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Survival of liver transplant candidates with acute renal failure receiving renal replacement therapy

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Background. Acute renal failure (ARF) in the setting of end-stage liver disease has a dismal prognosis without liver transplantation. Renal replacement therapy (RRT) is a common bridge to liver transplant despite a paucity of supportive data. We investigated our single-center patient population to determine efficacy of RRT in liver transplant candidates with ARF.

Methods. We identified 102 liver transplant candidates receiving RRT for ARF between April 30, 1999 and January 31, 2004. Patients that had initiated RRT intra- or postoperatively or received outpatient hemodialysis or peritoneal dialysis prior to admission were excluded. Survival to liver transplant, short-term mortality following liver transplant, and selected clinical characteristics were examined.

Results. Of patients who received RRT, 35% survived to liver transplant or discharge. Mortality was 94% in patients not receiving a liver and was associated with a higher Acute Physiological and Chronic Health Evaluation (APACHE) II, lower mean arterial pressure, and the use of continuous renal replacement therapy (CRRT). Patients receiving CRRT had greater severity of illness than those on hemodialysis. The 1-year mortality of patients initiating RRT prior to liver transplant was 30% versus 9.7% for all other liver recipients ($P < 0.0045$).

Conclusion. RRT is justifiable for liver transplant candidates with ARF. Though mortality was high, a substantial percentage (31%) of patients survived to liver transplant. Postoperative mortality is increased compared with all other liver transplant recipients, but is acceptable considering the near-universal mortality without transplantation.

Key words: mortality, liver transplantation, acute renal failure, dialysis.

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Nephrologists at organ transplant centers frequently provide renal replacement therapy (RRT) to liver transplant candidates with acute renal failure (ARF). These patients are often critically ill with an extremely poor prognosis [1–4]. Hemodynamic instability and coagulopathy make RRT in these patients difficult. Experiences in the 1970s using RRT in advanced liver disease were dismal, and it was concluded that this was a futile therapy [5]. The advent of liver transplantation and continuous renal replacement therapy (CRRT) led to renewed interest in RRT as a supportive modality for patients awaiting liver transplant [6–8]. Published series have reported mortality rates as low as 25% using RRT for pretransplant ARF [7–9]. Relatively few patients are described, and outcomes are generally limited to those who survive to liver transplant, raising issues of selection and reporting bias. The degree of renal dysfunction when RRT is initiated is variable from institution to institution and would be an additional source of bias. The largest published series reported 71% mortality for those treated with RRT pretransplant [10]. Our goal was to investigate the survival and characteristics of patients with ARF and a new requirement for RRT while awaiting liver transplant. We chose to study only patients who were functionally anephric and required RRT as a bridge to transplantation. We hypothesized that the efficacy of RRT in this setting has been overestimated, and sought to reexamine the practice of providing RRT to liver transplant candidates with ARF.

METHODS

We performed a retrospective study approved by the Institutional Review Board of the University of North Carolina. Using the comprehensive database of our transplant data coordinating office, we identified all patients on the liver or liver-kidney transplant list at

University of North Carolina Hospitals who initiated inpatient RRT between April 30, 1999 and January 31, 2004. We also considered patients being actively evaluated for liver transplant but not yet listed at the time of initiation of treatment. RRT was defined as intermittent hemodialysis or any form of CRRT, including continuous venovenous hemodialysis (CVVHD), hemofiltration (CVVHF), or hemodiafiltration (CVVHDF). Individual medical records were reviewed without blinding to patient outcomes.

Patients meeting all of the following criteria were included: (*1*) diagnosis of end-stage liver disease or fulminant hepatic failure, (*2*) listed for, or being actively evaluated for orthotopic liver transplantation, liver-kidney transplantation, or living donor liver transplantation, (*3*) age 18 or older, and (*4*) initiation of at least one RRT session for ARF prior to liver transplantation. Patients were excluded for any of these criteria: (*1*) chronic dialysis defined as any outpatient dialysis in the month prior to admission, (*2*) peritoneal dialysis of any duration, or (*3*) initiation of RRT intra- or postoperatively in patients receiving a transplant.

The diagnosis of ARF and decision to initiate RRT was determined by the consulting nephrologist. Uncuffed double-lumen dialysis catheters were placed for vascular access. Hemodialysis was performed using Cobe 500-HG or Gambro GFS-20 Hemophan biocompatible membranes. Treatment was typically provided three times a week for 2 to 4 hours. Target blood flow was 350 mL/min with a dialysate rate of 600 mL/min. CRRT was performed using Prisma machines with Hospal AN69 membranes and blood flows of 100 to 140 mL/min. Replacement fluids utilized $NaHCO_3$ buffer. Replacement fluid and dialysate rates averaged 1 to 2 L/hour. Due to theoretical advantages in liver disease, CVVHF is the predominant modality of CRRT at our institution [11, 12]. Net ultrafiltration was determined by the consulting nephrologist. Heparin-free protocols were generally employed because of concerns of bleeding [11].

Survival to liver transplant was the primary outcome of the study. Clinical characteristics at time of initiation of RRT were compared for groups of patients based on outcome and by initial RRT modality. RRT duration was defined as the length of time between the initiation of RRT and either death, transplant, discharge from the hospital, or documented discontinuation of RRT. The worst physiologic parameters in the 24 hours prior to initiating RRT were used to calculate Acute Physiolocial and Chronic Health Evaluation (APACHE) II [unadjusted APACHE II scores were calculated using the online program provided by the French Society of Anesthesia and Intensive Care (*www.sfar.org*)] and model for end-stage liver disease score (MELD) [MELD scores were obtained from the United Network for Organ Sharing (UNOS) online calculator (*www.unos.org*)] scores, similar to previous studies [13–15]. Oliguria was defined as <400 mL of urine output in the 24 hours prior to RRT. Infection was defined as a positive culture of any normally sterile body fluid or radiographic evidence of pneumonia within the 5-day period prior to starting RRT. Mortality of RRT liver transplant recipients in our study was compared at 3 months and 1 year to all other liver transplant recipients at our institution during the same period.

Statistical method

Chi-square two-sided tests were used to compare categorical variables across groups by survival status, death versus survived to transplantation, and by type of dialysis (CRRT vs. hemodialysis). To evaluate a small number of events, Fisher's exact test was performed at alpha level 0.05. The Wilcoxon rank-sum test evaluated differences in continuous measures between the groups of interest. Logistic regression identified predictors of mortality. Kaplan-Meier estimates were used to generate survival curves to determine survival/failure rates at specific time points. Statistical calculations were performed using SAS software, version 8 (SAS, Inc., Cary, NC, USA).

RESULTS

During the study period, 286 liver transplants were performed on 245 patients at our institution. We identified 159 potential subjects, and 102 patients met criteria for the study. Fifty seven patients were excluded for the following reasons: peritoneal dialysis ($N = 2$), chronic dialysis ($N = 7$), intra- or postoperative RRT ($N = 32$), age <18 years ($N = 2$), not eligible for transplant list ($N = 12$), never actually received RRT ($N = 1$), or records unavailable ($N = 1$). Overall, 31% ($N = 32$) of patients survived to transplant and 4% ($N = 4$) were discharged without a transplant. Sixty-five percent ($N = 66$) of patients died awaiting liver transplantation. Sixty-five percent ($N = 66$) of patients were initially treated with CRRT and 35% ($N = 36$) received hemodialysis. Kaplan-Meier survival curves are shown in Figure 1 with 10-day survival rate of 58% in the hemodialysis patients versus a 35% survival rate in the CRRT patients. There were 48 (78%) deaths in the CRRT group versus 18 (50%) in the hemodialysis group, representing an odds ratio of 2.67 (1.14–6.23) ($P = 0.02$, 95% CI). The slope of the overall survival curve only begins to plateau at 15 to 20 days after RRT initiation.

Demographic data are shown in Table 1. Most patients were white, male, and had chronic liver disease. Fifty percent of the patients had hepatitis C, alcoholic cirrhosis, or a combination thereof. Hepatic encephalopathy (23%), ARF (19%), and ascites (13%) were the leading admission diagnoses (data not shown). RRT was almost always initiated in the intensive care unit. Clinical characteristics are shown in Tables 2, 3, and 4. Hepatorenal syndrome

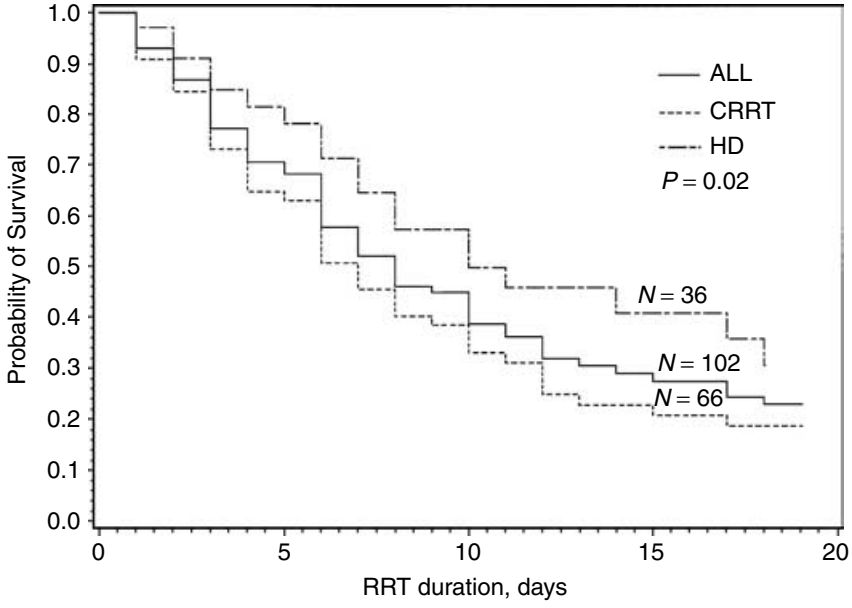

Fig. 1. Kaplan-Meier plot of overall patient survival and survival by initial renal replacement therapy (RRT) modality. *P value is calculated for comparing continuous renal replacement therapy (CRRT) versus hemodialysis (HD).

(HRS) and acute tubular necrosis (ATN) were the most frequent diagnoses of ARF. Volume overload was the most cited reason for initiating RRT.

Measures of illness severity are shown in Table 3 grouped by clinical outcomes and in Table 4 grouped by initial RRT modality. Patients who died had significantly higher APACHE II ($P = 0.005$) and lower mean arterial pressure ($P = 0.04$) compared to those who survived to transplant. Patients who received CRRT versus hemodialysis had significantly higher APACHE II ($P < 0.001$), lower mean arterial pressure ($P = 0.0021$), lower serum creatinine ($P = 0.0063$), were more likely intubated ($P < 0.0001$), and more likely to have infection ($P < 0.0001$). No significant differences existed between either survivors and nonsurvivors or patients receiving CRRT versus hemodialysis with respect to median duration of RRT. Sepsis was the leading cause of death (65.2%), followed by gastrointestinal bleeding/coagulopathy (10.6%), acute respi ratory distress syndrome/pneumonia (9.2%), and intracerebral event (7.6%) (data not shown). Multivariable logistic regression modeling incorporating age, gender, race, duration of RRT, mean arterial pressure, serum creatinine, oliguria, and history of diabetes revealed that higher mean arterial pressure was statistically associated with a lower risk of mortality (OR = 0.97, 95% CI = 0.93, 0.99, $P = 0.03$) as shown in Table 6.

Survival to liver transplant in our patient cohort study is compared with all other liver transplant recipients during the same period in Table 5. Three-month and 1-year postoperative mortality was significantly increased compared to all other liver transplant recipients [15.6% vs. 4.1% ($P < 0.02$)] and [30% vs. 9.7% ($P < 0.0045$)], respectively. We further examined the subgroup of patients who initiated RRT posttransplant ($N = 28$) and who were included in the "all other liver transplant recipients" group. The mortality in this subgroup of patients was similar to that of patients initiating RRT pretransplant.

DISCUSSION

Renal failure is a common complication in liver transplant candidates and predicts increased posttransplant mortality and reduced graft survival [3, 16–23]. The high mortality observed in this group has raised debate about resource utilization in the care of these patients [1]. Given the shortage of organs, lengthening wait times, and the negative association between renal insufficiency and patient and graft survival, resource allocation issues surrounding liver transplantation and renal failure are pertinent topics of debate [18, 21, 23]. Surprisingly, there are little data describing the effectiveness of RRT in pretransplant ARF [7–9]. Single-center reports have provided conflicting results, with hospital mortality ranging from 0% to 71% in patients receiving RRT while awaiting liver transplant [7–10]. Much of this variability may reflect differences in institutional policy with regard when RRT should be initiated. We have chosen to study only patients who were functionally anephric and required RRT in order to survive to transplantation. Providing RRT to these patients is challenging and fraught with complications [11, 24, 25]. Current prognostic models can help predict mortality in cirrhotics admitted to the intensive care unit, but cannot presage which liver transplant candidate

Table 1. Patient demographics grouped by outcomes

	All patients ($N = 102$)	Died awaiting transplantation ($N = 66$)	Survived to transplantation ($N = 32$)	Survived to discharge without transplant ($N = 4$)	P value[a]
Age (mean ± SD)	49.7 ± 10.3	50.6 ± 9.2	47.3 ± 11.7	53.5 ± 14.7	0.27
Male number (%)	65 (64)	41 (62)	23 (72)	1 (25)	0.34
White number (%)	82 (80)	53 (80)	27 (84)	2 (50)	0.63
Chronic end-stage liver disease number (%)	95 (93)	64 (97)	29 (91)	2 (50)	0.09[b]
Fulminant hepatic failure number (%)	7 (7)	2 (3)	3 (9)	2 (50)	
Intensive care unit number (%)	91 (89)	60 (90)	28 (88)	3 (75)	0.51
Etiology of liver failure number (%)					
Acetaminophen	4 (4)	1 (2)	2 (6)	1 (25)	
Alcohol	7 (7)	4 (6)	3 (9)	0	
Alpha$_1$ antitrypsin	5 (5)	4 (6)	1 (3)	0	
Autoimmune	5 (5)	4 (6)	1 (3)	0	
Cryptogenic	8 (8)	4 (6)	4 (13)	0	
Hepatitis B virus	3 (3)	3 (5)	0	0	
Hepatitis C virus	24 (24)	15 (23)	9 (28)	0	
Hepatitis C virus/alcohol	20 (20)	13 (20)	6 (19)	1 (25)	
Nonalchoholic fatty liver disease	9 (9)	7 (11)	2 (6)	0	
Primary biliary cirrhosis/primary sclerosing cholangitis	10 (10)	7 (11)	2 (6)	1 (25)	
Other	7 (7)	4 (6)	2 (6)	1 (25)	

[a]Comparing patients who died versus those who survived to transplantation.
[b]Comparing mortality rate of chronic end-stage liver disease versus fulminant hepatic failure.

Table 2. Clinical outcomes grouped by preoperative renal replacement therapy (RRT) modality and type of acute renal failure (ARF) in 102 patients

	Preoperative RRT modality		Type of ARF			
	CRRT	Hemodialysis	ATN	HRS	Prerenal	Other
Died awaiting transplantation ($N = 66$) (%)	48 (73)	18 (50)	26 (70)	30 (61)	8 (73)	2 (40)
Survived to transplantation ($N = 32$) (%)	17 (26)	15 (42)	9 (24)	19 (39)	1 (9)	3 (60)
Survived to discharge without transplantation ($N = 4$) (%)	1 (1.5)	3 (8)	2 (6)	0	2 (18)	0
Summary	66	36	37	49	11	5

Abbreviations are: CRRT, continuous renal replacement therapy; ATN, acute tubular necrosis; HRS, hepatorenal syndrome.

with ARF will or will not survive to transplantation after RRT is initiated [1, 4]. Is RRT an efficacious bridge to liver transplantation given these challenges and resource limitations?

Our results suggest an answer of yes. While the mortality observed in this cohort of patients was high, one third survived to transplant. Liver transplantation offers the best long-term survival rates for patients with advanced liver failure, particularly considering the grim outcomes of ARF without transplantation [2, 26]. A significant percentage of patients treated with RRT survived to liver transplantation, despite a high acuity of illness and need for other life-sustaining interventions. Though 65% mortality is severe, it is not dissimilar to that of other critically ill patients with ARF [10, 13, 15, 27]. Indeed, there has been little improvement in the prognosis of ARF despite decades of experience with RRT [15, 27, 28]. Thus, one should not classify mortality in liver transplant candidates receiving RRT as worse than comparably ill patients without liver failure.

Once renal failure develops in advanced liver disease, hospital mortality approaches 90%, but is less than 30% with a liver transplant [10]. In our cohort, 94% of patients died if they failed to receive a liver transplant, primarily of sepsis. This follows the observation that most deaths in patients with ARF are attributable to the underlying disease process and not ARF per se. Similarly, it would be an oversimplification to conclude that survival to transplant in our cohort was a result of RRT alone. We cannot identify those patients who survived because of RRT and those who would have survived to liver transplant without RRT. Patients who survived to transplant had relatively less severe indices of illness and may have been healthier at the onset of RRT. Other factors, such as the effect of timing of initiation of RRT and cointerventions were not examined. It is safe to assume that the improved survival seen in patients who received a liver was attributable primarily to the reversal of liver failure with transplantation. We acknowledge the limitations of RRT, but its contribution as a bridge to liver transplant is clinically important. Candidates who survived may have otherwise died from electrolyte disturbances or uremic complications or been too volume overloaded to undergo transplantation. Our findings reinforce the notion that once ARF develops, liver transplant candidates will likely not survive unless they are transplanted.

Our study raises the issue of the relationship between the duration of RRT and survival to liver transplant.

Table 3. Clinical characteristics grouped by outcomes[a] in 102 patients

	All patients ($N = 102$)	Died awaiting transplantation ($N = 66$)	Survived to transplantation ($N = 32$)	Survived to discharged without transplantation ($N = 4$)	P value[b]
RRT indication (%)					
Acidosis	10 (10)	7 (11)	3 (10)	0	
Hyperkalemia	7 (7)	2 (3)	4 (12)	1 (25)	
Uremia	7 (7)	4 (6)	3 (10)	0	
Volume	54 (53)	38 (58)	17 (53)	0	
Multiple	21 (21)	14 (21)	4 (12)	3 (75)	
Not specified	3 (2)	1 (3)	2 (6)	0	
APACHE II	28.7 ± 7.6	30.2 ± 7.3	25.9 ± 7.7	26.5 ± 6.2	0.005
RRT duration[c]	6.0 (3.0-12.0)	6.0 (3.0-10.0)	9.5 (3.0-18.0)	7.0 (2.5-45.0)	0.08
Model for end-stage renal disease	38.9 ± 8.8	39.5 ± 7.9	38.5 ± 10.2	32.3 ± 10.2	0.59
Mean arterial pressure mm Hg	61.3 ± 14.5	58.7 ± 13.3	64.5 ± 13.6	77.4 ± 26.2	0.04
Creatinine mg/dL	4.2 ± 2.0	4.1 ± 1.9	4.4 ± 2.1	4.7 ± 2.7	0.50
Oliguria[d]	56 (55)	38 (58)	18 (56)	0	0.90
Infection[e]	44 (43)	34 (52)	10 (31)	0	0.06
Intubated	42 (41)	32 (48)	9 (28)	1 (25)	0.06
Vasopressors	46 (45)	34 (52)	12 (38)	0	0.19

Abbreviations are: RRT, renal replacement therapy; APACHE II, Acute Physiological and Chronic Health Evaluation.
[a]Data presented as number (%) or mean ± SD unless otherwise specified.
[b]Comparing patients who died versus those who survived to transplantation.
[c]Median number of days (25% to 75% interquartile range).
[d]<400 mL urine output 24 hours prior to RRT.
[e]Positive culture of normally sterile body fluid or radiographic evidence of pneumonia in the 5 days prior to RRT.

Table 4. Clinical characteristics by initial preoperative renal replacement therapy (RRT) modality[a]

	CRRT ($N = 66$)	Hemodialysis ($N = 36$)	P value[b]
Hospital mortality[c] (%)	48 (73)	18 (50)	0.02
RRT duration[d]	6.0 (3.0-11.0)	7.5 (3.0-15.0)	0.28
APACHE II	31.2 ± 7.2	24.1 ± 6.1	<0.001
Model for end-stage renal disease	38.5 ± 8.7	39.6 ± 9.0	0.44
Mean arterial pressure *mm Hg*	58.0 ± 13.5	67.3 ± 14.4	0.0021
Creatinine mg/dL	4.0 ± 2.2	4.7 ± 1.4	0.0063
Oliguria[e] (%)	36 (55)	20 (56)	0.92
Infection[f] (%)	27 (41)	17 (47)	0.54
Intubated (%)	39 (59)	3 (8)	<0.0001
Vasopressors (%)	41 (62)	5 (14)	<0.0001

Abbreviations are: RRT, renal replacement therapy; APACHE II, Acute Physiological and Chronic Health Evaluation; CRRT, chronic renal replacement therapy.
[a]Data presented as number (%) or mean ± SD unless otherwise specified.
[b]Comparing CRRT versus hemodialysis.
[c]Censored at time of transplant for those who received an organ but subsequently died.
[d]Median number of days (25% to 75% interquartile range).
[e]<400 mL urine output 24 hours prior to RRT.
[f]Positive culture of normally sterile body fluid or radiographic evidence of pneumonia in the 5 days prior to RRT.

There was a steep decline in survival observed once RRT began. Approximately one half of patients died in the first 7 days after initiating RRT, though the overall survival curve did not plateau until 15 to 20 days. Possibly, some patients who died after initiating RRT were so sick they would have died regardless of whether or not they received treatment. Interestingly, though no significant differences in the median duration of RRT were observed between groups or between RRT modalities, a trend of increased survival and longer RRT duration was seen. This probably reflects two factors: the longer a patient survived on RRT, the better the chances an organ would become available, and patients who lived longer may have been less ill than nonsurvivors. Thus, duration of RRT cannot predict which liver transplant candidates will likely survive to organ transplantation. Our multivariate regression model demonstrates no independent relationship between RRT duration and survival. This finding may be particularly important in the setting of limited resources where nephrologists might consider withdrawing prolonged RRT in a critically ill liver transplant candidate awaiting an organ.

The retrospective nature of our study imposed limitations, and efforts were made to minimize the bias. The study criteria and outcome measures were established a priori, and we limited the number of variables in our logistic regression model. When outcomes were clearly confounded, we avoided statistical analysis or interpretation. By including all patients receiving RRT while awaiting liver transplant, and not just those who survived to liver

Table 5. Survival for pretransplant renal replacement therapy (RRT) liver recipients versus all other liver recipients

	Initiated RRT pretransplant ($N = 32$)	All other liver transplant recipients ($N = 220$)	Initiated RRT posttransplant[a] ($N = 28$)	P value
3-month mortality	5/32 (15.6)[b]	9/220 (4.1)	6/28 (21.4)[f]	0.02
1-year mortality	9/30 (30)[c,d]	20/206 (9.7)[e]	9/27 (33.3)[g,h]	0.0045

[a]Subgroup of all other liver transplant recipients not in primary study cohort.
[b]$P < 0.02$ versus all other liver transplant recipients.
[c]$P < 0.0045$ versus all other liver transplant recipients.
[d]Data missing for twp patients.
[e]Data missing for 14 patients.
[f]P = nonsignificant versus pre-transplant RRT group.
[g]P = nonsignificant versus pretransplant RRT group.
[h]Data missing for one patient.

Table 6. Multivariate analysis of clinical parameters as predictors of survival

Parameters	Odds Ratio	95% CI	P value
Age	1.03	(0.98, 1.08)	0.26
Gender male vs. female	1.13	(0.43, 2.97)	0.82
Race nonwhite vs. white	1.37	(0.41, 4.57)	0.59
Mean arterial pressure	0.96[a]	(0.93, 0.99)	0.03[a]
Creatinine	0.89	(0.69, 1.14)	0.38
Oliguria yes vs. no	1.02	(0.38, 2.74)	0.96
Diabetes yes vs. no	1.07	(0.37, 3.08)	0.96
RRT duration	0.99	(0.96, 1.03)	0.70

[a]Statistically significant using two-sided with alpha level 0.05.

transplantation, we attempted to reduce reporting bias, which could lead to an underestimate of mortality.

Our patients are likely similar to those encountered at other modern transplant centers. To our knowledge, this is the largest single cohort described thus far of liver transplant candidates receiving RRT for ARF while awaiting transplantation. Some of the apparent success in earlier studies may have been the result of selection or publication bias, where only healthier patients received RRT or positive experiences were published. In an earlier report, a small but significant increase from 1.8% to 3.9% of liver transplant recipients requiring preoperative RRT was observed with the advent of CRRT [9]. By comparison, 32/245 (13.1%) of liver transplant recipients at our institution received RRT for ARF preoperatively. As reported earlier, the acuity of illness encountered in liver transplant candidates has increased, with 89% of our patients initiating RRT in the intensive care unit [9].

We excluded seven patients who were on the transplant list, but who had previously undergone outpatient hemodialysis. None of these patients had been diagnosed with HRS. Four of these subjects had biopsy-proven intrinsic causes of renal failure (membranous nephropathy, focal and segmental glomerulosclerosis, and IgA nephropathy) that in some cases predated their end-stage liver disease. Patients stable enough to receive outpatient treatment are clinically distinct from patients who develop new-onset ARF requiring RRT. Inclusion of these individuals could have biased our results toward more favorable outcomes.

The high APACHE II and MELD scores observed illustrate the severity of illness in our cohort. The APACHE II score has been shown to have good prognostic value when applied to patients requiring RRT and those with cirrhosis [4, 13–15, 29]. The overall mean APACHE II score of 28.7 correlated well with the observed 65% mortality rate. The mean APACHE II was significantly higher in patients who died on RRT compared with eventual transplant recipients, 30.2 vs. 25.9 ($P < 0.005$). The MELD score estimates a patient's risk of dying while awaiting liver transplantation, and has been used by UNOS and organ procurement organizations since February 2002 to prioritize liver allocation. The mean overall MELD score was 38.9, and was not statistically different among survivors and nonsurvivors. Higher MELD scores also predict death after liver transplant, and the values in our cohort were extremely high by national standards [3, 22, 23, 30–33]. Because the MELD score was not utilized for organ prioritization in earlier members of our cohort and the impact of RRT on survival of later patients was confounded by the MELD score's effect on organ allocation (i.e., survival correlated in large part with getting a liver), we did not include it in our regression model. Ongoing controversy and debate remains about the MELD score's impact on overall organ resources and patient survival posttransplant [3, 22, 23, 30, 33–35].

Importantly, the MELD calculation and renal function deserves mention. Given that the mean serum creatinine of patients initiating RRT was 4.2 mg/dL, it is unlikely that the decision to provide RRT would have added much weight to the MELD calculation (which considers two RRT treatments in the previous week equivalent to a serum creatinine of 4.0 mg/dL). Considering this, and with average MELD scores already near the UNOS-defined maximum of 40 and substantially higher than the national mean of 23.9, it seems unlikely that initiating RRT impacted significantly on organ allocation [33, 35]. However, the dramatic increase in mortality observed after

RRT is initiated and the strong correlation between liver transplant and survival, indicates a discrepancy between the weight given to ARF requiring RRT in the MELD calculation and clinical observations. Simply, once a critically ill liver transplant candidate develops ARF and initiates RRT, our data suggest that survival depends on whether or not they rapidly receive a liver transplant, and that the current liver allocation scheme may not adequately account for this.

Because the definition of ARF was unspecified and there was no standardized criteria for initiating RRT, we accepted the diagnosis of ARF and the decision to initiate RRT without interpretation or proof of veracity [27, 36]. The percentage of patients with HRS (48%) was relatively high in our study, but similar to previous studies [12, 37]. ATN is often a consequence of prolonged HRS and is frequently difficult to distinguish from HRS in the oliguric patient. As a result, ATN may be misclassified as HRS, even in centers experienced in liver failure [3, 17, 25, 37]. Prerenal failure, HRS, and ATN all lay on the same continuum of ARF. The intense, irreversible renal vasoconstriction that characterizes HRS represents the most extreme form of prerenal failure, while ATN can result from prolonged prerenal failure, HRS, or numerous insults encountered in the intensive care unit [3, 17, 20, 25]. Diagnostic percutaneous renal biopsy is usually not feasible in critically ill coagulopathic patients [3, 17]. Due to the retrospective nature of the study, we did not examine outcomes based on these classifications. Regardless of etiology, ARF in advanced liver disease still has a poor prognosis, with mortality rates exceeding 90% [1–3, 37].

Our study was not intended to demonstrate the superiority of a particular RRT modality or to examine the dose or delivery of RRT. There is substantial uncertainty and conflicting data regarding the optimal modality, prescription, and timing of initiation of RRT in ARF; and no such information exists for patients with advanced liver failure [3, 7, 9, 10, 14, 24, 25, 27, 32, 38]. CRRT has been advocated for use in liver disease due to better hemodynamic stability and improved physiologic parameters [11, 12]. Prospective data are scant, and trials have actually shown increased mortality associated with CRRT in liver disease [9, 10, 14]. Our cohort clearly exhibited decreased survival in patients treated initially with CRRT. The implication that CRRT is inferior to hemodialysis requires further examination. Patients who initially received CRRT were much sicker, with higher mean APACHE II scores (31.2 v. 24.1), lower mean mean arterial pressure (58 vs. 67.3 mm Hg), and were more likely intubated (59% vs. 8%) and on vasopressors (62% vs. 14%). Thus, the choice of modality seemed to be largely predicated on severity of illness, with hemodynamic instability precluding standard hemodialysis and necessitating the default use of CRRT. Only 1/48 (2%) of patients who died after initiating RRT with CRRT switched to hemodialysis, while 8/18 (44%) of patients who died after initiating RRT with hemodialysis switched to CRRT (data not shown). Thus, patients sick enough to require CRRT at onset stayed on CRRT and those healthy enough to start hemodialysis frequently got sicker and later required CRRT. Numerous interruptions of CRRT, nonsteady-state physiologic conditions, and logistic issues affecting the availability of RRT make further analysis of RRT dose problematic. The optimal prescribed dose of RRT in ARF will be studied in an upcoming multicenter prospective trial [Paganini E, Palevsky P, National Kidney Foundation 2004 Clinical Meetings, Chicago, IL, USA] and is currently unknown.

Two traditional prognostic markers, serum creatinine and oliguria, were not helpful in our study. Creatinine and percentage of oliguric patients was not different between survivors and nonsurvivors. An unexpected finding was the higher mean serum creatinine measurements in the hemodialysis (4.7 mg/dL) versus the CRRT group (4.0 mg/dL). Survival in numerous studies has correlated with both pre- and post-liver transplant serum creatinine [21, 24, 25, 35]. Differences in creatinine metabolism and metabolism lead to overestimates of glomerular filtration rate (GFR) in liver disease, though mean levels greater than 4.0 mg/dL imply profound reductions in GFR in all subgroups in our study [17, 36]. Thus, the observed difference in creatinine is probably not clinically significant. Another unexpected finding was that oliguric patients did not have worse outcomes than those with nonoliguric ARF. Whether this lack of difference is because some of the patients who were initially nonoliguric later became oliguric is unclear.

Patients who initiated RRT preoperatively and met our study criteria had significantly worse 3-month and 1-year survival compared to all other liver transplant recipients at our institution. This is consistent with previous studies linking pretransplant renal failure and/or need for pretransplant RRT with poorer outcomes following successful liver transplant [10, 16, 18, 21, 22, 28]. Interestingly, when we identified patients who were not in our pretransplant RRT cohort who had initiated RRT for posttransplant renal failure, it became clear that this subgroup accounted for most of the mortality among all other liver transplant recipients at our center. Again, this reinforces data that associates posttransplant RRT and worse renal function with worse outcomes [9, 10, 19, 31, 39]. In a larger sense, the 1-year 70% survival rate of liver transplant recipients receiving pretransplant RRT compared to 4% hospital survival without liver transplant reflects a tremendous improvement in mortality.

In our regression model, mean arterial pressure was the sole independent predictor of mortality. Patients with greater hemodynamic instability were more likely to be placed on CRRT. It appears that the choice of CRRT

over hemodialysis was determined largely by severity of illness and low mean arterial pressure. Though existing studies have not demonstrated a survival advantage of CRRT in liver failure, our nephrologists likely chose CRRT more frequently due to severe hypotension. There is growing interest in short daily hemodialysis and slow, prolonged, low-efficiency dialysis (SLED) as better tolerated alternatives to triweekly hemodialyis or CRRT. So far, only one randomized controlled trial exists demonstrating an advantage of daily over intermittent hemodialysis for ARF [40]. While there are no data yet to support these practices in liver transplant candidates, they do have theoretic advantages and deserve further study. The molecular adsorbent recirculating system (MARS) and more recently, simultaneous albumin dialysis and high-flux hemodialysis in patients with advanced liver failure have attracted recent interest [41–43]. Though results are promising, these systems are expensive and not available at many transplant centers. Wider experience is needed to determine the role of MARS and other nonconventional dialytic modalities in managing the liver transplant candidate with ARF.

Our study was not designed to investigate the role of combined liver-kidney transplant. Only four patients in our cohort received liver-kidney transplant, with 75% 1-year survival. These small numbers preclude any meaningful conclusions, though this topic is currently of great interest and should be further investigated.

CONCLUSION

ARF requiring RRT in patients with liver failure is a strong predictor of mortality both pre- (65%) and post- (30%) liver transplantation. Despite this, many patients (>30% in this series) survive to liver transplantation with the support of RRT. These patients, with average APACHE II scores of 29 and average MELD scores of 39 in our series, have an acceptable 70% 1-year survival posttransplantation. Although sicker patients clearly suffer higher mortality, RRT should not be withheld in a liver transplant candidate because of the severity of illness alone. With lengthening wait times and organ shortages, the incidence and cumulative burden of ARF in patients with advanced liver disease is likely to increase. Our data demonstrate that once a patient initiates RRT, they have a limited and rapidly shrinking opportunity for survival: liver transplant.

Unfortunately, the solution is not within ready grasp due to geographic disparities in access to organs as prioritized by MELD scores. Differences in geographic allocation of livers based upon local organ procurement agencies have resulted in a disparate number of organs being allocated to centers with smaller waiting lists and less severely ill candidates [33]. It is imperative to provide our patients with a liver graft in a more reasonable period of time after initiating RRT. This is another call to implement the 1999 Institute of Medicine's recommendation to establish organ allocation areas serving a population base of at least 9 million people [44]. Until these changes are made, it is the responsibility of the nephrologist to initiate RRT promptly for ARF in liver transplant candidates and to provide supportive care until an organ becomes available.

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