Exploratory study of relationship between hospitalized heart failure patients and chronic renal replacement therapy

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Abstract

Background. Chronic kidney disease (CKD) is common in heart failure (HF) and is associated with poor outcomes. Renal replacement therapy (RRT) may be deferred over concerns regarding tolerability and outcomes in HF. Our objectives were to ascertain the incidence of RRT, changes in RRT incidence over time and the association between RRT and survival in hospitalized HF patients.

Methods. A retrospective cohort study of consecutive hospitalized HF patients was performed at a single centre from 1987 to 2002 with RRT data from the United States Renal Data System.

Results. Of 6276 HF patients without RRT on admission, 304 commenced chronic (≥3 months) RRT (280 dialysis only; 24 transplant) at a median of 475 days after dismissal. Overall incidence was 1.6% per year. Risk-adjusted incidence increased over time and was similar in those with preserved or reduced (<50%) ejection fraction. RRT patients were younger but had worse renal function and anaemia, and more diabetes, hypertension and coronary disease. Unadjusted survival was worse in the RRT group. However, risk-adjusted survival was similar in RRT and non-RRT groups (HR = 1.11, 95% CI 0.94–1.29, P > 0.05).

Conclusions. Our data show that although RRT is increasingly used in HF patients, the impact on risk-adjusted mortality remains to be established. Further studies should focus on defining the appropriate clinical settings in which RRT should be used in HF, the timing and type of RRT and whether RRT can improve specific outcomes.

Keywords: cardiorenal failure; end-stage renal disease; heart failure; renal replacement therapy; survival

Introduction

Chronic kidney disease (CKD) is common in heart failure (HF) [1] and is attributable to similar underlying risk factors as well as adverse effects of HF itself on renal function over time [2]. The presence of CKD accelerates the progression of cardiovascular disease and ventricular remodelling to HF and the progression of HF to death [2,3]. In HF, both the level of CKD and the development of worsening renal function (WRF) during treatment of HF are potently and independently associated with poor outcomes [1,4–12]. This is increasingly relevant as the average level of renal...
function in patients hospitalized with HF has decreased dramatically over time [13] and WRF occurs in 25–30% of patients hospitalized for HF [6,8,12,13].

Management of combined HF and CKD is difficult. When CKD and volume overload persist despite maximal HF therapy, consideration is sometimes given to use of renal replacement therapy (RRT). Renal transplantation was associated with improved ventricular function in small numbers of select HF patients [14,15]. While the incidence of RRT has steadily increased worldwide [16–18] the incidence and impact of RRT on outcomes in the general HF population have not been studied. Use of RRT in HF is often deferred over concerns regarding ability of HF patients to tolerate RRT and uncertainty regarding the impact of RRT on outcomes [19]. The aim of this study is to describe the progression to chronic (≥3 months) RRT, the incidence of RRT over time and the association between use of RRT and survival in a large cohort of patients admitted for HF treatment at a single tertiary care centre over a 16-year time period. We hypothesized that use of RRT in HF is increasing and RRT is associated with improved long-term survival in patients with chronic HF.

Subjects and methods

Study design and setting

The study was approved by the Mayo Foundation Institutional Review Board. The institution maintains an integrated medical record system of all encounters whereby each patient is identified with a unique number and patient data can be retrieved electronically for research purposes [13,20]. All subjects gave authorization for use of their medical records for research.

Case identification: HF

Using administrative datasets, all consecutive HF patients admitted to Mayo Clinic hospital in Rochester, MN, between 1 January 1987 and 31 December 2002, were identified using diagnosis-related group (DRG) 127 as previously described [13,20]. We validated the frequency with which patients identified in this manner met the modified Framingham criteria [21] or ‘Clinical Criteria’ (HF diagnosis recorded on the chart by the attending physician) during the index hospitalization by manual chart abstraction of a random sample of 135 hospitalizations (2% of the study population). Data regarding these patients have been previously reported [13,20].

Data extraction

All data were extracted electronically as previously described [13,20]. Briefly, for each patient, date of birth, gender, admission and dismissal dates, weight and height were collected; co-morbid conditions including hypertension, coronary artery disease, diabetes and atrial fibrillation were assessed using all relevant ICD-9 codes. Admission creatinine (Cr), systolic blood pressure, and indicated primary cause of renal disease (based on ICD-9 codes). Of note, HF was not a category option for aetiology of renal disease in the USRDS database.

Definition of covariates

We estimated glomerular filtration rate (GFR) using the simplified Modification of Diet in Renal Disease (MDRD) equation [GFR = 186.3 × (Cr)−1.154 × age−0.203 × (0.742 if female)]. Because ≥97% of patients were Caucasian, no correction for race was used. As suggested by Coresh et al., estimated GFR values over 200 mL/min were set equal to 200 mL/min [23]. Change in Cr was calculated as the difference between the peak Cr within 14 days of admission and the admission Cr. WRF was defined by the presence of a ≥25% increase in Cr over admission value or an absolute increase of >0.3 mg/dL or a GFR decline of >25% [6–12]. Reduced ejection fraction, or systolic HF, was defined as EF <50%.

Mortality data

Survival status was determined through the Mayo Clinic registration database and ACCURINT™, a private fee-based information management and technology company that provides access to social security death data and a number of other data sources as previously described [13,20].

Statistical methods

Patient characteristics were summarized with the mean ± standard deviation (SD) for continuous variables, and with proportions for categorical variables. For variables that were not normally distributed, medians and interquartile ranges (IQRs) were reported. Survival and progression to RRT were determined with the Kaplan–Meier method, using the date of discharge as the origin point and date of death or start of RRT (first service date in the USRDS database) or date of last follow-up as censoring endpoints. The risk of initiation of RRT was presented as a percent per person-year of follow-up to allow comparison to other published data. Univariate and multivariate risk factors for these endpoints were evaluated using Cox proportional hazards models. Recognizing that death and RRT are follow-up events and competing risks, RRT was treated as a time-dependent covariate in both univariate and multivariate models for comparison of patient characteristics and/or survival. In addition, a propensity score predictive of the rate of progression to RRT was constructed using a Cox proportional hazard model. This propensity score was used to adjust for potential risk factors for RRT in the final models evaluating RRT as a time-dependent covariate in the survival models. Only factors that were significantly related to initiation of RRT were included in the final model for this propensity score. In the survival analysis, we adjusted for characteristics at HF admission that were predictive of the rate of progression to RRT using the propensity score as well as other pertinent covariates. We adjusted for the impact of covariates on outcomes using a backward elimination approach and only covariates predictive of outcomes were used in the final models. All analyses were two sided, and a P-value of <0.05 was considered statistically significant.

Results

There were 6440 patients with first or only admissions for HF with 164 already receiving chronic RRT, leaving 6276 patients in the study.

Incidence of RRT in HF patients

Of the 6276 patients, 304 (4.8%) ultimately progressed to RRT. Of these 304 patients, 293 (96.4%) underwent chronic dialysis, and 24 (7.9%) received a renal transplant. Of the 293 dialysis patients, 278 patients underwent haemodialysis, 12 patients underwent peritoneal dialysis and 3 patients had unknown dialysis modality. Of the 293 dialysis patients,
280 received dialysis only and 13 received both dialysis and a renal transplant. Eighteen patients (0.29%) of the 6276 patients received a renal transplant without ever requiring dialysis. Median time to RRT was 475 days (interquartile range 125–1253 days). The overall incidence of RRT was 304 cases in 19 292 patient-years of follow-up or 1.6% per year where % indicates the percentage per person-year.

The number of HF admissions increased over time, particularly comparing the first 5 years versus the latter 11 years. The first 5-year era (1987–1991) had 1748 admissions, the second 5-year era (1992–1996) had 2108 admissions and the third 6-year era (1997–2002) had 2420 admissions. The number of nephrologists available and the number of dialysis patients in the institution did not change significantly over time.

The admission Cr was lower in the first 5-year era compared to the latter 11 years. The average median admission Cr was 1.16 mg/dL for the era 1987–1991, 1.30 mg/dL for the era 1992–1996 and 1.32 mg/dL for the era 1997–2002. Likewise, the admission GFR by MDRD equation for the era 1992–1996 and 1.32 mg/dL for the era 1997–2002. The peak Cr during hospitalization also differed among eras, with lower peak Cr in the first 5-year era compared to the latter 11 years. The average median peak Cr was 1.30 mg/dL for the era 1987–1991, 1.53 mg/dL for the era 1992–1996 and 1.52 mg/dL for the era 1997–2002. The peak Cr during hospitalization was 0.08 mg/dL for the era 1987–1991, 0.16 mg/dL for the era 1992–1996 and 0.18 mg/dL for the era 1997–2002.

The rate of progression to RRT in the second (1995–2002) half of the study was greater than in the first (1987–1994) half of the study (2.1 versus 1.2% per year; HR = 1.55, P = 0.0003), and the increased use of RRT in the second time period persisted after adjustment for the prevalence of diabetes, hypertension and coronary disease (HR = 1.43, P = 0.003).

Echocardiography within 30 days of admission was available in 4773 patients. Of these patients, a total of 241 patients (5.0%) ultimately received RRT. Among those with reduced EF, 136 patients received RRT over 7261 patient-years of follow-up (1.9% per year). Among those with preserved EF, 105 patients received RRT over 8062 days of follow-up (1.3% per year). There was no significant difference in the incidence of RRT in the two subgroups of HF (P = 0.25).

The aetiology of renal disease in RRT patients was diabetes (46%), hypertension/large vessel disease (27%), miscellaneous conditions (vasculitis, neoplasm, missing data, cystic, congenital and hereditary disorders) (13%) and aetiology uncertain (8%).

The mean (±SD) Cr within 45 days of initiating RRT was 4.96 ± 2.46 mg/dL. The median Cr was 4.60 mg/dL (interquartile range 3.30–6.10 mg/dL).

**Patient characteristics at HF admission**

The demographics, clinical and laboratory characteristics of patients at the time of HF admission who ultimately did not receive RRT are summarized in Table 1. Patients who progressed to RRT in this HF population were younger, had higher admission creatinine, lower GFR, lower haemoglobin, greater increase in creatinine during hospitalization, greater incidence of WRF, higher prevalence of hypertension, coronary artery disease and diabetes mellitus, but lower prevalence of atrial fibrillation. Among those patients with EF measurement, EF was similar in patients who did or did not receive RRT. In multivariate analysis, factors present at HF admission which were predictive of the rate of progression to RRT included age, haemoglobin, greater increase in creatinine during hospitalization, development of WRF, higher prevalence of hypertension, coronary artery disease and diabetes mellitus, but lower prevalence of atrial fibrillation. Among those patients who had echocardiography, EF was similar in patients who did or did not receive RRT. Table 2. Propensity score for predicting rate of progression to RRT

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI for RR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.965</td>
<td>0.957–0.973</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>0.789</td>
<td>0.742–0.840</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.461</td>
<td>1.296–1.650</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1/Admission Cr</td>
<td>0.001</td>
<td>0.001–0.003</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cr−1/Peak Cr</td>
<td>47.269</td>
<td>12.650–167.479</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Association between RRT and survival in HF patients**

The median follow-up among survivors was 4.8 years. By time-dependent covariate analysis, unadjusted survival was poorer in those receiving RRT (HR 1.62, 95% CI 1.41–1.86, P < 0.0001) (Figure 1). Adjusting for baseline differences using the propensity score and other pertinent covariates,
survival was similar between the two groups (HR 1.11, 95% 
CI 0.94–1.29, P > 0.05). Overall survival in HF patients 
improved over time after adjusting for changes in base-
line characteristics and in patients with reduced LV systolic 
function.

**Discussion**

In this large cohort of patients hospitalized for HF, we found 
that the incidence of RRT was 1.6% per year, and that the 
rate of progression to RRT was similar among those with 
HF and preserved or reduced EF. Patients admitted during 
the first 5-year era (1987–1991) had less severe renal dys-
function on admission as well as a smaller rise in Cr during 
hospitalization. Over the course of the study, the incidence 
of progression to RRT increased even after adjustment for 
differences in the prevalence of diabetes, hypertension and 
coronary disease over time, suggesting increased willing-
ness to offer RRT in HF patients in more recent years. 
Among patients with HF, those who progress to RRT have 
multiple adverse prognostic factors at the time of HF admit-
sion, and adjusting for these factors, patients progressing to 
RRT have similar survival to those who do not receive RRT. 
While these data are retrospective and likely confounded by 
selection bias, they do provide preliminary support for the 
concept that appropriately timed RRT may improve out-
comes in HF. Additionally, given the high prevalence of 
CKD in patients with HF and the increasing use of RRT in 
HF, these data also underscore the need for further stud-
ies to inform HF cardiologists and nephrologists as to the 
appropriate role for RRT in HF.

**Renal dysfunction and HF**

As expected, patients ultimately receiving RRT had worse 
renal function at HF admission and a higher preva-
ience of risk factors for CKD (hypertension, diabetes and 
atherosclerosis) than those not progressing to RRT. While 
the CKD was likely due in part to these risk factors, chronic 
HF leads to chronic renal congestion and hypoperfusion 
with hypoxia, oxidative stress and irreversible renal damage 
[2,24]. This study cannot elucidate the degree of CKD re-
lated to underlying disease and that related to HF itself. Con-
versely, chronic CKD exacerbates HF via multiple effects 
including pressure and volume overload, neurohumoral ac-
tivation and other metabolic effects [2,24].

In HF patients with CKD and volume overload despite 
aggressive use of diuretics and other standard HF medica-
tions, management options are limited. After optimization 
of non-inotropic HF medications, frequently used strategies 
include intravenous systemic or renal-specific vasodilators 
[25], inotropes (if EF is reduced) or advanced HF device 
therapy [26]. However, in general, inotropes are associated 
with poor outcomes [27], and many HF patients are not 
candidates for therapies that may more dramatically im-
prove cardiac performance such as transplantation, cardiac 
resynchronization therapy (CRT) or left ventricular assist 
devices. While CRT may improve renal function in some 
patients, CKD is associated with poorer response rates to 
CRT [28]. Thus, in the face of progressive CKD and volume 
overload, consideration is sometimes given to temporary or 
permanent RRT.

We found that admission Cr was higher and GFR was 
lower in the latter decade (1992–2002) compared to the first 
5-year era (1987–1991), which suggests that there may have 
been more aggressive diuretic use and use of agents that 
block the renin–angiotensin–aldosterone system (RAAS), 
including angiotensin-converting enzyme (ACE) inhibitors 
and angiotensin receptor blockers (ARB) during the more 
recent decade. Furthermore, the peak Cr and rise in Cr 
during hospitalization was greater in the latter decade ver-
sus the first 5-year era. This observation also may reflect 
more aggressive medical therapy for fluid overload in the 
setting of decreased effective arterial blood volume. Such 
aggressive medical therapy in the setting of diuretic resis-
tance may have impacted on renal function and ultimately 
the propensity to dialyze for fluid overload and worsening 
renal function. This would explain the higher rate of pro-
gression to RRT in the second (1995–2002) half of the study 
versus the first (1987–1994) half of the study, even after 
adjustment for the prevalence of diabetes, hypertension and 
coronary artery disease.

**RRT in HF**

Approximately 0.03% of the United States (US) population 
commenced RRT in 2004 [22]. The number of patients re-
ceiving RRT has been increasing steadily since 1978, with 
annual growth rates estimated between 6 and 8% [16–18]. 
Over this time, there has also been an increase in diabetes, 
myocardial infarction, stroke survivors and the general popu-
lation size and age. The current data suggest that the use 
of RRT in HF has been increasing in parallel to the global 
increase in RRT and out of proportion to increases in the 
prevalence of CKD risk factors. However, these utiliza-
ization rates may be inappropriately low. As noted by Kumar 
et al. [19], there has been a general reluctance among car-
diologists and nephrologists alike to initiate RRT for man-
age ment of HF due to concerns over availability of dialysis

![Kaplan–Meier survival curves treating renal replacement therapy (RRT) as a time-dependent outcome. Patients who eventually received RRT had significantly worse survival after hospitalization compared to those who did not.](image-url)
facilities, tolerability of dialysis and lack of data regarding impact of RRT on outcomes in HF. From a societal view, increased use of RRT in HF would add substantially to the already high cost of HF [29] and yet, could be cost effective if quality of life was improved and hospitalizations were reduced.

In the general ESRD population studied during the same time period as this study, renal function at initiation of RRT is markedly low, with a mean serum creatinine of 8.5 ± 3.8 mg/dL and mean GFR of 7.1 ± 3.1 mL/min/1.73 m² [22]. The mean (± SD) serum creatinine within 45 days of initiating dialysis in our HF cohort was nearly half that observed in typical ESRD populations. These data suggest that RRT was being used in part to address volume overload rather than uraemic symptoms in these HF patients, although creatinine levels may be deceivingly low in some chronic HF patients due to cardiac cachexia.

Impact of RRT on survival in HF

Renal transplantation is associated with improved ventricular function and outcomes in select HF patients [14,15]. Temporary ultrafiltration (UF), haemofiltration, haemodialysis or peritoneal dialysis may be effective for volume removal in diuretic-refractory HF patients, with improvement in signs and symptoms of congestion [30–33]. However, no study has examined the effect of chronic RRT on outcomes in HF. In our dataset, there were not enough peritoneal dialysis patients (N = 12) nor transplant patients (N = 24) to draw conclusions regarding the impact of type of RRT on survival.

In our study, longer-term mortality rates did not differ between RRT and non-RRT patients when adjusting for adverse prognostic factors in the RRT group. Longer-term survival may be similar due to the effects of chronic underlying comorbidities and chronic progression of both cardiac and renal dysfunction. However, given all the potential confounders, drawing conclusions on outcomes such as mortality would require a different cohort and study design than our study provides.

As most HF patients are elderly, it is of note that Murtagh et al. found improved survival in elderly (age > 75 years) patients with ESRD treated with dialysis versus conservative care. However, in this small study, the survival advantage with RRT was lost in those with high comorbidity scores, particularly those with ischaemic heart disease [34]. In contrast, a recent randomized study reported improved short-term, event-free survival with transient ultrafiltration versus diuretics as first-line therapy in HF patients with moderate CKD [33]. While not powered to definitively address the impact of UF on outcomes in HF, this study was provocative and provides some conceptual support for a prospective randomized trial design which would compare earlier RRT versus standard HF care (e.g. high dose diuretics and standard HF medications to achieve similar volume removal as the RRT group) in HF patients with significant CKD and persistent volume overload despite aggressive HF therapy. Following these patients prospectively for survival endpoints would help to answer the interesting questions raised by this and other studies regarding impact of RRT on mortality.

Limitations

This study is subject to the limitations inherent in retrospective studies based on data collected during routine clinical care. Use of electronic data collection and the USRDS database limits the extent of patient characterization. While use of DRG 127 to identify patients introduces potential for bias based on changes in coding practices, the accuracy of the HF diagnosis was validated by manual chart review of a random representative sample (135 patients) of the population [13,20]. We may also have underestimated the incidence of RRT as the USRDS may not capture patients initiating and terminating RRT within 3 months. The design also limits our ability to adjust for all potential confounders of interest, such as patient preference regarding RRT, parathyroid hormone levels, nutritional parameters, reasons for RRT initiation and quality of life indices. Furthermore, we did not have comprehensive data on medication use, including ACE inhibitor, ARB, beta-blocker and aldosterone receptor blocker use. Data on biventricular pacemaker and implantable cardiac defibrillator use were also not available. Patients selected for RRT may have had more aggressive care with these agents than non-RRT patients, which would bias the results towards improved survival in RRT patients. However, we did adjust for several important factors, including age, sex, renal function and comorbidities. We were unable to ascertain the cause of death. Furthermore, this study was performed at a tertiary referral centre serving a predominately Caucasian population and may not generalize to other populations. In addition, our study cohort only included hospitalized HF patients, and criteria for hospitalization may have differed over time, so the findings may not be applicable to the current refractory HF population in the community.

Conclusions

Currently, the appropriate role for RRT in the HF population remains poorly defined in terms of patient selection, timing, type of RRT and impact on HF progression and outcomes. The current study indicates that use of RRT in HF is increasing over time and is not associated with EF. Furthermore, despite worse prognostic factors and comorbidities, those receiving RRT have similar survival compared to those who do not. These findings suggest that RRT may be useful clinically in the end-stage HF population. Future prospective studies should focus on identifying the appropriate clinical setting and timing for RRT in HF with a view to establishing outcome benefit.

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Conflict of interest statement. KVL and MMR were responsible for protocol development, data abstraction, data analysis, reviewing the literature and writing the paper. ELG, AWW and CAH were responsible for editing and revising the protocol and paper. DOH was responsible for statistical analysis. TEO was responsible for assisting in data analysis and revising the paper. All authors have read and approve the manuscript. The
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