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Renal Recovery and Mortality Risk among Patients with Hepatorenal Syndrome Receiving Chronic Maintenance Dialysis

Sophie McAllister[1], *Jennifer C. Lai*[2], *Timothy P. Copeland*[3], *Kirsten L. Johansen*[4], *Charles E. McCulloch*[5], *Yuenting D. Kwong*[3], *Divya Seth*[3,6], *Barbara Grimes*[5], *and Elaine Ku*[3,5,6]

Key Points

- Patients with hepatorenal syndrome (HRS) receiving maintenance dialysis have a lower likelihood of recovery of kidney function compared with patients with acute tubular necrosis (ATN).
- Patients with HRS receiving maintenance dialysis have a higher likelihood of mortality compared with patients with ATN.
- Younger age, history of alcohol use, and absence of comorbidities were predictors of recovery of kidney function in patients with HRS receiving maintenance dialysis.

Abstract

Background Kidney replacement therapy is controversial for patients with hepatorenal syndrome who may not be liver transplant candidates. Data surrounding the likelihood of recovery of kidney function and mortality after outpatient dialysis initiation in patients with dialysis-requiring hepatorenal syndrome could inform discussions between patients and providers.

Methods We performed a retrospective cohort study of patients with hepatorenal syndrome who were registered in the United States Renal Data System between 1996 and 2015 (n=7830) as receiving maintenance dialysis. We characterized patients with hepatorenal syndrome by recovery of kidney function using Fine and Gray models. We also examined hazard of recovery of kidney function and death among those with hepatorenal syndrome versus those with acute tubular necrosis (n=48,861) using adjusted Fine–Gray and Cox models, respectively.

Results Of the patients with hepatorenal syndrome, 11% recovered kidney function. Those with higher likelihood of recovery were younger, non-Hispanic White, and had a history of alcohol use. Compared with patients with acute tubular necrosis, patients with hepatorenal syndrome as the attributed cause of kidney disease had a lower hazard of recovery (HR, 0.22; 95% CI, 0.21 to 0.24) and higher hazard of death within 1 year (HR, 3.10; 95% CI, 2.99 to 3.23) in fully adjusted models.

Conclusions Patients with hepatorenal syndrome receiving chronic maintenance dialysis had a lower likelihood of recovery of kidney function and higher mortality risk compared with patients with acute tubular necrosis. Among patients with hepatorenal syndrome, those most likely to recover kidney function were younger, had a history of alcohol use, and lacked comorbid conditions. These data may inform prognosis and discussions surrounding treatment options when patients with hepatorenal syndrome need chronic maintenance dialysis therapy.

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Introduction

Hepatorenal syndrome (HRS) is a severe complication of liver disease that develops in about 20% of patients with cirrhosis and ascites after 1 year (1,2). Prognosis is poor for both HRS-AKI (formerly type-1 HRS) and HRS-CKD (formerly type-2 HRS), with a median survival of 2 weeks and 6 months, respectively (1,3–6). Many patients with HRS succumb to their illness as inpatients, so the transition of care to the outpatient setting for patients with HRS is not well described (5,6). Currently, orthotopic liver transplant (OLT) is the definitive treatment of end stage liver

[1]School of Medicine, University of California San Francisco, San Francisco, California
[2]Division of Gastroenterology and Hepatology, Department of Medicine, University of California San Francisco, San Francisco, California
[3]Division of Nephrology, Department of Medicine, University of California San Francisco, San Francisco, California
[4]Division of Nephrology, Department of Medicine, Hennepin Healthcare and University of Minnesota, Minneapolis, Minnesota
[5]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California
[6]Division of Pediatric Nephrology, Department of Pediatrics, University of California San Francisco, San Francisco, California

Correspondence: Sophie McAllister, Division of Nephrology, University of California, San Francisco, 533 Parnassus Avenue, U404, Box 0532, San Francisco, CA 94143-0532. Email: Sophie.mcallister@ucsf.edu

disease and leads to resolution of HRS in the majority of patients (7,8). However, due to a scarcity of organs, even patients who are eligible for transplant often require supportive therapy as a bridge to liver transplant, including the use of systemic vasoconstrictors, the transjugular intrahepatic portosystemic shunt procedure, and dialysis. This leaves outpatients who are ineligible for OLT with few options beyond supportive or palliative measures.

Currently, it remains controversial whether patients with HRS who may be unlikely to receive OLT should be treated with chronic maintenance dialysis, especially in the outpatient setting (7). Recommendations regarding whether dialysis should be offered to patients with HRS often conflict. For example, the European Association for the Study of the Liver guidelines recommend offering dialysis to patients with HRS who do not respond to other treatments, regardless of OLT eligibility, whereas the Acute Dialysis Quality Initiative recommends withholding dialysis for patients who are not eligible for OLT without an acute, reversible etiology of HRS (8,9). Data on the survival of patients with HRS receiving maintenance dialysis are limited, and outcomes are highly variable depending on the population included for study (8,10–13). Additionally, most of the available data are limited by small sample size and are often restricted to patients receiving inpatient dialysis during hospitalizations or patients awaiting OLT (12–16). The rates of recovery of kidney function that allow for sufficient recovery and dialysis independence in patients with HRS treated as outpatients have rarely been reported outside of the post-OLT context.

Few studies have identified predictors of recovery of kidney function in the population of patients with HRS who receive outpatient maintenance dialysis, and most of the available data are focused on characteristics of patients who received OLT and recovered kidney function thereafter (15). Understanding the prognosis and outcomes of patients with HRS receiving maintenance dialysis may allow for more informed counseling of patients who are facing the decision of whether to pursue maintenance dialysis in the outpatient setting, identify patients who may have a chance of recovery of kidney function and need closer monitoring, and guide prognostication.

In this study, we examined outcomes in a large, national cohort of patients receiving chronic maintenance dialysis due to kidney disease attributed to HRS to better inform discussions surrounding the option of initiating chronic maintenance dialysis. Specifically, we examined predictors of recovery of kidney function in patients with HRS and determined the hazard of recovery of kidney function and death within 1 year of initiation of chronic dialysis. To place the rates of recovery of kidney function and mortality in context, we compared the hazard for both outcomes in patients with ESKD attributed to HRS versus patients with acute tubular necrosis (ATN) from any etiology.

Materials and Methods

Study Population and Data Source

We performed a retrospective cohort study of adults ≥18 years of age who were registered in the United States Renal Data System (USRDS) between January 1, 1996 and December 31, 2015. Patients were registered within the USRDS after provider certification of the Centers for Medicare and Medicaid (CMS) Medical Evidence Form (CMS-2728) in the MEDEVID file, which is required within 45 days of outpatient dialysis initiation in all patients treated with dialysis in the United States. Patient demographic characteristics (age, sex, race), cause of kidney disease, insurance coverage (none, Medicare and/or Medicaid, private/other), zip code, date of chronic dialysis initiation, and race and ethnicity (categorized as non-Hispanic white, Hispanic, non-Hispanic Black, Asian, or other) at time of initiation of maintenance dialysis were abstracted from the CMS-2728 MEDEVID Form and Patients File in the USRDS. Zip code was used to determine median neighborhood income on the basis of the American Community Survey conducted between 2006–2010 and 2011–2015 (17). The first date of maintenance dialysis is the date the provider reported to the USRDS that the patient developed ESKD, which could be in the inpatient, outpatient, or home setting. Initial maintenance dialysis modality (peritoneal dialysis versus hemodialysis) was determined at the first date of dialysis service according to the RXHIST and MEDEVID files. The RXHIST file amalgamates data from Medicare claims, CROWNWeb, the CMS-2728 form, the CMS Death Notification Form, and the Organ Procurement Transplant Network Transplant files to update treatment status sequentially over time (18). Using the Primary Disease causing ESRD (PDIS) variable from the MEDEVID file, we identified patients receiving maintenance dialysis attributed to HRS (572.4, 572.4A, 572.4Y, 572.4Z, and K76.7) and ATN from any etiology (583.6, 583.6A, 584.9, N17.0, N17.1, and N17.9). Death due to dialysis withdrawal was determined on the basis of the CMS Death Notification Form. We excluded patients who were known to have an OLT before chronic maintenance dialysis initiation when feasible (on the basis of the availability of Medicare claims data), given that the outcomes in this group may differ (n=3100 for any ESKD; Figure 1).

Outcome Ascertainment

We used the RXHIST files to ascertain the discontinuation of dialysis in patients registered in the USRDS as recipients of chronic maintenance dialysis. The RXHIST files contain a new record for each change in treatment modality (including recovery of kidney function or changes in dialysis modality). Patients were considered to have recovered from the need for maintenance dialysis if (*1*) they were noted to have recovered kidney function according to RXHIST and did not restart dialysis for a 90-day period; (*2*) the patient did not die within 90 days of stopping dialysis treatment; and (*3*) the patient did not receive a kidney transplant within 90 days of stopping dialysis. A 90-day, dialysis-free period was required for our definition of "recovery" on the basis of standard definitions according to the USRDS (18). Patients were only considered to have recovered from the need for maintenance dialysis if recovery occurred within 365 days after the date of maintenance dialysis initiation, as reported by providers on the CMS-2728 form (FIRST_SE). Date of kidney transplant was determined using the TX1date variable from the Patients file. In addition, for those with Medicare as their insurer at time of chronic dialysis initiation, we identified the receipt of OLT using

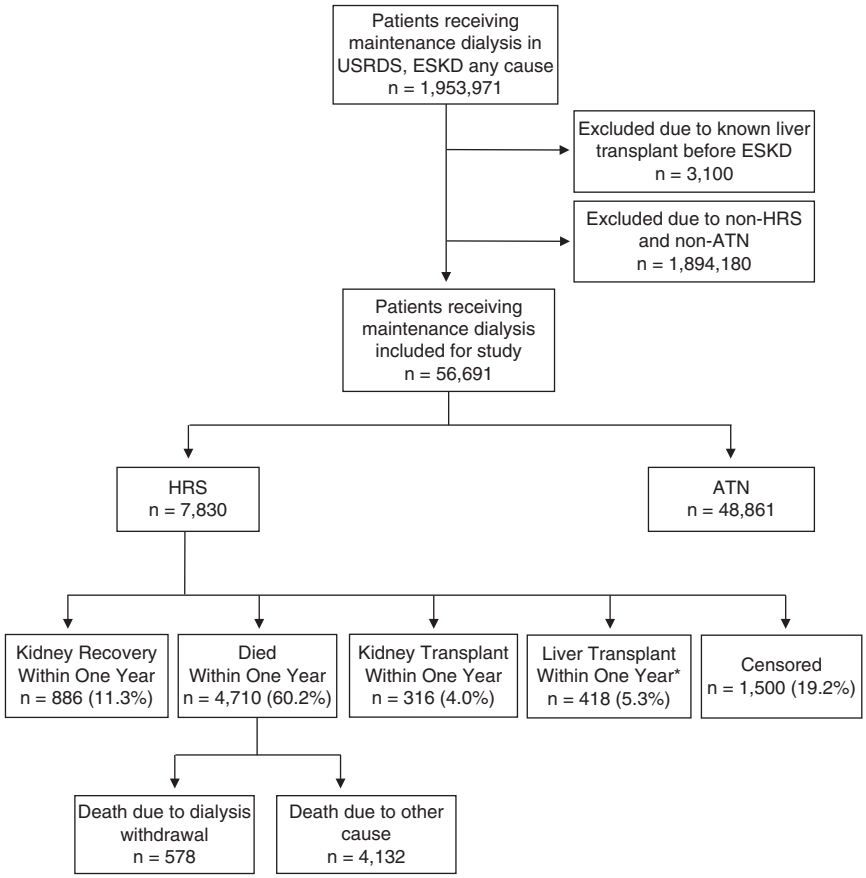

Figure 1. | A large proportion of patients with HRS receiving maintenance dialysis died and a small proportion recovered kidney function within 1 year. ATN, acute tubular necrosis; HRS, hepatorenal syndrome; USRDS, United States Renal Data System.

International Classification of Diseases, Ninth Revision (ICD-9) and -10 codes (V42.7, 996.82, 50.51, 50.59, Z48.23, Z94.4, 0FY00Z0, 0FY00Z1, T86.40, T86.41, T86.42, T86.43, and T86.49) during our 1-year period of follow-up. We also identified simultaneous liver-kidney transplantation (SLKT) events that occurred in this time period by comparing the date of claims for OLT with the date of kidney transplantation. In the Medicare population, cirrhosis was identified using ICD-9 and ICD-10 codes (571.2, 571.5, 571.6, K70.30, K70.31, K71.7, K72.10, K72.11, K74.3, K74.4, K74.5, K74.60, and K74.69).

Follow-up of all patients began at the first episode of dialysis initiation and ended at the date of renal recovery, death, liver or kidney transplant (or SLKT), or 365 days after dialysis initiation. Dates of death were determined using the Patients files.

Characteristics and Predictors of Recovery of Kidney Function for Patients with HRS

We first examined the demographic, socioeconomic, and comorbid characteristics of all patients with HRS and by status of recovery of kidney function. Characteristics of interest included age (categorized as 18 to <30, 30 to <65, and ≥ 65 years), sex, race, presence or absence of insurance at dialysis initiation, median income by neighborhood zip code, and comorbid conditions present at time of dialysis initiation.

Next, we used adjusted Fine and Gray models to examine the predictors of recovery of kidney function among those with HRS. We accounted for the competing risks of death and kidney transplant and adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period (in 5-year intervals), first treatment modality (peritoneal dialysis versus hemodialysis), insurance status, and region of the United States (model 1). We then additionally adjusted these models for comorbid conditions, including hypertension, heart failure, diabetes mellitus, coronary artery disease, malignancy, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, drug use, tobacco use, and alcohol use (model 2).

Hazard of Recovery of Kidney Function and Death Comparing Patients with HRS versus ATN

We compared the overall hazard of recovery of kidney function among those with a diagnosis of HRS (versus ATN) in Fine and Gray models adjusted for the same covariates as described above (model 1 and 2).

We used Cox models to examine the risk of death among those with HRS versus ATN, adjusted for the same covariates as above. In these models, we censored follow-up at date of renal recovery, liver or kidney transplant (or SLKT), or 365 days after dialysis initiation.

In sensitivity analysis, we repeated our Fine and Gray and Cox models for the outcome of recovery of kidney function and death only among the subset of patients who had Medicare at time of chronic dialysis initiation or who had Medicare claims available after chronic dialysis initiation. In this population, we also compared the hazard of recovery of kidney function or mortality for patients with HRS compared with patients with ATN and cirrhosis.

The University of California San Francisco (UCSF) Institutional Review Board considers this study not human subjects research. Analyses were conducted in STATA 16.1 (StataCorp LLC, College Station, TX).

Results

Study Population

We included 56,691 patients receiving maintenance dialysis due to HRS or ATN between January 1, 1996 and December 31, 2015. Of these patients, 7830 (14%) had their kidney disease attributed to HRS, and 48,861 (86%) had their kidney disease attributed to ATN (Figure 1). The mean±SD

Table 1. Characteristics of patients with HRS who started maintenance dialysis

Characteristics	Percentage or Median (IQR) (n=7830)	
	All HRS[a]	Recovered among Those with HRS[b]
Age		
18 to <30 yr	1	31
30 to <65 yr	73	14
≥65 yr	26	4
Race		
Non-Hispanic White	71	12
Non-Hispanic Black	11	8
Hispanic	14	12
Asian	2	12
Other	2	10
Sex		
Male	65	12
Female	35	11
Insurance at onset of maintenance dialysis		
None	0.7	12
Medicaid, private, other	10	13
Medicare	89	11
Median income in zip code in $1000s (IQR)[c]	50.1 (40.0–65.9)	51.5 (40.9–67.7)
Dialysis modality		
Hemodialysis	99	11
Peritoneal dialysis	2	3
Region		
West	24	15
Midwest	27	11
South	28	11
East	21	9
Comorbid condition		
Coronary artery disease	9	8
Malignancy	7	7
Heart failure	19	7
Stroke	2	6
Diabetes mellitus	29	7
Hypertension	46	9
Drug dependence	3	16
Peripheral vascular disease	5	7
Smoker	9	16
Chronic obstructive pulmonary disease	7	9
Alcohol dependence	37	16

HRS, hepatorenal syndrome; IQR, interquartile range.
[a]Column percentage.
[b]Row percentage.
[c]Median income in zip code among patients with HRS and among those who recovered.

age at first onset of maintenance dialysis among patients with HRS was 56.8±12.1 years, which was younger than those with ATN (66.4±14.4 years). The majority of patients with HRS were non-Hispanic White, men, and between 30 and <65 years (Table 1).

The median follow-up duration for patients with HRS was 92 days. Of the patients with HRS, 60% (n=4710) died within 1 year of first receiving maintenance dialysis (Figure 1), with 85% (n=4027) of those dying within the first 6 months. About 12% (n=578) of patients with HRS who died had their cause of death attributed to withdrawal from dialysis. Approximately 11% (n=886) of all patients with HRS recovered kidney function within 1 year of follow-up (Figure 1), with 81% (n=721) recovering kidney function within 6 months. A small proportion of the cohort (5%) received liver transplantation within 1 year of follow-up, and 19% were censored at the end of the follow-up period without any event of interest (Figure 1).

We examined the frequency of OLT among individuals who had Medicare at the first date of chronic maintenance dialysis and who had HRS as the attributed cause of ESKD (n=6957) to determine their liver transplant status after kidney replacement therapy, which we treated as a censoring event. We found that 6% (n=393) of patients on dialysis with HRS received OLT within 365 days of first recorded date of maintenance dialysis, of which 216 (55%) were SLKT. Overall, 45% (n=177) of those who received liver transplantation (either SLKT or OLT alone) died during our 1-year follow-up period (Supplemental Figure 1).

Predictors of Recovery from Maintenance Dialysis

Younger patients (<30 years) with HRS were more likely to recover kidney function compared with older patients in minimally adjusted and fully adjusted models (Table 2). Non-Hispanic Black individuals were statistically significantly less likely to recover kidney function compared with non-Hispanic White individuals in adjusted analyses. Additionally, patients whose initial dialysis treatment modality was peritoneal dialysis were less likely to recover kidney function in adjusted analyses (Table 2).

Table 2. Predictors of recovery of kidney function within 1 year of first date of maintenance dialysis using adjusted Fine and Gray models among patients with HRS, accounting for the competing risk of death

Predictors	HR (95% CI) (n=7830)	
	Model 1[a]	Model 2[b]
Age		
18 to <30 yr	Reference	Reference
30 to <65 yr	0.36 (0.26 to 0.51)	0.42 (0.30 to 0.59)
≥65 yr	0.10 (0.07 to 0.15)	0.15 (0.10 to 0.22)
Women (versus men)	0.99 (0.87 to 1.14)	1.05 (0.92 to 1.21)
Race		
Non-Hispanic White	Reference	Reference
Non-Hispanic Black	0.64 (0.50 to 0.82)	0.68 (0.53 to 0.88)
Hispanic	0.90 (0.74 to 1.10)	0.94 (0.77 to 1.15)
Asian	1.01 (0.61 to 1.67)	1.14 (0.69 to 1.89)
Other	0.67 (0.42 to 1.06)	0.66 (0.42 to 1.04)
Median income in zip code per $10,000	1.03 (1.00 to 1.06)	1.02 (0.99 to 1.05)
Peritoneal dialysis (versus hemodialysis)	0.22 (0.07 to 0.70)	0.24 (0.08 to 0.75)
Insured (versus no insurance)	1.13 (0.55 to 2.33)	1.31 (0.64 to 2.68)
Region of United States		
West	Reference	Reference
Midwest	0.78 (0.65 to 0.94)	0.77 (0.64 to 0.93)
South	0.79 (0.65 to 0.94)	0.81 (0.67 to 0.97)
East	0.65 (0.53 to 0.80)	0.67 (0.54 to 0.82)
Comorbid conditions (versus without condition)		
Coronary artery disease	—	1.21 (0.91 to 1.60)
Malignancy	—	0.73 (0.52 to 1.02)
Chronic obstructive pulmonary disease	—	0.94 (0.70 to 1.26)
Heart failure	—	0.80 (0.65 to 0.98)
Stroke	—	0.77 (0.42 to 1.39)
Diabetes mellitus	—	0.70 (0.59 to 0.84)
Hypertension	—	0.88 (0.76 to 1.01)
Drug dependence	—	1.18 (0.85 to 1.64)
Peripheral vascular disease	—	0.86 (0.58 to 1.28)
Smoker	—	1.16 (0.94 to 1.42)
Alcohol dependence	—	1.40 (1.22 to 1.61)

HRS, hepatorenal syndrome; HR, hazard ratio.
[a]Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, insurance status, and region of the United States.
[b]Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, insurance status, region of the United States, and comorbid conditions (hypertension, heart failure, diabetes mellitus, coronary artery disease, malignancy, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, drug use, tobacco use [current smokers], and alcohol use).

Comorbid conditions associated with lower hazard of recovery of kidney function included the presence of heart failure and diabetes. Patients with a history of alcohol dependence were more likely to recover kidney function compared with those without a history of alcohol dependence (Table 2).

Patient insurance status, sex, and median neighborhood income were not statistically significantly associated with recovery of kidney function in fully adjusted models (model 2).

Hazard of Recovery of Kidney Function and Mortality in HRS versus ATN

We compared the hazard of recovery of kidney function and death among patients with kidney disease attributed to HRS versus ATN (Figures 2 and 3, Table 3). Among those with HRS, the rate of recovery of kidney function was 27.6 per 100 person-years, and the rate of death was 146.6 per 100 person-years. The hazard of recovery for patients with HRS was 0.22 (95% CI, 0.21 to 0.24) compared with those with ATN from any cause in fully adjusted model (model 2).

In terms of mortality risk, patients with HRS were 3.10 times (95% CI, 2.99 to 3.23) more likely to die compared with those with ATN in adjusted analyses (model 2; Table 3). The most common attributed causes of death for patients with HRS were cirrhosis (24%); liver failure, unknown cause (13%); and cardiac arrest, unknown cause (11%).

In sensitivity analysis, we repeated our models for recovery of kidney function and mortality among the subset of individuals with Medicare, and the results were similar. Compared with patients with ATN and cirrhosis, patients with HRS were 1.37 times (95% CI, 1.25 to 1.49) more likely to die and 0.54 times (95% CI, 0.33 to 0.65) less likely to recovery kidney function in adjusted analyses (Supplemental Table 1).

Discussion

There have been limited data surrounding the outcomes of patients with HRS treated with outpatient maintenance dialysis. Our study is unique in our focus on the subpopulation of patients with HRS who survived to receive maintenance dialysis and who were registered in the USRDS. Among this group, 11% of patients recovered kidney function within 1 year of the first date of maintenance dialysis. The characteristics of patients most likely to recover kidney function included those who were younger; patients who were not Black; or those without other chronic comorbid conditions, such as diabetes or heart failure. However, the overall mortality rate in this group of patients was high, with a rate of death of 146.6 per 100 person-years among patients with HRS. These data add to our understanding of the prognosis of patients with kidney disease attributed to HRS receiving chronic maintenance dialysis as outpatients, and may guide the counseling of patients with regard to the benefits—or lack thereof—of transitioning to outpatient chronic maintenance dialysis, particularly in a subset who may not be eligible for liver transplantation.

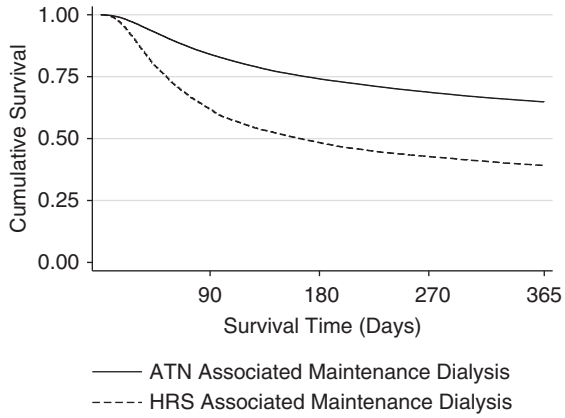

Figure 2. | Patients with HRS have a lower cumulative survival compared to patients with ATN in unadjusted Kaplan-Meier survivalanalysis. The solid and dashed lines represent the cumulative survival for patients over time with ATN-associated maintenance dialysis and HRS-associated maintenance dialysis, respectively.

In this study, we found that a small subset of patients with HRS who received chronic maintenance dialysis ultimately recovered kidney function at an absolute rate of 27.6 per 100 person-years. Few studies have described the rate of recovery of kidney function in patients with HRS receiving maintenance dialysis, and most prior studies on this issue have been relatively limited in terms of sample sizes or only provided single-center data (5,19–21). We found the rate of recovery of kidney function for patients with HRS was significantly lower than that of patients who received maintenance dialysis due to ATN, which we would expect to be associated with the highest rates of recovery given the acute nature of the insult leading to maintenance dialysis (11,22,23). Furthermore, in analysis comparing the mortality risk of those with HRS versus ATN, we found HRS was also associated with a 3.1 times greater risk of death compared with patients receiving maintenance dialysis due to ATN, suggesting that the overall prognosis is much poorer in those with HRS requiring maintenance dialysis. The incidence of mortality and recovery of kidney function was highest in the first 6 months of outpatient maintenance dialysis, suggesting continuation of maintenance dialysis >6 months may not improve chances of recovery of kidney function. Additionally, even among Medicare patients who received OLT or SLKT, 1-year mortality remained high, although we note this could be related to our focus on a population with Medicare who may be older at time of transplantation and have more comorbid conditions. These findings may support prevailing beliefs regarding the poor outcomes of patients with HRS who fail inpatient dialysis therapy.

Not surprisingly, younger patients (18 to <30 year old) with HRS were more likely to recover kidney function, whereas patients with comorbid conditions (including heart failure and diabetes) were less likely to recover kidney function. These data are consistent with predictors of recovery of kidney function in other causes of kidney disease requiring dialysis (24,25). Patients receiving peritoneal dialysis were also less likely to recover kidney function. This may be due to a number of possibilities, including the less frequent use of peritoneal dialysis for the treatment of AKI in the United States or smaller sample size of this population (26,27). Patients with a history of alcohol use were also more likely to recover kidney function, which is consistent with

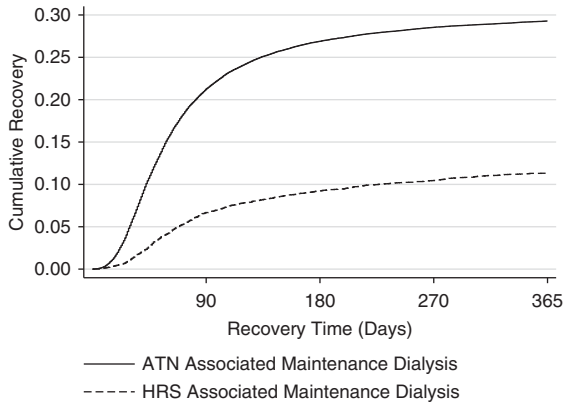

Figure 3. | Patients with HRS have a lower hazard of recovery of kidney function compared with patients with ATN inunadjusted cumulative incidence functionanalysis. The solid and dashed lines represent the cumulative recovery for patients over time with ATN-associated maintenance dialysis and HRS-associated maintenance dialysis, respectively.

a study by Allegretti *et al.* (19) that found those with alcoholic cirrhosis as the etiology of their liver disease had better recovery of kidney function. However, it is worth noting that some studies have found that alcoholic cirrhosis was a predictor of dialysis nonrecovery for patients with HRS after OLT, although those who go on to receive liver transplantation may differ from our study population, because we censored patients if liver transplantation occurred during follow-up (15). Identifying the characteristics of patients with HRS who are more likely to recover kidney function can help inform providers and patients regarding the likelihood of benefit from a trial of outpatient dialysis.

Notably, a lower proportion of patients with HRS receiving chronic maintenance dialysis were non-Hispanic Black compared with the general population of patients receiving chronic maintenance dialysis for any indication (18). Although the distribution of HRS by race has not been previously described in large cohorts in the outpatient setting, this racial breakdown aligns with a previous study of 2542 patients hospitalized with HRS that found that 14% of inpatients with HRS across the United States were Black (28). Whether these observed racial differences in the proportion of Black patients requiring outpatient dialysis for HRS versus other causes of kidney disease are due to differences in the proportion of Black patients who are offered outpatient dialysis, differences in survival to hospital discharge, or other forms of structural racism is unknown and deserves further study.

The strengths of our study include the relatively large size of this cohort, along with the nationally representative data included for study. Furthermore, this study includes the general population of patients with HRS on maintenance dialysis, which extends beyond the relatively limited population of peri-OLT patients who are typically included in studies on HRS and dialysis. A significant limitation to this study is the lack of access to granular data surrounding the diagnosis of HRS or ATN beyond administrative codes, and the attributed causes of maintenance dialysis are likely not proven by biopsy specimen, although these diagnoses are frequently presumptive in routine clinical care. Another major limitation is that misclassification of liver transplant status may be present given the inability to ascertain liver transplant status in non-Medicare patients; however, overall, the rates of OLT were low in the Medicare population with HRS (6%). Other limitations to the USRDS dataset include the lack of granular data surrounding the severity of liver disease, including presence or absence of ascites and Model for End-Stage Liver Disease scores, which may be prognostic of recovery of kidney function (12,13,19). Our dataset also does not include comprehensive data on OLT waitlist status, which may be important when deciding whether outpatient dialysis is appropriate for patients with HRS. In addition, we are unable to ascertain liver transplant status in the subset of individuals who do not have Medicare, which could have biased our results toward the null if such misclassification occurred. Finally, our study is observational and may be subject to residual confounding.

Our study focuses on a cohort of patients who survived to receive outpatient maintenance dialysis, and these individuals are likely healthier than the population of patients with HRS who may succumb to their illness while hospitalized. However, our study was specifically designed to focus on this more robust population because the management of this

Table 3. Hazard of recovery of kidney function and death for HRS versus ATN

Model	HR (95% CI) (N=56,691)[a]	
	Risk of Recovery of Kidney Function	Risk of Death
Unadjusted HRS (versus ATN)	0.34 (0.32 to 0.37)	2.30 (2.23 to 2.37)
Model 1 HRS (versus ATN)[b]	0.26 (0.25 to 0.28)	3.09 (2.98 to 3.19)
Model 2 HRS (versus ATN)[c]	0.22 (0.21 to 0.24)	3.10 (2.99 to 3.23)

HRS, hepatorenal syndrome; ATN, acute tubular necrosis; HR, hazard ratio.
[a]HRS, n=7830; ATN, n=48,861.
[b]Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, insurance status, and region of the United States.
[c]Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, insurance status, region of the United States, and comorbid conditions (hypertension, heart failure, diabetes mellitus, coronary artery disease, malignancy, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, drug use, tobacco use [current smokers], and alcohol use).

population is often debated, and we were interested in the outcomes of individuals who do not subsequently receive liver transplantation after the initiation of outpatient dialysis. We acknowledge that inconsistencies with HRS diagnosis may be present due to our reliance on ICD coding for HRS determination, and changes in HRS definition by the International Club of Ascites—notably in 1996, 2007, and 2015—may contribute to some differences in the diagnosis of HRS over time (23–25). However, because diagnoses of patients with ATN and HRS are seldom proven by biopsy specimen and are clinical diagnoses, we believe our data remain informative surrounding the differences in outcomes of these two groups of patients.

In conclusion, patients with HRS treated with outpatient maintenance dialysis have high rates of mortality compared with patients with ATN from any cause. Overall, the absolute rate of recovery is low among patients with HRS, and recovery of kidney function is less likely compared with ATN. Recognition of patient characteristics that predict higher rates of recovery of kidney function may help identify patients who may benefit from a time-limited trial of outpatient dialysis and close monitoring for recovery. Further studies are needed to understand whether the provision of outpatient maintenance dialysis to patients who are not candidates for OLT improves quality of life or patient-centered outcomes of interest.

Disclosures

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Author Contributions

T.P. Copeland, B. Grimes, K.L. Johansen, E. Ku, Y.D. Kwong, J.C. Lai, C.E. McCulloch, and D. Seth provided supervision; T.P. Copeland and E. Ku were responsible for data curation and validation; T.P. Copeland, E. Ku, and S. McAllister conceptualized the study and were responsible for formal analysis, investigation, and methodology; E. Ku was responsible for project administration, resources, and software; E. Ku and J.C. Lai were responsible for funding acquisition; S. McAllister wrote the original draft; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0005182020/-/DCSupplemental.

Supplemental Table 1. Hazard of recovery of kidney function and death for HRS versus ATN in the subset of patients with Medicare.

Supplemental Figure 1. Cohort outcomes flow diagrams for Medicare subset receiving confirmed OLT at any time point.

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Supplemental Tables and Figures

Supplemental Table S1. Hazard of Recovery of Kidney Function and Death for HRS versus ATN in the Subset of Patients with Medicare.

N = 52,863*	**Risk of recovery of kidney function HR (95% CI)**	**Risk of death HR (95% CI)**
Unadjusted HRS (vs. ATN)	0.35 (0.32-0.37)	2.28 (2.21-2.36)
Model 1 HRS (vs. ATN)	0.27 (0.25-0.29)	3.05 (2.94-3.16)
Model 2 HRS (vs. ATN)	0.23 (0.21-0.24)	3.08 (2.96-3.21)
Model 2 HRS (vs. ATN with cirrhosis)	0.54 (0.33-0.65)	1.37 (1.25-1.49)

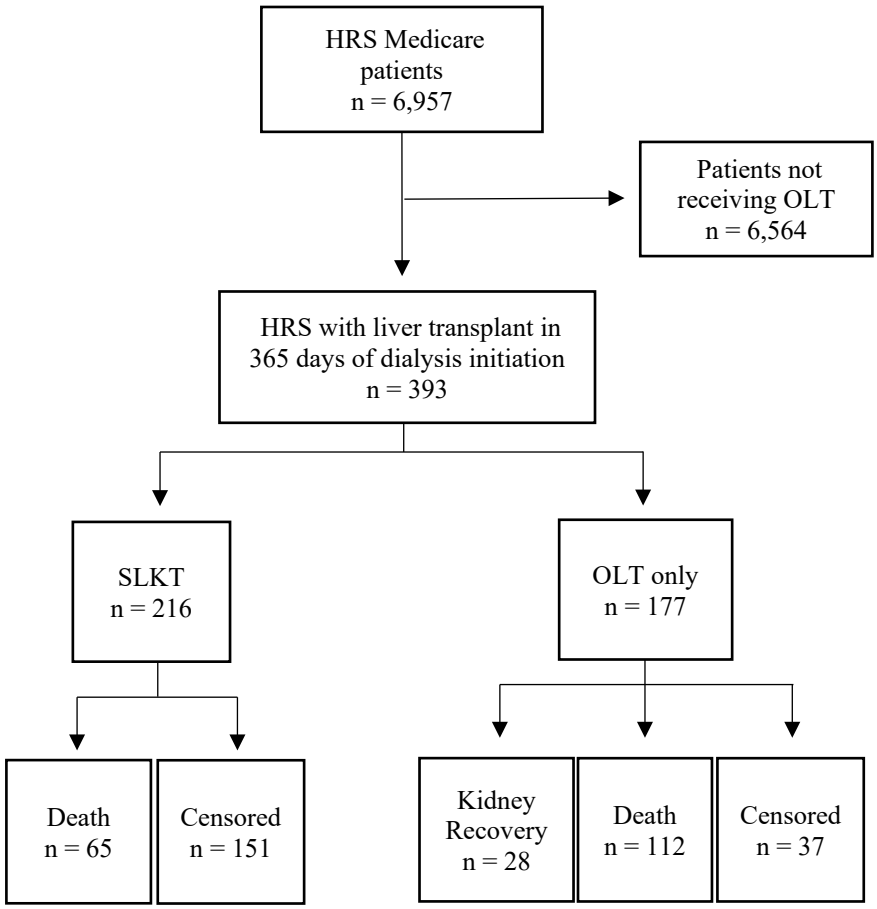
***HRS: n = 6,957**
ATN: n = 45,906
ATN with cirrhosis: n = 1,046

Model 1: Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, and region of the US.

Model 2: Adjusted for age category, sex, race/ethnicity, median neighborhood income, calendar period, initial treatment modality, region of the US, and comorbid conditions (hypertension, heart failure, diabetes mellitus, coronary artery disease, malignancy, chronic obstructive pulmonary disease, peripheral vascular disease, stroke, drug use, tobacco use (current smokers), and alcohol use).

Abbreviations: HRS, hepatorenal syndrome; ATN, acute tubular necrosis; HR, hazard ratio; CI, confidence interval.

Supplemental Figure S1: Cohort Outcomes Flow Diagrams for Medicare Subset Receiving Confirmed OLT at Any Timepoint



All end points (kidney recovery, death, censorship) are within one year of first date of maintenance dialysis.

Abbreviations: OLT, orthotopic liver transplantation; ESKD, end stage kidney disease; HRS, hepatorenal syndrome; SLKT, simultaneous liver-kidney transplant