 47% (62 of 131) were diagnosed with HRS and 53% (69 of 131) were diagnosed with ATN. Sixty-four percent (84 of 131) were listed before initiating RRT. Subjects were less likely to be initiated on RRT for HRS if they were not listed for liver transplant (relative risk, 0.59; 95% CI, 0.48 to 0.72; $P<0.001$).

Demographics and baseline characteristics of subjects stratified by transplant listing status and cause of AKI are presented in Table 1. Age, sex, race, and ethnicity were similar between those with HRS and ATN in both nonlisted and listed subgroups. Among nonlisted subjects, those with HRS had higher MELD and CLIF-C ACLF scores at the start of RRT compared with those with ATN. Sepsis, admission to the intensive care unit, use of intravenous vasopressors, and mechanical ventilation were more common among those with ATN compared with HRS in both subgroups. Fifty-seven percent (271 of 472) of all subjects initially started on HD. Among these 271 subjects, 128 later transitioned to CVVH for a total usage rate of 70% (329 of 472) for CVVH.

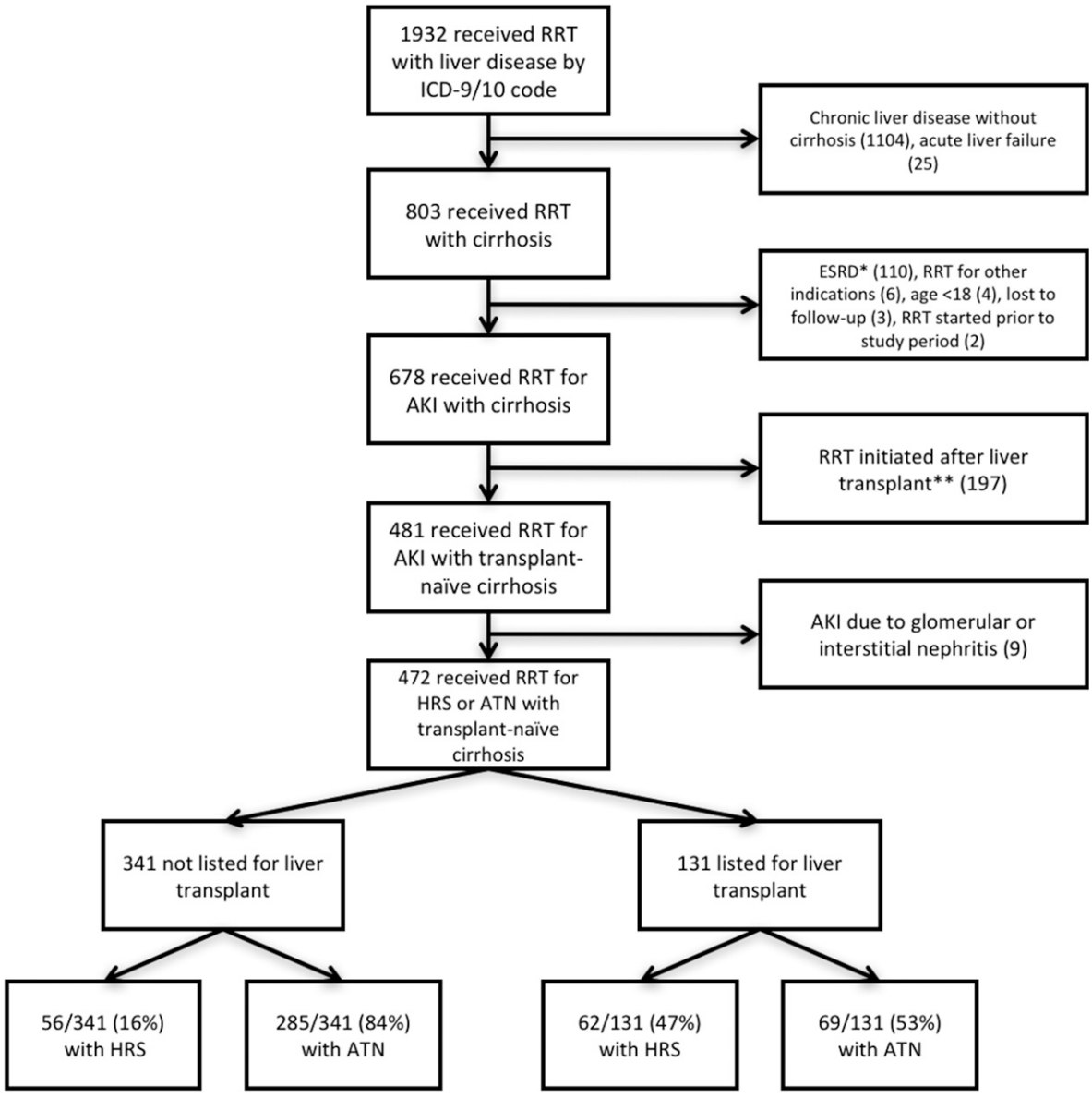

Figure 1. | **Flow diagram of patient selection.** *Includes subjects with a prior kidney transplant or on chronic dialysis. **Includes subjects initiated on RRT immediately postoperatively and subjects with a prior history of liver transplant. ATN, acute tubular necrosis; HRS, hepatorenal syndrome; ICD-9/10, International Classification of Diseases 9/10.

A reference group of 159 hospitalized subjects with cirrhosis, severe AKI (serum creatinine >4 mg/dl), and documentation that RRT was not offered due to patient/provider decision was compared with the 341 nonlisted subjects who did receive RRT (see Supplemental Table 2). Subjects treated with RRT were similar to those not treated with RRT in sex, race, ethnicity, comorbidities, and cause of cirrhosis. Subjects not treated with RRT were slightly older (61 [95% CI, 59 to 63] versus 58 [95% CI, 57 to 59] years; P=0.02), had higher MELD scores (40 [95% CI, 39 to 42] versus 34 [95% CI, 33 to 35]; P<0.001), were more likely to be diagnosed with HRS versus ATN (43% versus 16%; P<0.001), were more likely to have hepatocellular carcinoma (25% versus 9%; P<0.001), were less likely to use intensive care unit resources, had shorter median hospital length of stay (10 [IQR, 5, 16] versus 17 [IQR, 8, 28] days; P<0.001), and had shorter median survival (2 [IQR, 1, 7] versus 14 [IQR, 4, 50] days; P<0.001).

Six-Month Survival: All Subjects

Twenty-four percent (114 of 472) of all subjects were alive at 6 months. Table 2 summarizes demographics and characteristics of all subjects by vital status at 6 months. Age, sex, and ethnicity were similar between those who were alive versus died by 6 months. Those alive at 6 months were more likely to be of white race, were more commonly initiated on HD compared with CVVH, and had lower CLIF-C ACLF scores. Figure 2 summarizes raw outcomes at 6 months for all subjects, stratified by transplant listing status.

Table 1. Demographics and baseline characteristics of 472 patients with cirrhosis initiated on RRT for AKI

Characteristic	Not Listed for Liver Transplant			Listed for Liver Transplant		
	All Not Listed	HRS	ATN	All Listed	HRS	ATN
	n=341	*n*=56	*n*=285	*n*=131	*n*=62	*n*=69
Age, yr	58 (57 to 59)	57 (53 to 60)	58 (57 to 60)	55 (54 to 57)	56 (54 to 59)	54 (52 to 57)
Female sex	111 (33)	17 (30)	94 (33)	51 (39)	26 (42)	25 (36)
White race	257 (75)	40 (71)	217 (76)	112 (86)	55 (89)	57 (83)
Non-Hispanic ethnicity	317 (93)	53 (95)	264 (93)	124 (95)	59 (95)	65 (94)
Comorbidities						
Diabetes mellitus	126 (37)	20 (36)	106 (37)	44 (34)	22 (36)	22 (32)
Coronary artery disease	98 (29)	17 (30)	81 (28)	28 (21)	14 (23)	14 (20)
CKD	54 (16)	18 (32)	36 (13)	25 (19)	12 (19)	13 (19)
Hypertension	187 (55)	32 (57)	155 (54)	76 (58)	41 (66)	35 (51)
Reason for admission						
Complications of cirrhosis	96 (28)	28 (50)	68 (24)	75 (57)	41 (66)	34 (49)
AKI	43 (13)	15 (27)	28 (10)	23 (18)	15 (24)	8 (12)
Infection	126 (37)	8 (14)	118 (41)	23 (18)	4 (6)	19 (28)
Other	76 (22)	5 (9)	71 (25)	10 (8)	2 (3)	8 (12)
Other hospitalization characteristics						
Sepsis	206 (60)	17 (30)	189 (66)	73 (56)	27 (44)	46 (67)
Admission/transfer to intensive care unit	287 (85)	34 (61)	253 (89)	99 (76)	41 (66)	58 (84)
Intravenous vasopressor use	260 (76)	28 (50)	232 (81)	91 (69)	35 (56)	56 (81)
Mechanical ventilation	197 (58)	9 (16)	188 (66)	54 (41)	19 (31)	35 (51)
Length of stay, d	21 (19 to 23)	18 (14 to 23)	21 (18 to 24)	35 (30 to 39)	33 (26 to 39)	36 (29 to 43)
Initial renal replacement modality						
Intermittent hemodialysis	195 (57)	41 (73)	154 (54)	76 (58)	39 (63)	37 (54)
Continuous veno-venous hemofiltration	146 (43)	15 (27)	131 (46)	55 (42)	23 (37)	32 (46)
Cause of cirrhosis[a]						
Alcohol	135 (40)	24 (45)	111 (39)	40 (31)	23 (37)	17 (25)
Hepatitis C	59 (17)	7 (13)	52 (18)	27 (21)	12 (19)	15 (22)
Nonalcoholic steatohepatitis	21 (6)	5 (9)	16 (6)	20 (15)	10 (16)	10 (14)
Multifactorial	45 (13)	9 (16)	36 (13)	14 (11)	6 (10)	8 (12)
Other	79 (23)	10 (18)	69 (24)	30 (23)	11 (17)	19 (28)
Prior complications of liver disease						
Ascites	263 (77)	53 (95)	210 (74)	124 (95)	62 (100)	62 (90)
Encephalopathy	186 (55)	36 (64)	150 (53)	93 (71)	49 (79)	44 (64)
Gastrointestinal bleeding	215 (63)	39 (70)	176 (62)	86 (66)	44 (71)	42 (61)
Spontaneous bacterial peritonitis	61 (18)	9 (16)	52 (18)	53 (40)	30 (48)	23 (33)
Hepatocellular carcinoma	29 (9)	8 (14)	21 (7)	12 (9)	4 (6)	8 (12)
MELD score	34 (33 to 34)	36 (34 to 38)	33 (32 to 34)	36 (35 to 37)	37 (35 to 38)	35 (33 to 37)
CLIF-C ACLF score	60 (59 to 62)	50 (47 to 53)	62 (60 to 63)	58 (56 to 60)	55 (52 to 58)	59 (56 to 63)
Laboratory values						
Sodium, meq/L	136 (135 to 136)	134 (133 to 136)	136 (135 to 137)	135 (134 to 136)	135 (133 to 136)	135 (134 to 137)
BUN, mg/dl	65 (61 to 69)	61 (53 to 68)	66 (61 to 70)	65 (60 to 70)	70 (63 to 77)	61 (54 to 68)
Creatinine, mg/dl	4.3 (4.1 to 4.5)	5.3 (4.9 to 5.8)	4.1 (3.9 to 4.4)	4.1 (3.9 to 4.4)	4.6 (4.2 to 4.9)	3.8 (3.4 to 4.2)
Urine sodium, mmol/L[b]	36 (29 to 42)	33 (1 to 66)	36 (32 to 40)	24 (19 to 29)	20 (14 to 25)	29 (21 to 36)
White blood count, K/μl	14.8 (13.7 to 15.9)	10.5 (8.7 to 12.3)	15.6 (14.4 to 16.9)	10.4 (9.2 to 11.6)	9.6 (8.3 to 10.9)	11.1 (9.1 to 13.2)
Hemoglobin, g/dl	9.3 (9.2 to 9.5)	9.4 (8.9 to 9.9)	9.3 (9.1 to 9.5)	9.0 (8.7 to 9.2)	9.0 (8.6 to 9.3)	9.0 (8.6 to 9.3)
Platelets, K/μl	102 (95 to 110)	88 (72 to 104)	105 (97 to 113)	76 (68 to 85)	72 (61 to 83)	80 (67 to 93)
Albumin, g/dl[c]	2.9 (2.8 to 3.0)	3.2 (3.1 to 3.4)	2.8 (2.8 to 2.9)	3.3 (3.2 to 3.4)	3.4 (3.2 to 3.5)	3.2 (3.0 to 3.4)
International normalized ratio	2.1 (2.0 to 2.2)	2.0 (1.8 to 2.3)	2.1 (2.0 to 2.2)	2.2 (2.1 to 2.3)	2.1 (2.0 to 2.3)	2.2 (2.0 to 2.4)
Total bilirubin, mg/dl	12 (10 to 13)	14 (10 to 19)	11 (10 to 13)	16 (13 to 18)	16 (12 to 20)	16 (13 to 19)
Aspartate aminotransferase, U/L[d]	577 (390 to 764)	452 (−20 to 924)	602 (397 to 807)	254 (−20 to 528)	101 (46 to 156)	391 (−130 to 913)
Alanine aminotransferase, U/L[d]	189 (137 to 241)	177 (11 to 344)	192 (139 to 244)	120 (−8 to 250)	40 (29 to 52)	191 (−54 to 436)
Alkaline phosphatase, U/L[d]	162 (145 to 178)	146 (112 to 181)	165 (146 to 183)	114 (102 to 126)	113 (97 to 130)	116 (98 to 133)

Cells represent *N* (percent) for categoric variables and mean (95% confidence interval) for continuous variables. HRS, hepatorenal syndrome; ATN, acute tubular necrosis; MELD, Model for End Stage Liver Disease; CLIF-C ACLF, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure Score.

[a]*n*=470 available.

[b]*n*=357 available.

[c]*n*=471 available.

[d]*n*=468 available.

Table 2. Characteristics of 472 patients with cirrhosis initiated on RRT for AKI, by vital status at 6 mo

Characteristic	Alive at 6 mo (*n*=114)	Died by 6 mo (*n*=358)	*P* Value
Age, yr	56 (54 to 58)	58 (56 to 59)	0.28
Female sex	39 (34)	123 (34)	0.97
White race	97 (85)	272 (76)	0.04
Non-Hispanic ethnicity	109 (96)	332 (93)	0.28
Comorbidities			
Diabetes mellitus	51 (45)	119 (33)	0.03
Coronary artery disease	32 (28)	94 (26)	0.70
CKD	24 (21)	55 (15)	0.15
Hypertension	74 (65)	189 (53)	0.02
Reason for admission			<0.001
Complications of cirrhosis	53 (46)	118 (33)	
AKI	25 (22)	41 (11)	
Infection	20 (18)	129 (36)	
Other	16 (14)	70 (20)	
Other hospitalization characteristics			
Sepsis	57 (50)	222 (62)	0.02
Admission/transfer to intensive care unit	71 (63)	315 (88)	<0.001
Intravenous vasopressor use	65 (57)	286 (80)	<0.001
Mechanical ventilation	41 (36)	210 (59)	<0.001
Length of stay, d	38 (32 to 44)	20 (18 to 22)	<0.001
Initial renal replacement modality			0.01
Intermittent hemodialysis	77 (68)	194 (54)	
Continuous veno-venous hemofiltration	37 (32)	164 (46)	
Cause of cirrhosis[a]			0.10
Alcohol	36 (32)	139 (39)	
Hepatitis C	17 (15)	69 (19)	
Nonalcoholic steatohepatitis	16 (14)	25 (7)	
Multifactorial	16 (14)	43 (12)	
Other	29 (25)	80 (22)	
Prior complications of liver disease			
Ascites	95 (83)	292 (82)	0.67
Encephalopathy	78 (68)	201 (56)	0.02
Gastrointestinal bleeding	74 (65)	227 (63)	0.77
Spontaneous bacterial peritonitis	35 (31)	79 (22)	0.06
Hepatocellular carcinoma	10 (9)	31 (9)	0.97
MELD score	33 (32 to 35)	35 (34 to 35)	0.12
CLIF-C ACLF score	55 (52 to 57)	61 (60 to 63)	<0.001
Cause of AKI			<0.001
Hepatorenal syndrome	43 (38)	75 (21)	
Acute tubular necrosis	71 (62)	283 (79)	
Laboratory values			
Sodium, meq/L	135 (134 to 136)	136 (135 to 136)	0.27
BUN, mg/dl	62 (56 to 68)	66 (62 to 69)	0.26
Creatinine, mg/dl	4.6 (4.2 to 5.0)	4.2 (4.0 to 4.4)	0.02
Urine sodium, mmol/L[b]	31 (25 to 37)	33 (27 to 38)	0.66
White blood count, K/μl	11.5 (10.0 to 13.1)	14.2 (13.2 to 15.2)	0.01
Hemoglobin, g/dl	9.0 (8.7 to 9.2)	9.3 (9.2 to 9.5)	0.04
Platelets, K/μl	96 (83 to 108)	95 (88 to 102)	0.92
Albumin, g/dl[c]	3.1 (3.0 to 3.2)	3.0 (2.9 to 3.0)	0.03
International normalized ratio	1.9 (1.8 to 2.0)	2.2 (2.1 to 2.3)	<0.001
Total bilirubin, mg/dl	12 (9 to 14)	13 (12 to 15)	0.32
Aspartate aminotransferase, U/L[d]	306 (−17 to 629)	544 (366 to 721)	0.20
Alanine aminotransferase, U/L[d]	89 (40 to 137)	195 (129 to 261)	0.01
Alkaline phosphatase, U/L[d]	128 (113 to 143)	155 (139 to 171)	0.01

Cells represent *N* (percent) for categoric variables and mean (95% confidence interval) for continuous variables. MELD, Model for End Stage Liver Disease; CLIF-C ACLF, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure Score.
[a]*n*=470 available.
[b]*n*=357 available.
[c]*n*=471 available.
[d]*n*=468 available.

Twenty candidate variables were entered into a stepwise algorithm to evaluate 6-month mortality in multivariable Cox regression. MELD score was included over CLIF-C ACLF score due to colinearity and its wider current clinical use. Seven variables were significantly associated with mortality in the final model (see Table 3), including nonlisted transplant status, MELD score, age, admission to the intensive care unit serum alanine aminotransferase, mechanical ventilation, and initiation with CVVH.

Fifty-nine subjects who were alive at 6 months and did not receive a liver transplant were analyzed for factors associated with kidney recovery. Thirty-four of 59 (58%) recovered off dialysis by 6 months. Those who recovered were similar in sex, race, ethnicity, comorbidities, and MELD/CLIF-C ACLF scores compared with those who did not recover. Those who recovered were younger (54 [95% CI, 50 to 59] versus 62 [95% CI, 56 to 67] years; *P*=0.05), were less likely to have preadmission CKD (33% versus

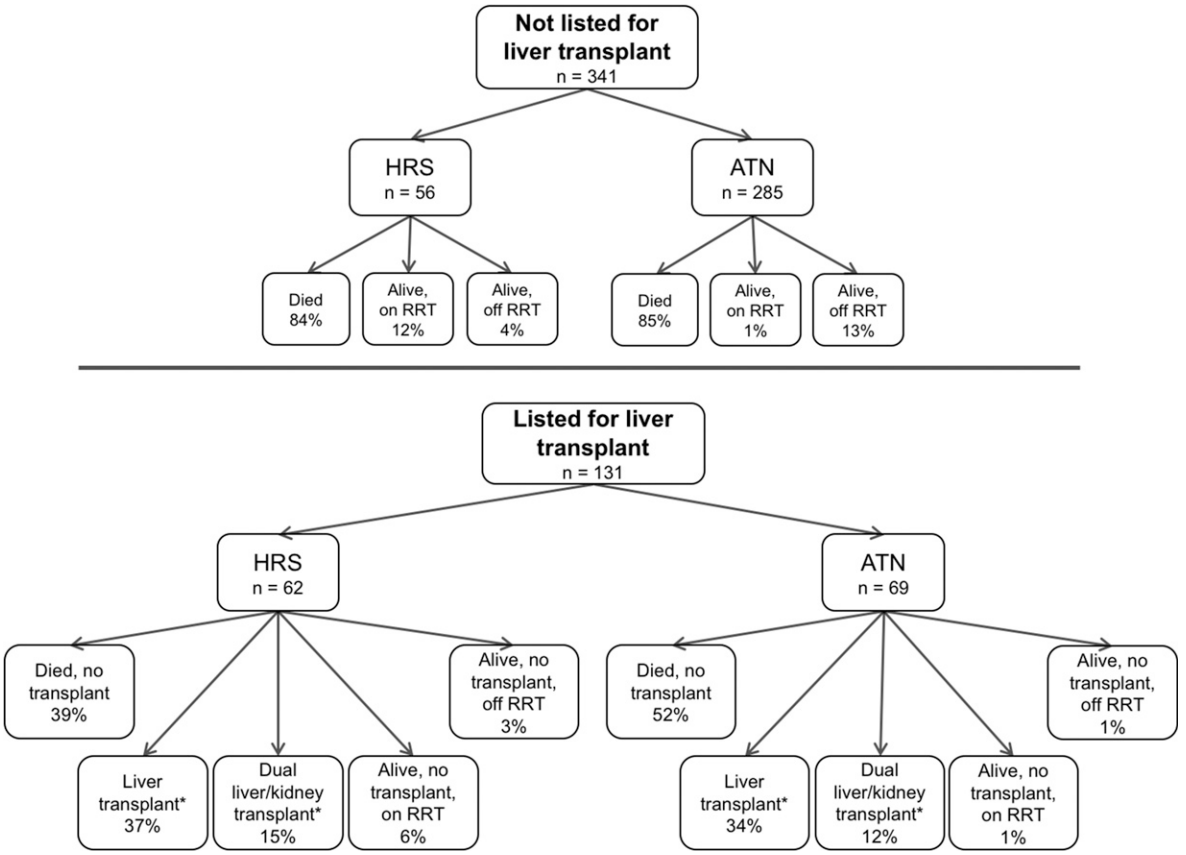

Figure 2. | **Summary of unadjusted outcomes at 6 months among 472 patients with cirrhosis initiated on RRT for AKI.** *Includes subjects who died within 6 months after liver or liver/kidney transplant (*n*=8). ATN, acute tubular necrosis; HRS, hepatorenal syndrome.

67%; *P*=0.02), were less likely to have a prior history of ascites (49% versus 82%; *P*=0.02), and were more likely to have alcoholic cirrhosis (41% versus 21%; *P*=0.01). During their admission, those who recovered were more likely to be diagnosed with ATN versus HRS (69% versus 29%; $P<0.01$), have sepsis (74% versus 45%; *P*=0.02), have higher white blood cell count (13.3 [95% CI, 9.8 to 16.9] versus 9.3 [95% CI, 7.1 to 11.5]; *P*=0.05), and require mechanical ventilation (77% versus 47%; *P*=0.02) and CVVH (81% versus 50%; *P*=0.03).

Outcomes for Nonlisted Subjects

Among nonlisted subjects, 15% (51 of 341) were alive at 6 months after initiating RRT. Survival was similar between HRS and ATN subgroups, with an unadjusted median survival of 21 (IQR, 8, 70) days for HRS, 12 (IQR, 3, 43) days for ATN (*P*=0.25; Figure 3A), and 14 (IQR, 4, 50) days for all nonlisted subjects. In a model adjusting for age, MELD score, and initial RRT modality, subjects diagnosed with HRS had similar risk of death as ATN (HR, 0.81; 95% CI, 0.59 to 1.11; *P*=0.19; Table 4). Sensitivity analyses showed similar results when (*1*) substituting CLIF-C ACLF score for MELD score and age, (*2*) substituting other indicators of critical illness for initial RRT modality (admission to the intensive care unit, use of intravenous vasopressors, use of mechanical ventilation), and (*3*) including cause of cirrhosis as an additional covariate. Seventy-eight percent (40 of 51) who were alive at 6 months recovered kidney function and were off dialysis (2 of 9 for HRS and 38 of 42 for ATN).

Outcomes for Listed Subjects

Among listed subjects, survival was similar between HRS and ATN subgroups (*P*=0.12; Figure 3B). In a model adjusting for age, MELD score, and initial RRT modality, subjects with HRS had similar risk of death as ATN (HR, 0.73; 95% CI, 0.44 to 1.19; *P*=0.21; Table 4). This was also true for transplant-free survival in unadjusted analysis (median transplant-free survival of 15 [IQR, 5, 37] days for HRS and 14 [IQR, 4, 31] days for ATN; *P*=0.60; Figure 3C) and adjusted analysis (HR, 0.93; 95% CI, 0.64 to 1.35; *P*=0.70; Table 4). Median transplant-free survival was 14 (IQR, 4, 34) days for all listed subjects. As with the nonlisted subgroup, sensitivity analyses substituting other critical illness indicators, CLIF-C ACLF score, and including cause of cirrhosis did not change results.

Once listed, 48% (63 of 131) of subjects later received a liver transplant. Twenty-nine percent (18 of 63) of those who received a liver transplant also received dual kidney transplant. Liver transplantation rates were similar between HRS and ATN subgroups (52% versus 45%; *P*=0.44). Among listed subjects who did not receive a liver transplant, 38% (3 of 8) of those who were alive at 6 months recovered kidney function and were off dialysis (2 of 6 with HRS and 1 of 2 with ATN).

Table 3. Multivariable Cox regression model for 6-mo mortality among 472 patients with cirrhosis initiated on RRT for AKI

Variable	Wald Chi Square Score	Hazard Ratio	95% CI	*P* Value
Not listed for liver transplant	48.4	2.67	(2.02 to 3.51)	<0.001
MELD score (per five points)	28.7	1.20	(1.12 to 1.29)	<0.001
Age (per 10 yr)	17.4	1.21	(1.11 to 1.33)	<0.001
Admission to the intensive care unit	13.1	1.99	(1.37 to 1.68)	<0.001
Serum ALT (per 100 U/L)	12.8	1.03	(1.02 to 1.05)	<0.001
Mechanical ventilation	5.1	1.32	(1.04 to 1.67)	0.02
Initial renal replacement: CVVH	3.9	1.25	(1.00 to 1.57)	0.05

Twenty candidate variables from key demographics and a univariate screen of significant univariate associations with 6-mo mortality were entered into a stepwise selection algorithm for this Cox regression. Variables were entered in the model if $P<0.10$ and were retained in the final model if $P<0.05$. 95% CI, 95% confidence interval; MELD, Model for End-Stage Liver Disease; ALT, alanine aminotransferase; CVVH, continuous veno-venous hemofiltration.

Discussion

Those with AKI and cirrhosis represent an extremely challenging and highly morbid group of patients. Current therapies for AKI are largely supportive, with no drug therapies approved for ATN. Although terlipressin is an effective therapy for HRS, it is not available in North America (45,46). Thus, it is essential that we carefully employ existing therapies, such as RRT. Given a paucity of evidence around nonlisted cirrhotic patients who require RRT, we provide an important prognostic update for this

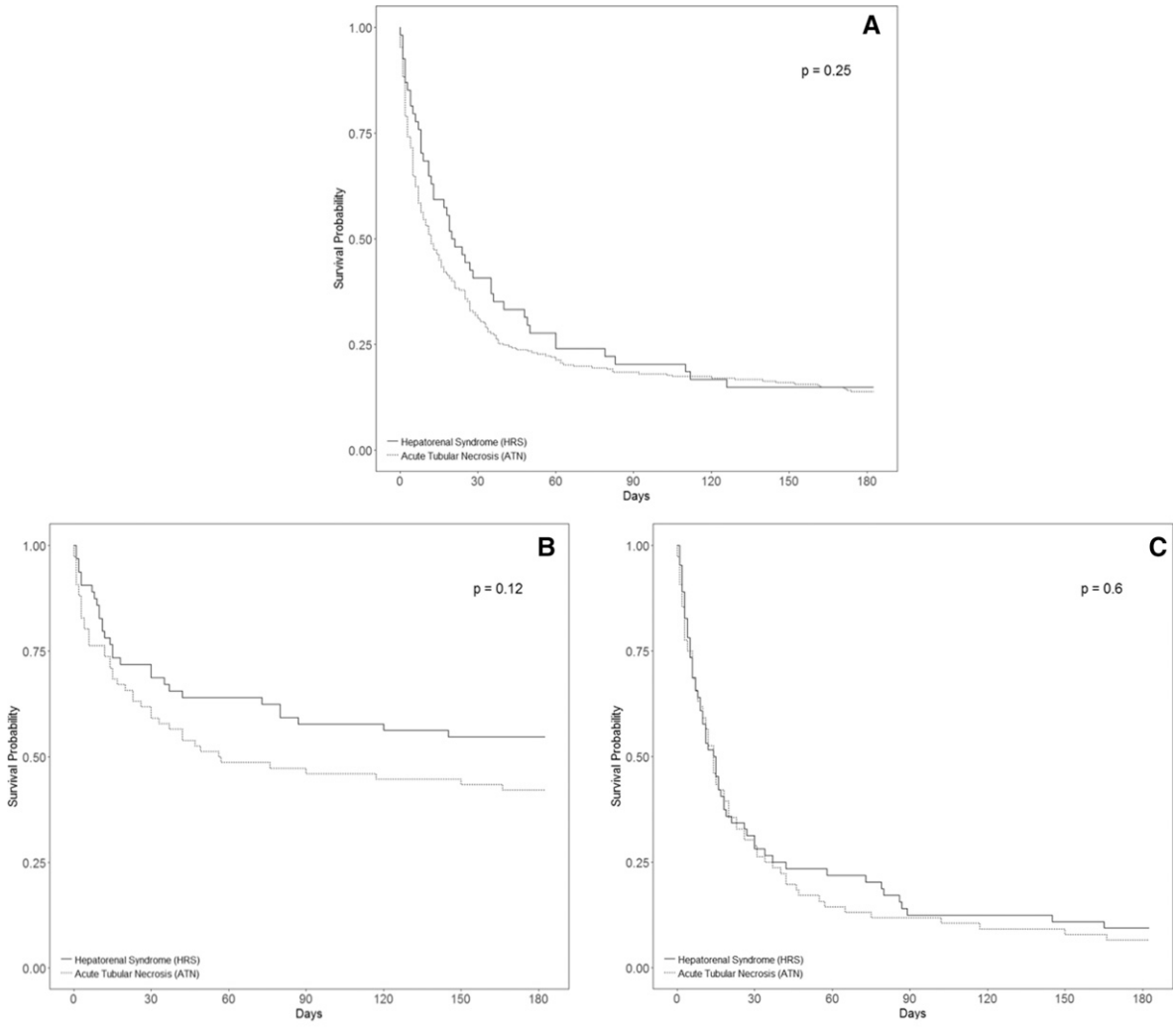

Figure 3. | Survival of 472 patients with cirrhosis acutely initiated on RRT, according to clinical diagnosis at dialysis initiation. (A) Survival among subjects not listed for liver transplant. (B) Survival among subjects listed for liver transplant. (C) Transplant-free survival among subjects listed for liver transplant.

Table 4. Multivariable Cox regression models for 6-mo outcomes among 472 patients with cirrhosis initiated on RRT for AKI

Model	Hazard Ratio	95% CI	*P* Value
A. Not listed for liver transplant, death by 6 mo			
Hepatorenal syndrome[a]	0.81	(0.59 to 1.11)	0.19
Age (per 10 yr)	1.17	(1.06 to 1.28)	0.001
MELD score (per 5 points)	1.28	(1.19 to 1.37)	<0.001
Initial renal replacement: CVVH[b]	1.63	(1.28 to 2.08)	<0.001
B. Listed for liver transplant, death by 6 mo			
Hepatorenal syndrome[a]	0.73	(0.44 to 1.19)	0.21
Age (per 10 yr)	1.05	(0.81 to 1.36)	0.71
MELD score (per 5 points)	0.88	(0.73 to 1.07)	0.21
Initial renal replacement: CVVH[b]	1.95	(1.19 to 3.19)	<0.01
C. Listed for liver transplant, death or transplant by 6 mo			
Hepatorenal syndrome[a]	0.93	(0.64 to 1.35)	0.70
Age (per 10 yr)	1.22	(1.00 to 1.50)	0.05
MELD score (per 5 points)	1.25	(1.07 to 1.46)	<0.01
Initial renal replacement: CVVH[b]	2.58	(1.72 to 3.87)	<0.001

95% CI, 95% confidence interval; MELD, Model for End-Stage Liver Disease; CVVH, continuous veno-venous hemofiltration.
[a]Reference group: acute tubular necrosis.
[b]Reference group: initial renal replacement: hemodialysis.

growing population. We confirmed a high mortality overall, especially in the nonlisted subgroup; however, we found no significant differences in outcomes between those diagnosed with HRS and those diagnosed with ATN within listed or nonlisted groups.

As context, there are only three studies examining survival after acute initiation of RRT among nonlisted subjects with cirrhosis (25–27). Two were published in the 1970s and had 100% short-term mortality in small cohorts of 14 and 25 cirrhotic patients (25,26). In a third 2004 study of 30 patients, mortality was 100% among those treated with CRRT and mechanical ventilation (27). This literature has guided our approach to RRT in cirrhosis, suggesting that offering RRT to nonlisted patients with HRS may not be of benefit, but may not reflect the effect of recent advances in the general care of the cirrhotic patient (43,47).

Our observation that mortality was similar between HRS and ATN warrants further discussion. Several prior studies, including work at our center, have shown a mortality difference when comparing HRS, ATN, and prerenal injury across a wide spectrum of AKI severity (3,4). However, when isolating those with severe AKI requiring RRT, we did not observe a statistically significant difference between HRS and ATN subgroups. Although we should acknowledge that sample size and site-specific practice patterns raise the possibility of a false-negative statistical result, the short overall median survival of 14 days in the nonlisted population suggests that AKI cause may not translate into a clinically meaningful factor in the dialysis-requiring cirrhotic population. Complications of dialysis are not AKI-cause–specific and their clinical effect may supersede that of underlying HRS versus ATN in this group (9–19). Alternatively, AKI requiring RRT in severe liver failure may be a marker of the likelihood of further deterioration or other organ dysfunction that may not necessarily be improved by the provision of RRT. Our stepwise multivariable model showed that several known predictors of survival in cirrhosis (such as MELD score, age, and transplant listing status) and indicators of critical illness (such as initiation with CVVH and mechanical ventilation) were more closely associated with mortality and thus should be emphasized more than cause of AKI when deciding to employ RRT. Of note, our results likely apply best to patients in North America, where first-line vasoconstrictor therapy is limited to midodrine/octreotide (an ineffective, off-label therapy) (48), and therefore does not capture terlipressin's effect on the natural history of HRS (49).

In addition, it is worth considering the potential for confounding-by-indication bias in this population. RRT was offered less frequently to those with HRS who were not listed for transplant. Our data show that those treated with RRT with ATN represented a sicker population compared with HRS. This suggests that the decision to employ RRT was dependent on underlying AKI diagnosis. However, given 6-month mortality after initiation of RRT was similar among nonlisted patients with ATN and a more selected group with HRS (approximately 85%), a wider appreciation of the extremely high mortality associated with ATN in cirrhosis is needed, as are further studies that improve understanding of best care practices regarding the intensity of care and the role of supportive services in this setting.

Overall, we would encourage clinicians to continue a thoughtful, evidence-based approach when employing RRT in the nonlisted cirrhotic population, acknowledging the guarded prognosis in this group. Although mortality is high in both HRS and ATN, there may be a select group of patients where a time-limited trial of RRT is appropriate, particularly those who exhibit fewer signs of critical illness. Chance of kidney recovery may also factor into this clinical decision making. Still, this population utilizes tremendous medical resources and has long hospital lengths of stay, with a majority requiring intensive care unit level of care. Our data confirms that use of RRT as a bridge to transplant in the listed population should be a straightforward treatment decision. In this group, we included 47 patients who were listed after initiation of RRT, which adds generalizability to those where transplant candidacy is unknown when RRT is required. Although the use of time-limited trials of RRT was not easily quantifiable in this

study, it is reasonable to incorporate this approach in these high-risk groups.

This study should be interpreted in the context of its limitations. This was a retrospective analysis; thus, all findings should be viewed as associations rather than causal relationships. However, it is unlikely that a prospective or randomized trial will be conducted in this population; thus, this may be the optimal practical study design. Although data were obtained from five acute care hospitals, only one was a liver transplant center, which evaluated a majority of patients in this study. Thus, results may be colored by local practice patterns and these findings should be confirmed at other liver transplant centers. Potential for confounding-by-indication bias in patient selection was outlined in detail above. In the listed subgroup, competing risks between death, transplant listing, and receipt of transplant should be acknowledged. There was no significant difference between time from RRT initiation to transplant listing date between subjects with HRS versus ATN, and results were similar when analyzing survival versus transplant-free survival; thus, we feel this was unlikely to have a major statistical effect on our overall conclusions. Several clinical diagnoses were made by a range of treating physicians; thus, there may be variability in interpretation of clinical guidelines. Overall, this study reflects actual practice patterns without influence of the study team and we believe this adds interpretability to our results.

The cause of AKI (HRS versus ATN) was not significantly associated with mortality in patients with cirrhosis who required RRT. Transplant listing status, MELD score, and indicators of critical illness were more closely associated with survival. Among those not listed for liver transplant, mortality rates were extremely high in patients both with HRS and ATN. These findings should be validated at other high-volume liver transplant referral centers to improve generalizability of the results.

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Disclosures

None.

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