Published in final edited form as:

Am J Kidney Dis. 2011 July ; 58(1): 84–92. doi:10.1053/j.ajkd.2011.01.029.

Heart Failure Severity Scoring System and Medical- and Health-Related Quality-of-Life Outcomes: The HEMO Study

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Abstract

Background—Cardiac disease is the leading cause of death in US prevalent hemodialysis (HD) patients. There is a lack of data about the impact of the severity of heart failure (HF) on outcomes and health-related quality of life (HRQoL) in HD patients. We aimed to determine the prognostic importance of the Index of Disease Severity (IDS) of the Index of Coexistent Disease (ICED) scoring system as an HF severity measure.

Study Design—Subanalysis of the Hemodialysis (HEMO) Study, a randomized controlled trial. Relationships between HF severity and mortality and cardiac hospitalizations were determined using Cox proportional hazards models. The relationship between HF severity and HRQoL scores was modeled using linear regression and generalized estimating equations.

Setting & Participants—1,846 long-term HD patients at 15 clinical centers including 72 dialysis units.

Predictor or Factor—HF severity classified using the IDS of the ICED scoring system.

Outcomes—Mortality (all cause and cause specific), cardiac hospitalizations, and HRQoL.

Measurements—All-cause, cardiac, and infectious deaths; cardiac hospitalizations; and HRQoL scores from the Kidney Disease Quality of Life–Long Form.

Results—HF was present in 40% of HD patients. Increasing severity of HF was associated with older age, greater likelihood of diabetes, and lower serum albumin level (all $P < 0.001$). Adjusted HRs for all-cause mortality were 1.31 (95% CI, 1.12–1.53), 1.48 (95% CI, 1.19–1.85), and 2.11 (95% CI, 1.43–3.11) for mild, moderate, and severe HF, respectively ($P < 0.001$). All-cause, cardiac, and infectious mortality and cardiac hospitalizations increased with increasing severity of

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Financial Disclosure: Dr Unruh has served as consultant for Sigma-Tau and Merck and scientific advisor for Baxter. The remaining authors declare that they have no relevant financial interests.

HF. Increasing HF severity was associated with decreases in HRQoL, particularly in physical functioning and sleep quality.

Limitations—This study is limited by the small sample size in the most severe HF group.

Conclusions—Increasing severity of HF is associated with increased mortality and cardiac hospitalizations and worse HRQoL, especially in perceived physical limitations. These findings emphasize the utility of the IDS of the ICED score as a valid prognostic tool for medical and HRQoL outcomes in the HD population with HF.

INDEX WORDS

Heart failure; outcomes; hemodialysis; mortality; hospitalizations; health-related quality of life

Heart failure (HF) is one of the most prevalent diseases in the United States, particularly in the elderly, affecting ~5 million Americans (2.3% of the population). As many as 36% of patients initiating dialysis therapy each year may have HF as one of their diagnoses. An additional 7% develop it while on long-term dialysis therapy.¹ Increases in the incidence of major cardiac and renal risk factors, such as obesity, hypertension, and diabetes mellitus, in the American population during the last decade may contribute to changes in the prevalence of combined cardiac and renal disease.

Cardiac disease is the leading cause of death in US prevalent hemodialysis (HD) patients, accounting for ~45% of deaths.^{2,3} Dialysis patients have 10–20 times greater risk of cardiovascular death than the general population.⁴ This increased cardiac mortality likely is due to the high prevalence of cardiac risk factors or frank cardiac disease in patients with chronic kidney disease.^{5–7} In addition, patients with cardiac disease who are on dialysis therapy have worse long-term survival after acute myocardial infarction than those who are not on dialysis therapy.⁸ Therefore, identification of the types and severity of cardiac diseases and strategies for the prevention and treatment of these diseases in patients with chronic kidney disease is of utmost importance. These issues were addressed in part by a subanalysis of the Hemodialysis (HEMO) Study focused on the contributions of underlying cardiac diseases to subsequent cardiac events.⁹ The prevalence of cardiac disease at baseline was 80%, and HF was the single most prevalent type of heart disease. The presence of any cardiac disease at baseline predicted cardiac death during follow-up, and there were no significant effects of dose or flux interventions on all-cause mortality or first cardiac hospitalization.⁹ However, we are not aware of any study analyzing how the severity of HF influences outcomes and quality of life in HD patients.

The patient population in the HEMO Study provides a unique well-characterized HD population for which the diagnosis of HF and its severity has been rigorously categorized using the Index of Disease Severity (IDS) of the Index of Coexistent Disease (ICED) score. ICED score has been shown to be a powerful prognostic factor in patients with end-stage renal disease (ESRD) in several studies.^{10–17} We aimed to determine the prognostic importance of the IDS as a measurement of HF severity. Therefore, we conducted a subanalysis of the HEMO Study examining associations between baseline HF severity with

all-cause and cause-specific mortality, cardiac hospitalizations, and health-related quality of life (HRQoL) in prevalent HD patients.

METHODS

Participants

The HEMO Study was a randomized clinical trial of 1,846 long-term HD patients at 15 clinical centers. It was designed to study the effects of HD dose and membrane flux on mortality and morbidity in patients undergoing long-term dialysis therapy.¹⁸ Patients were randomly assigned to either standard or high-dose (equilibrated Kt/V, 1.05 vs 1.45, respectively) and either high- or low-flux membranes (β_2 -microglobulin clearance, <10 or >20 mL/min, respectively). Patient eligibility criteria have been described previously.¹⁸ Patients with New York Heart Association class IV symptoms despite medical therapy were excluded. The patient population was followed up longitudinally with scheduled maximum follow-up of 0.9–6.6 years and mean actual follow-up of 2.84 ± 1.84 years.⁹ The present secondary analyses were approved by the University of Pittsburgh Institutional Review Board.

At randomization and annually during follow-up, HEMO Study patients responded to HRQoL surveys as previously described.^{10–12,19–22} The Kidney Disease Quality of Life–Long Form (KDQoL-LF) assesses generic HRQoL using the 36-Item Short-Form Health Survey (SF-36) questionnaire and kidney disease–targeted HRQoL domains including Sleep Quality scores for patients in the HEMO Study.^{21–26} The SF-36 yields 8 multi-item scales that measure Physical Functioning, Bodily Pain, Mental Health, General Health, Vitality, Role–Emotional, Role–Physical, and Social Functioning. The range of scores for the SF-36 sub-scales is 0–100, with higher scores reflecting better health and well-being. The SF-36 also produces 2 summary measures of physical and mental health^{27,28}: the Physical (PCS) and Mental Component Summary (MCS) scores. KDQoL-LF assessment of sleep quality provides an overall score, with a higher value reflecting better sleep quality.¹²

Comorbidity Assessment

Comorbidity was assessed at baseline using the ICED. ICED score was determined by condensing the 2 index grades from the IDS and the Index of Physical Impairment, or Functional Severity, and categorized into 4 levels, with higher numbers indicating more severe disease and/or functional impairment.¹⁷ Comorbid conditions were divided into 19 disease categories, of which the category congestive HF score was used to assess the severity of HF in the present study. The score was treated as an ordinal variable reflecting HF severity (0 =none, 1 =mild, 2 =moderate, and 3 = severe HF). HF severity scores were assigned as follows: (1) diagnosis of any HF or history of pulmonary edema pre- or post-ESRD, (2) HF requiring medications or hospitalizations in past year (post-ESRD), and (3) multiple episodes of hypotension during HD related to cardiomyopathy or hospitalized more than twice in the past year for HF (post-ESRD).

The ICED score used in this report was recomputed excluding the HF and circulatory disorder components for use as a separate variable when adjusting the survival models.

Classification of Cause-Specific Mortality in HEMO

The determination of cause-specific mortality in the HEMO Study has been described previously.¹¹ Cause-specific infectious, cardiac, and cardiovascular deaths were selected for this report because these are the most common causes of death in HD patients. The 4 cardiac causes of death were: (1) ischemic heart disease, (2) congestive HF, (3) arrhythmias and conduction problems, and (4) other heart diseases. The category of other heart diseases included patients with left ventricular hypertrophy (LVH) on an echocardiogram, LVH on an electrocardiogram, cardiomegaly on a chest radiograph, valvular disease, or pericarditis. The categorization of cardiovascular deaths included cardiac, cerebrovascular, and vascular causes of death.

Selection of Covariates for All-Cause and Cause-Specific Mortality

To account for residual confounding on mortality, we adjusted our survival analyses for baseline patient characteristics associated with the mortality of patients with ESRD in previous studies.^{11,18,29,30}

1. Demographic and clinical: age, sex, race, body mass index, weight, blood pressure, and smoking status.
2. Dialysis-related factors: duration of dialysis therapy, residual renal function (absent or present based on residual urine output <200 mL/d), and dialysis access (dialysis catheter vs all other [arteriovenous fistula, arteriovenous graft, or other]).
3. Laboratory tests: calcium (milligrams per deciliter), phosphorus (milligrams per deciliter), serum total cholesterol (milligrams per deciliter), and serum albumin (grams per deciliter). Albumin in HEMO was measured using immunonephelometry, a technique that yields smaller values than the relatively nonspecific bromocresol green and bromocresol purple assays used by clinical laboratories.³¹
4. Comorbid conditions: ICED score (scored with and without HF) and diabetes mellitus.
5. Treatment arms: because these data were collected in the setting of a randomized trial, we included treatment arms as covariates.

Statistical Analysis

Baseline variables were summarized using mean $\pm$ standard deviation for continuous variables and percentages for categorical variables. Differences in summary statistics were tested using: (1) generalized linear models for continuous variables, (2) χ^2 tests for nominal variables, and (3) Jonckheere-Terpstra for ordinal tests of trend. Kruskal-Wallis tests were used if data had a non-normal distribution.

To understand the relationship between HF and mortality, cause-specific hazards analyses were used and single-covariate Cox models, with subsequent tests of proportionality, were fit to the data. To calculate adjusted cause-specific hazard rates for mortality, model selection methods were used as follows. To determine a single set of covariates for

modeling, single-variable Cox proportional hazards models were fit to all covariates. Any covariate significant at $P < 0.2$ in any mortality model was kept for inclusion in subsequent multivariate mortality models. It was decided a priori that age, sex, race, dialysis flux and dose group, and diabetic status were to be forced into the models as known confounders of HF with mortality.

Any variables violating the proportionality assumption were entered into the multiple variable models as interactions with time and declared significant at $P < 0.05$. Other interactions with HF of interest, such as age, sex, race, dialysis dose and flux group, and dialysis duration >3.7 years, were investigated for all-cause mortality only, also with a strict $P < 0.05$. Hazard rates then were tabulated with upper and lower 95% confidence intervals. Variables included in adjusted analyses were age, sex, race, dose and flux group, diabetes, HF score (ie, ICED score for HF), duration of HD therapy, access, ICED score with HF excluded, diastolic blood pressure, body mass index, smoking status, and serum albumin level. We also performed ordered tests for trend for all-cause, cardiac, and infectious mortality without covariates using 2-sided tests to determine if there was a graded decrease in survival with increasing HF severity. Baseline HRQoL variables were modeled using generalized linear models and estimates were tabulated with their upper and lower 95% confidence intervals. For longitudinal data, generalized estimating equation models were fit with time and HF score as predictors. Longitudinal analyses for the 8 domains of the SF-36, PCS, MCS, and Sleep Quality scores were performed using a regression model to reflect a linear ordinal trend. There was no interaction with time or a quadratic trend; therefore, these effects were dropped from the model.

We also investigated nonproportional cause-specific hazards (nonproportional hazards) by using a spline-based approach (Gray's model) and found that only serum albumin level violated the proportional hazards assumption using $P < 0.05$ among the covariates examined in this report. Final cause-specific hazard ratios were reported, adjusting for covariates plus the serum albumin–time interaction.

RESULTS

Baseline Characteristics

Baseline characteristics of patients with HF are listed in Table 1. Compared with the entire cohort and those without HF, patients with increasingly severe HF were significantly older and more likely to have diabetes. They had lower dialysis vintage, postdialysis weight, and total-body water. There were no differences in proportions of patients with mild, moderate, and severe HF based on Kt/V or flux assignment or with access type (permanent catheter or arteriovenous fistula/arteriovenous graft/other). Postdialysis systolic blood pressure was similar for all groups of patients with HF, but diastolic blood pressure was lower as HF severity increased. There were no differences in smoking status among the HF severity groups. There were no differences in serum creatinine, calcium, or phosphorus levels among the HF severity groups. Serum albumin level was significantly lower in those with more severe HF.

Mortality, Cause-Specific Mortality, and Cardiac Outcomes

Figure 1 shows Kaplan-Meier survival curves for each strata of HF severity and shows worse survival with increasing severity of HF. These survival curves were similar for all-cause, cardiac, and infectious mortality (Fig 1A, B, and C). In addition, survival free of first cardiac hospitalization or cardiac death was worse with increasing severity of HF (Fig 1D).

Severity of HF was associated with increased all-cause mortality, cause-specific mortality, and the composite outcomes of cardiac hospitalization or all-cause mortality and cardiac hospitalization or cardiac death (Table 2). Severity of HF was associated strongly with higher risk of death from any cause. This pattern also was shown for cardiac death and the subgroup of ischemic heart disease death. Of note, infectious deaths also increased significantly with increasing HF severity. Hazard ratios for first cardiac hospitalization or all-cause mortality, as well as first cardiac hospitalization or cardiac death, also increased substantially with increasing severity of HF.

Adjusted for multiple predictors, increased severity of HF was associated with increased all-cause, cardiac, and infectious deaths, although the hazard ratio for each was attenuated compared with unadjusted analyses (Table 3). Adjusted hazard ratios for all-cause and infectious mortality increased sequentially for mild, moderate, and severe HF, with an ~1.5-fold increase in risk in moderate HF and ~2-fold increase in risk in the most severe HF subgroup. Cardiac mortality risk increased ~2-fold in both the moderate and severe HF subgroups. We tested for interactions of flux, dose, age, sex, race, and dialysis vintage with HF for all-cause mortality, and the test for the overall contribution to the model was not significant ($P = 0.3$). We performed ordered tests of trend without covariates for all-cause, cardiac, and infectious mortality and found a significant increase in mortality with increasing severity of HF (P for all 2-sided trend tests < 0.001). Therefore, survival curves not only are different, but decrease sequentially with increasing HF severity.

Severity of HF and HRQoL Outcomes

Baseline HF severity was associated strongly with HRQoL scores in physical health domains (Table 4). There were significant decreases in Physical Functioning, Role–Physical, General Health, Vitality, and Social Functioning scores with higher levels of HF severity. There were weaker associations in the Mental Health domain ($P = 0.02$). No significant decrease was seen in perceived Bodily Pain ($P = 0.08$) or Role–Emotional scores ($P = 0.2$). Similarly, PCS scores decreased significantly with increasing HF severity ($P < 0.001$), but MCS scores did not decrease significantly ($P = 0.1$). Sleep Quality scores also decreased with increasing severity of HF, but only with severe HF ($P = 0.01$).

HRQoL scores, with the exception of Role–Emotional and MCS, showed a significant decrease over time (Table 5). Adjusting for the time effect, increasing HF severity was associated with decreases in scores for all HRQoL scores except Physical Functioning and Role–Emotional (Table 5). For example, after adjusting for the time effect, General Health would decrease by -2.27 units with each increase in HF severity level ($P < 0.001$ for both time and HF severity effect). Also, Sleep Quality score would decrease by -1.52 units with

increasing HF severity level ($P = 0.001$) after accounting for the time effect. There were no interactions between HF severity and time in HRQoL scores.

DISCUSSION

In long-term HD patients with HF, increasing severity of HF assessed using the IDS score was associated with increased all-cause and cause-specific (both cardiac and infectious) mortality, increased first cardiac hospitalization or all-cause mortality, and increased first cardiac hospitalization or cardiac death. Increasing HF severity is associated with increased risks of death from cardiac causes, including ischemic heart disease, HF, and arrhythmias, as well as infectious causes. As expected, the risk of death from HF was associated with disease severity, and these findings highlight the substantial increase in mortality with increasingly severe HF after accounting for potential explanatory variables. Increasing severity of HF also was associated with lower quality of life, particularly in perceived physical limitations and sleep quality. Although the association of HF severity with worse outcomes may not be surprising, this study represents the first study analyzing how severity of HF affects outcomes in HD patients.

Use of the IDS score of the ICED scoring system for HF severity in this study is unique, and our findings suggest that this ascertainment method for HF has considerable prognostic implications, including impact on measures of HRQoL and survival and cardiac hospitalization rates, although there is little objective evidence in the definition for HF (no measurements of brain natriuretic peptide, echocardiogram, etc). Compared with other scores, including the full ICED score and other comorbidity instruments that may be available for use in dialysis patients, definitions used in the HF IDS are relatively simple and reproducible and can be ascertained by trained nurses, allied health professionals, or other nonphysician personnel. Hence, it may be a useful tool for risk prediction in the ESRD population with HF independent of other prognostic parameters, such as brain natriuretic peptide level, cardiac troponin level, and ejection fraction.

Another important finding is the increased risk of first cardiac hospitalization with increasing severity of HF. First cardiac hospitalization alone was not analyzed separately because cardiac death and mortality are competing risks. Longer time spent in the hospital with increasingly severe HF is likely to affect quality of life and health care costs for these individuals. It is well established that LVH is associated with hypertension and increased mortality in patients with chronic kidney disease,^{7-9,33} although paradoxically, hypertension has an inverse association with mortality in patients with ESRD.³³ The prevalence of coronary artery disease is 40% and LVH is 75% in patients with ESRD, both of which may lead to the development of HF or exacerbate pre-existing HF.^{4,34} Our findings suggest that in addition to these established risk factors, the IDS of the ICED score is another potentially useful predictor for increased morbidity and mortality in the ESRD population with HF. Further studies are needed to determine the most effective treatment approaches to these clinically challenging patients.

Our study also found that severity of HF was associated with decreases in HRQoL. This finding was expected because more severe HF is associated with greater volume overload,

which directly affects physical functioning and symptoms (eg, dyspnea with exertion, lower-extremity edema, and orthopnea) and is associated with sleep apnea. These findings corroborate the hypothesis that increasing severity of HF leads to worse physical function and are reflected directly in the Physical Function domain and PCS of the SF-36. Our study shows that HF severity is an independent cause of lower HRQoL, but not of the decrease in HRQoL over time (Tables 4 and 5).

In patients with HF, disease symptoms and functional capacity have a greater adverse effect on quality of life than clinical indicators of disease severity, such as ejection fraction or abnormal wall motion.^{35–39} In a cross-sectional study from the HART (Heart Failure Adherence and Retention Trial) assessing the role of psychosocial status on HRQoL in HF, de Leon et al⁴⁰ found that depression and social support have a greater role in satisfaction with quality of life than for perceived limitations in basic physical functions. Functional HF class and number of comorbid conditions were associated with physical functions, but not with satisfaction with quality of life. These findings are in keeping with our findings that severity of HF in the HEMO Study population was associated with Physical Functioning scores, but not mental component scores, of the SF-36 questionnaire. HRQoL instruments used in the HEMO Study do not directly address satisfaction with quality of life, as assessed in the study by de Leon et al.⁴⁰ However, satisfaction with HRQoL would be expected to correlate with mental rather than physical components of the SF-36 used in our study. Further studies are needed to analyze the impact of severity of HF on mental components of HRQoL, such as depression.

This study is limited by the small number of patients with severe HF compared with those with mild or moderate HF, which made it impossible to analyze cause-specific mortality for deaths due to HF, arrhythmia, and other heart diseases in this subgroup. In addition, many patients with severe HF died (approximately half) within the first year of follow-up. The severe HF subgroup had only 35 patients, making estimates of relationships with HRQoL or mortality for this subgroup imprecise. Hence, we conducted analyses combining HF severity levels 2 and 3 and found similar results. In presenting our findings, we chose to keep the most severe HF group separate despite the small number of patients to show the trends of graded severity (not just that having HF is worse than not having it) because clinicians would be interested in how much prognosis worsens for those with moderate versus severe HF. This finding is novel and has not been shown in other studies linking HF with poor outcomes. Another limitation is the lack of information in the HEMO Study and ICED definitions about what type of HF patients had (eg, systolic vs diastolic HF).

By analyzing the effect of severity of HF on outcomes, this study is timely and significant because it has implications for the case-mix adjustment being incorporated in the recent Medicare Improvements for Patients and Providers Act of 2008 (MIPPA), which outlines legislation regarding bundled payment to providers of patients with ESRD.^{41–47} Case-mix adjustment factors in the proposed prospective payment system for patients with ESRD on HD therapy have already been determined and currently include cardiac arrest and pericarditis as proposed cardiac comorbid conditions requiring adjustment, but do not include HF.⁴⁵ Based on our study findings, inclusion of HF and its severity should be

reconsidered for inclusion in case-mix adjustments because of the considerable independent effects of HF severity on clinical and HRQoL outcomes.

Results of the present study show the significant association of HF severity, assessed using IDS score, on mortality, hospitalization rates, and HRQoL. These findings have important implications for clinical care of patients because the IDS of the ICED score may be a useful tool for counseling patients as an independent prognostic factor for mortality and HRQoL. Furthermore, these findings have important implications for case-mix adjustments because this work shows that severity of HF is associated with worse clinical outcomes and should be included in case-mix adjustments in the proposed prospective payment system for patients with ESRD on HD therapy. These findings also may provide clinicians with prognostic information that can be used to counsel HD patients with HF because these patients may choose instead to pursue other end-of-life options (eg, hospice or palliative care). Further studies are needed to determine the reasons for increased infectious deaths in patients with more severe HF, as well as examine whether targeting modifiable risk factors in early stages of HF may delay HF progression and improve quality of life and sleep in the cardiorenal failure population.

Acknowledgments

The authors wish to thank the HEMO Study investigators and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) data repository for the data used in this study. The HEMO Study was performed by the HEMO Study investigators and supported by the NIDDK. This manuscript was not prepared in collaboration with the investigators of the HEMO Study and does not necessarily reflect the opinions or views of the HEMO Study or the NIDDK.

Support: Dr Unruh has received grant/research support from Dialysis Clinics Inc, Baxter Extramural Grant Program, and Satellite Dialysis.

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Figure 1.

All-cause and cause-specific mortality and cardiac hospitalizations over time for patients with different levels of congestive heart failure (HF) severity. (A) All-cause mortality, (B) cardiac mortality, (C) infectious mortality, and (D) first cardiac hospitalization or cardiac death increase with increasing severity of HF.

Table 1

Baseline Characteristics of the Study Cohort

Factors	Congestive HF					P
	Cohort (N = 1,786)	Absent (n = 1,113)	Mild (n = 515)	Moderate (n = 183)	Severe (n = 35)	
Age (y)	57.78 ± 14.04	55.32 ± 14.48	61.15 ± 12.18	62.53 ± 13.03	61.67 ± 13.44	<0.001
Women (%)	56.23	55.53	57.09	56.83	62.86	0.8
Black race (%)	62.62	64.42	63.11	50.27	62.86	0.01
Diabetic (%)	44.58	37.20	55.34	59.02	45.71	<0.001
BMI (kg/m ²)	25.46 ± 5.28	25.51 ± 5.15	25.65 ± 5.47	24.97 ± 5.45	23.71 ± 5.21	0.07
Time on dialysis (y)	3.90 ± 4.35	4.19 ± 4.71	3.63 ± 3.95	3.13 ± 3.14	2.97 ± 2.57	0.01
Postdialysis weight (kg)	69.15 ± 14.70	69.52 ± 14.53	69.34 ± 15.06	67.45 ± 14.66	63.31 ± 13.72	0.04
Postdialysis TBW (L)	37.30 ± 9.37	37.54 ± 9.45	37.32 ± 9.30	36.69 ± 9.00	32.95 ± 9.05	0.03
High Kt/V (%)	49.84	49.87	50.29	50.82	37.14	0.9
High flux (%)	49.89	49.06	50.87	49.73	62.86	0.3
Access (%)						0.09
Permanent catheter	5.80	5.12	6.41	6.56	14.29	
AVF/AVG/other	94.20	94.88	93.59	93.44	85.71	
Blood pressure (mm Hg)						
Systolic	151.02 ± 25.64	150.38 ± 25.22	151.73 ± 26.68	152.93 ± 25.59	151.11 ± 24.15	0.7
Diastolic	81.27 ± 15.23	82.56 ± 14.87	79.41 ± 15.60	79.28 ± 15.35	78.37 ± 17.11	<0.001
Smoking (%)						0.4
Never	50.24	51.94	49.13	44.51	42.86	
Past	32.39	29.43	36.11	39.09	37.14	
Current	17.36	18.63	14.76	16.40	20.00	
ICED score (%) ^a						<0.001
0–1	35.59	42.14	28.74	21.86	0	
2	31.26	29.92	35.34	33.88	0	
3	33.15	27.94	35.92	44.26	100	
SCr (mg/dL)	10.29 ± 3.0	10.32 ± 3.00	10.16 ± 2.99	10.26 ± 3.02	11.05 ± 3.28	0.5
Calcium (mg/dL)	9.28 ± 0.97	9.28 ± 0.98	9.26 ± 0.95	9.28 ± 0.99	9.44 ± 0.95	0.6
Phosphorus (mg/dL)	5.82 ± 1.88	5.76 ± 1.87	5.92 ± 1.92	6.06 ± 1.70	6.95 ± 0.67	0.3

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Factors	Congestive HF					P
	Cohort (N = 1,786)	Absent (n = 1,113)	Mild (n = 515)	Moderate (n = 183)	Severe (n = 35)	
Serum albumin (g/dL)	3.62 ± 0.35	3.65 ± 0.36	3.59 ± 0.33	3.54 ± 0.34	3.48 ± 0.33	<0.001

Note: Continuous variables are shown as mean ± standard deviation. Categorical variables are given as percentage. No, mild, moderate, and severe HF were defined based on Index of Disease Severity score of 0, 1, 2, or 3 for HF comorbidity, respectively. Conversion factors for units: SCr in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; serum calcium and phosphorus in mg/dL to mmol/L, $\times 0.357$.

Abbreviations: AVF, arteriovenous fistula; AVG, arteriovenous graft; BMI, body mass index; HF, heart failure; ICED, Index of Coexistent Disease; SCr, serum creatinine; TBW, total-body water (estimated from anthropometric measurements and demographic data³²).

^aICED score calculated with HF excluded.

Table 2
Relationship of Severity of Congestive HF to All-Cause and Cause-Specific Mortality and Cardiac Hospitalization

Outcome	Congestive HF				<i>P</i> ^a
	Absent (n = 1,115)	Mild (n = 515)	Moderate (n = 183)	Severe (n = 35)	
All-cause mortality	1.00 (ref)	1.61 (1.39–1.87)	2.05 (1.66–2.53)	2.73 (1.86–4.02)	<0.001
Cause-specific mortality					
Cardiac death	1.00 (ref)	1.87 (1.45–2.39)	2.99 (2.16–4.13)	2.33 (1.17–4.63)	<0.001
IHD death	1.00 (ref)	1.62 (1.21–2.19)	2.21 (1.47–3.32)	2.41 (1.10–5.27)	<0.001
HF death	1.00 (ref)	4.56 (1.92–10.79)	11.76 (4.80–28.83)	<i>b</i>	<0.001
Arrhythmia death	1.00 (ref)	1.38 (0.76–2.48)	2.68 (1.28–4.99)	<i>b</i>	0.02
Death from other heart diseases	1.00 (ref)	1.22 (0.59–2.54)	1.95 (0.77–4.92)	<i>b</i>	0.3
Infectious death	1.00 (ref)	2.02 (1.47–2.78)	2.49 (1.58–3.95)	2.89 (1.31–6.36)	<0.001
First cardiac hospitalization or all- cause mortality	1.00 (ref)	1.59 (1.39–1.81)	2.34 (1.95–2.81)	3.22 (2.26–4.61)	<0.001
First cardiac hospitalization or cardiac death	1.00 (ref)	1.67(1.43–1.94)	2.68 (2.18–3.29)	3.26 (2.19–4.85)	<0.001

Note: Data are presented as hazard ratio (95% confidence interval). There were no violations of proportional hazards.

Abbreviations: HF, heart failure; IHD, ischemic heart disease; ref, reference.

^aThe No HF group serves as the referent. *P* values reflect a test of trend for ordered survival curves.

^bCollapsed to mild and moderate versus none due to insufficient data and excessively wide confidence intervals.

Table 3

Adjusted Cox Proportional Cause-Specific HRs for Mortality by Baseline Severity of Congestive HF

Outcome	Congestive HF				<i>P</i> ^a
	Absent (n = 1,115)	Mild (n = 515)	Moderate (n = 183)	Severe (n = 35)	
All-cause mortality	1.00 (ref)	1.31 (1.12–1.53)	1.48 (1.19–1.85)	2.11 (1.43–3.11)	<0.001
Cause-specific mortality					
Cardiac death	1.00 (ref)	1.46 (1.12–1.90)	2.07 (1.47–2.91)	1.88 (0.94–3.76)	<0.001
IHD death	1.00 (ref)	1.21 (0.89–1.66)	1.53 (1.01–2.32)	1.82 (0.83–4.01)	0.02
HF death	1.00 (ref)	3.20 (1.24–8.25)	7.94 (2.98–21.12)	<i>b</i>	<0.001
Arrhythmia death	1.00 (ref)	1.20 (0.66–2.21)	1.82 (0.87–3.81)	<i>b</i>	0.1
Death from other heart diseases	1.00 (ref)	1.29 (0.60–2.74)	2.34 (0.89–6.12)	<i>b</i>	0.1
Infectious death	1.00 (ref)	1.29 (1.12–1.47)	1.57 (1.29–1.92)	2.02 (1.41–2.90)	<0.001
First cardiac hospitalization or all-cause mortality	1.00 (ref)	1.33 (1.16–1.52)	1.85 (1.53–2.25)	2.65 (1.84–3.81)	<0.001
First cardiac hospitalization or cardiac death	1.00 (ref)	1.40 (1.19–1.64)	2.17 (1.75–2.69)	2.92 (1.95–4.37)	<0.001

Note: Data are presented as HR (95% confidence interval). HRs after adjusting for predictors through model selection methods, including age, sex, race, dose and flux group, diabetes, HF score (ie, ICED score for HF), duration of HD, access, ICED score with HF excluded, diastolic blood pressure, body mass index, smoking status, and serum albumin.

Abbreviations: HF, heart failure; ICED, Index of Coexistent Disease; IHD, ischemic heart disease; HR, hazard ratio; ref, reference.

^aThe No HF group serves as the referent. *P* values reflect an ordered test of trend.

^bCollapsed severe category into moderate category due to insufficient data and excessively wide confidence intervals.

Table 4**Health-Related Quality of Life and Severity of Congestive HF**

Outcome	Congestive HF				P for Trend
	Absent	Mild	Moderate	Severe	
Physical Functioning	51.81 ± 26.93	43.06 ± 26.20	42.32 ± 26.14	32.97 ± 23.45	<0.001
Role-Physical	46.20 ± 40.50	41.63 ± 39.97	40.33 ± 41.66	25.00 ± 36.48	<0.001
Bodily Pain	63.77 ± 27.36	61.27 ± 28.77	61.08 ± 28.27	60.66 ± 26.37	0.08
General Health	48.34 ± 21.32	43.89 ± 21.33	42.05 ± 20.68	40.02 ± 18.94	<0.001
Vitality	51.73 ± 21.70	48.17 ± 22.30	46.16 ± 21.15	40.78 ± 19.88	<0.001
Social Functioning	72.46 ± 26.18	68.49 ± 28.18	66.60 ± 29.02	57.42 ± 28.19	<0.001
Role-Emotional	64.81 ± 41.49	63.37 ± 42.01	61.88 ± 42.66	55.21 ± 45.29	0.2
Mental Health	72.36 ± 18.60	71.04 ± 20.22	70.52 ± 19.31	64.69 ± 19.84	0.02
PCS score	36.94 ± 10.26	34.17 ± 9.66	33.77 ± 10.04	31.20 ± 9.93	<0.001
MCS score	50.01 ± 10.57	49.77 ± 11.43	49.12 ± 11.04	46.50 ± 11.65	0.1
Sleep Quality	59.56 ± 22.21	58.28 ± 23.18	56.38 ± 22.59	50.78 ± 25.58	0.01

Note: Scores are reported as mean ± standard deviation.

Abbreviations: HF, heart failure; PCS, Physical Component Summary; MCS, Mental Component Summary.

Table 5

Longitudinal Analysis for Health-Related Quality of Life and Sleep Quality Scores

Outcome	HF Effect ^a	Time Effect ^b	<i>P</i>	
			HF Effect	Time Effect
Physical Functioning	−2.50 (−12.19 to 7.18)	−4.50 (−9.15 to 0.15)	0.6	<0.001
Role–Physical	−2.68 (−4.35 to −1.02)	−1.07 (−1.79 to −0.35)	0.002	0.006
Bodily Pain	−1.64 (−2.74 to −0.55)	−1.39 (−1.85 to −0.92)	0.004	<0.001
General Health	−2.27 (−3.10 to −1.44)	−0.71 (−1.03 to −0.39)	<0.001	<0.001
Vitality	−2.51 (−3.40 to −1.62)	−0.71 (−1.04 to −0.38)	<0.001	0.001
Social Functioning	−2.64 (−3.75 to −1.53)	−0.79 (−1.27 to −0.31)	<0.001	0.004
Role–Emotional	−1.10 (−2.91 to 0.70)	−0.62 (−1.38 to 0.13)	0.2	0.1
Mental Health	−1.64 (−2.43 to −0.85)	−0.49 (−0.82 to −0.17)	<0.001	0.004
PCS score	−1.35 (−1.77 to −0.94)	−0.60 (−0.77 to −0.43)	<0.001	<0.001
MCS score	−0.49 (−0.95 to −0.02)	−0.16 (−0.35 to 0.04)	0.05	0.1
Sleep Quality	−1.52 (−2.43 to −0.61)	−0.48 (−0.84 to −0.12)	0.001	0.01

Note: Values shown are beta (95% confidence interval).

Abbreviations: HF, heart failure; MCS, Mental Component Summary; PCS, Physical Component Summary.

^aChange in score per change in HF level.

^bChange in score per unit time.