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Echocardiography Criteria for Structural Heart Disease in Patients With End-Stage Renal Disease Initiating Hemodialysis

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ABSTRACT

BACKGROUND Cardiovascular disease among hemodialysis (HD) patients is linked to poor outcomes. The Acute Dialysis Quality Initiative Workgroup proposed echocardiographic (ECHO) criteria for structural heart disease (SHD) in dialysis patients. The association of SHD with important patient outcomes is not well defined.

OBJECTIVES This study sought to determine prevalence of ECHO-determined SHD and its association with survival among incident HD patients.

METHODS We analyzed patients who began chronic HD from 2001 to 2013 who underwent ECHO ≤1 month prior to or ≤3 months following initiation of HD (n = 654).

RESULTS Mean patient age was 66 ± 16 years, and 60% of patients were male. ECHO findings that met 1 or more and ≥3 of the new criteria were discovered in 87% and 54% of patients, respectively. Over a median of 2.4 years, 415 patients died: 108 (26%) died within 6 months. Five-year mortality was 62%. Age- and sex-adjusted structural heart disease variables associated with death were left ventricular ejection fraction (LVEF) ≤45% (hazard ratio [HR]: 1.48; confidence interval [CI]: 1.20 to 1.83) and right ventricular (RV) systolic dysfunction (HR: 1.68; CI: 1.35 to 2.07). An additive of higher death risk included LVEF ≤45% and RV systolic dysfunction rather than neither (HR: 2.04; CI: 1.57 to 2.67; p = 0.53 for test for interaction). Following adjustment for age, sex, race, diabetic kidney disease, and dialysis access, RV dysfunction was independently associated with death (HR: 1.66; CI: 1.34 to 2.06; p < 0.001).

CONCLUSIONS SHD was common in our HD study population, and RV systolic dysfunction independently predicted mortality. (J Am Coll Cardiol 2016;67:1173–82) © 2016 by the American College of Cardiology Foundation.

Heart failure (HF) contributes significantly to morbidity in patients with end-stage renal disease (ESRD) requiring dialysis (1–5). However, the causes of HF and HF symptoms in dialysis patients are often poorly defined and/or misclassified. Dyspnea or volume overload can be multifactorial and may not be related to underlying structural heart disease (SHD) (6). The Acute Dialysis

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ABBREVIATIONS AND ACRONYMS

ADQI = Acute Dialysis Quality Initiative

ASE = American Society of Echocardiography

EAE = European Association of Echocardiography

ECHO = echocardiography

ESRD = end-stage renal disease

HD = hemodialysis

HF = heart failure

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

RV = right ventricle

RWMA = regional wall motion abnormalities

SD = standard deviation

SHD = structural heart disease

Quality Initiative (ADQI) XI Workgroup recently proposed a new classification of HF in patients with ESRD that specifically excludes patients with volume overload and a normal heart and focuses on those with underlying SHD as defined by echocardiography (ECHO). The goal of the classification was to optimize diagnostic and therapeutic approaches to HF and address the unique complexities associated with nonphysiological periodic volume removal (6). The 3 elements of the proposed staging system included: 1) standardized ECHO evidence of structural and/or functional heart abnormalities; 2) dyspnea occurring in the absence of primary lung disease, including isolated pulmonary hypertension; and 3) response of congestive symptoms to dialysis/ultrafiltration. Standardized ECHO criteria, adapted from the American Society of Echocardiography (ASE) and European Association of Echocardiography (EAE) consensus guidelines (7–10), assess 8 ECHO abnormalities, of which at least 1 must be present to fulfill the diagnosis of SHD.

SEE PAGE 1183

The prevalence of SHD based on the proposed criteria and its impact on overall survival in dialysis patients are unknown, and the ADQI XI Workgroup called for research focused on the epidemiology and prognosis of dialysis patients classified with this new scheme. Our study was undertaken to ascertain prevalence of SHD based on the proposed ADQI criteria and to examine prognostic implications of SHD in ESRD patients who were starting maintenance hemodialysis (HD) therapy.

METHODS

PATIENT SELECTION. Mayo Clinic Dialysis Services provides all HD in the Mayo Clinic Health System, a comprehensive integrated healthcare network for 395,000 residents in southeastern Minnesota, northern Iowa, and southwestern Wisconsin, through 8 community-based outpatient HD facilities as previously described (11,12). This study included patients ≥18 years of age who began chronic outpatient HD therapy between January 1, 2001, and May 31, 2013 (n = 1,357), who remained on dialysis ≥30 days (n = 1,187), and who underwent ECHO examination at Mayo Clinic ≤1 month prior to or ≤3 months after initiation of HD (n = 654). Primary outcome was all-cause mortality by study end (December 31, 2013). Minnesota research authorization was provided for all participants. The Mayo Clinic Institutional Review Board approved this study.

DATA COLLECTION. Baseline characteristics, comorbidities, and laboratory test results were collected through review of the electronic medical record. Data included cause of ESRD, type of initial dialysis access, and initial dialysis location. First dialysis access was categorized as arteriovenous fistula, arteriovenous graft, or central venous catheter. Catheters were further classified as temporary (nontunneled, noncuffed) or tunneled (cuffed). HF diagnosis included congestive HF, systolic HF, diastolic HF, or cardiomyopathy based on manual review of medical records. The Charlson comorbidity index score, consisting of 19 comorbid conditions, was obtained by a previously validated automatic note-search strategy (automated digital algorithm) (13). HD initiation was categorized as occurring before or after the release of the 2005 Kidney Disease Outcomes Quality Initiative clinical practice guidelines (14).

ECHOCARDIOGRAPHY. ECHOs performed ≤1 month prior to or ≤3 months after dialysis initiation were identified through the Mayo Clinic Echocardiographic Laboratory database. Indications for ECHO are included in Online Table 1. ECHO was performed according to ASE and EAE guidelines for assessment of valves and chamber size and function (7–10). SHD was defined according to the proposed criteria from the ADQI XI Workgroup (6), except for left ventricular (LV) regional wall motion abnormalities (RWMA). The 16-segment model was used for RWMA assessment, and any RWMA was included (instead of >10% of the myocardium); and right ventricular (RV) systolic dysfunction included semiquantitative assessment. Measurement definitions matched the proposed ADQI XI criteria. Left ventricular hypertrophy (LVH) was defined as LV mass index >110 g/m^2 for women and >130 g/m^2 for men or LV mass index >47 g/m$^{2.7}$ for women and >50 g/m$^{2.7}$ for men. Increased LV volume index was defined as >86 ml/m^2 end diastolic volume or >37 ml/m^2 end systolic volume. RV systolic dysfunction was defined as lateral tricuspid annulus velocity (S′) <9.5 cm/s or abnormal systolic function by semiquantitative assessment and LV systolic dysfunction as left ventricular ejection fraction (LVEF) ≤45%. Other ADQI XI criteria included left atrial (LA) enlargement (volume index ≥34 ml/m^2), diastolic dysfunction grade ≥2, and mitral and/or aortic valvular disease with moderate to severe stenosis or regurgitation. Methods and references for quantitation of the above ECHO variables are provided in the supplemental Materials section in the Online Appendix.

STATISTICAL ANALYSIS. Continuous variables were reported as mean ± SD or median with interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were expressed as count (percent). Comparison of proportions between groups was made using the chi-square test. Continuous variables were compared using 2-sample Student *t* test or Wilcoxon rank sum test. Primary outcome was all-cause mortality between dialysis start and study period end. Subjects were censored at time of kidney transplantation, transfer to a non-Mayo Clinic dialysis services facility, transition to home dialysis therapies such as peritoneal dialysis or home HD, and study period end. Kaplan-Meier methods were used to summarize event rates, and comparison between groups was done using log-rank test. Age- and sex-adjusted survival curves were created using a semiparametric approach, assuming age and sex followed the proportional hazards assumption, whereas proportional hazards were not required for the grouping variables (15). The association of SHD with mortality was assessed by Cox proportional hazards regression models for long-term outcomes after adjustment for age and sex. Additional models further adjusted for other predictors of mortality (race, diabetes as cause of ESRD, type of dialysis access). For SHD variables with missing values, a missing value indicator was included to estimate the effect of missing values. Multivariate models included only SHD variables that were statistically significant after age and sex adjustment. SHD variables significant in multivariate analysis were simplified into groups for ease of interpretation.

We conducted a series of additional analyses to further evaluate parameters beyond the ADQI proposed criteria. To determine whether pulmonary hypertension (pulmonary artery systolic pressures >35 mm Hg) was also a predictor of survival, Cox regression analyses were performed in those with available pulmonary artery systolic pressures. To minimize the confounding effect of nonphysiological volume overload either prior to start of dialysis or between treatments, Cox regression analyses were repeated among those who had ECHO performed after dialysis initiation and who were further subgrouped to those undergoing dialysis within 24 h before ECHO. Statistical significance was set at a p value of <0.05 (2-sided), and statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

RESULTS

OVERALL INCIDENT DIALYSIS COHORT. From January 2001 to May 2013, N = 1,187 patients started and remained on HD ≥1 month. Among these patients, 654 (55%) underwent ECHO ≤1 month prior to or ≤3 months after HD initiation. Baseline demographic characteristics of patients without ECHOs meeting study entry criteria (n = 533 [45%]) are shown in **Table 1** and are compared to the study population. Patients without ECHOs had fewer comorbidities including coronary artery disease (48% vs. 56%, respectively, p = 0.003), HF (36% vs. 56%, respectively, p < 0.001), and Charlson score ≥8 (45% vs. 52%, respectively, p = 0.02) but were more likely to have an AV fistula or graft dialysis access present at first dialysis treatment (39% vs. 20%, respectively, p < 0.001) (Online Table 2). Overall survival also differed between groups (**Figure 1A**). Study patients who underwent ECHOs and did not have SHD had survival rates similar to those of patients without ECHOs who were not included in the study (p = 0.97) (**Figure 1B**). However, patients with SHD had worse overall survival than those without ECHOs (p < 0.001).

STUDY COHORT. For patients with ECHOs who met study inclusion criteria (n = 654 [55%]), baseline demographics are shown for the overall study group and also were divided by the presence or absence of SHD (**Table 1**). Mean age of the study was 66 ± 16 years (median 68 years; IQR: 56 to 78 years), and 56% had HF. The mean ± SD Charlson comorbidity index score was 7.5 ± 3.4 (median 8; IQR: 5 to 10). The most common causes of kidney disease were diabetes mellitus (29%), hypertension (15%), and glomerulonephritis (12%). One or more ECHO findings of SHD were present in 567 patients (87%). Compared to those without SHD, patients with ≥1 ECHO finding of SHD at baseline were older (66.7 ± 15.8 years of age vs. 58.5 ± 16.4 years of age, respectively, p < 0.001), had higher prevalence of coronary artery disease (60% vs. 34%, respectively, p < 0.001) and HF (60% vs. 26%, respectively, p < 0.001), and a higher Charlson comorbidity score (7.7 ± 3.3 vs. 6.1 ± 3.4, respectively, p < 0.001).

ECHO FINDINGS AND SHD. Baseline ECHO findings among patients with SHD are shown in **Table 2**. Median time between ECHO and HD initiation was 0 days (IQR: −4 to 8 days). Most patients (85%) had ≥5 baseline SHD variables documented, and 53% had 7 or 8. A total of 266 patients (44%) had other ECHOs performed within the year preceding the index ECHO that met inclusion criteria, which indicates that repeated acquisition of data for some SHD variables may not have been performed. Within available data, the prevalence of SHD, defined by the presence of ≥1 SHD finding, was high (87% [n = 567]). Among

TABLE 1 Comparison of Baseline Patient Characteristics and ECHO Findings

	Comparison Group Without ECHO	Patients Included in the Study		
	No ECHO (n = 533)	ECHO Total (n = 654)	ECHO-No SHD (n = 87)	ECHO-SHD (n = 567)
Age, yrs	63.9 ± 17.3	65.6 ± 16.1	58.5 ± 16.4	66.7 ± 15.8*
	67.8 (52.4–77.2)	68.4 (56.2–78.5)	58.3 (48.5–69.6)	69.7 (57.7–78.8)*
Age ≥75	173 (32)	218 (33)	16 (18)	202 (36)
Demographics				
Male	335 (63)	390 (60)	38 (44)	226 (40)
Female	198 (37)	264 (40)	49 (56)	341 (60)
Caucasian	462 (87)	582 (89)	79 (91)	503 (89)
Diabetes mellitus	275 (52)	328 (50)	39 (45)	289 (51)
Coronary artery disease	254 (48)	369 (56)	30 (34)	339 (60)*
HF	191 (36)	366 (56)	23 (26)	343 (60)*
Previous outpatient nephrology evaluation	437 (82)	407 (62)	51 (59)	356 (63)
Charlson comorbidity score	7.3 ± 3.5	7.5 ± 3.4	6.1 ± 3.4	7.7 ± 3.3*
	7.0 (5.0–10.0)	8.0 (5.0–10.0)	6.0 (3.0–8.0)	8.0 (5.0–10.0)*
Charlson score ≥8	240 (45%)	341 (52%)	27 (31%)	314 (55%)*
ESRD cause				
Diabetes mellitus	180 (34)	192 (29)	17 (20)	175 (31)
Hypertension	100 (19)	99 (15)	11 (13)	88 (16)
Glomerulonephritis/tubulointerstitial nephritis	73 (14)	79 (12)	13 (15)	66 (12)
Polycystic kidney disease	15 (3)	12 (2)	1 (1)	11 (2)
Refractory acute tubular necrosis	9 (2)	54 (8)	9 (10)	43 (8)
Failing kidney transplant	35 (7)	38 (6)	11 (13)	27 (5)
Other/unknown	104 (20)	182 (28)	25 (29)	157 (28)
First dialysis access used				
Noncuffed, temporary catheter	106 (20)	256 (39)	42 (48)	214 (38)
Cuffed tunneled catheter	296 (56)	318 (49)	36 (41)	282 (50)
Arteriovenous fistula/graft	130 (24)	80 (12)	9 (10)	71 (13)
AVF/AVG present at first dialysis	210 (39)	132 (20)	16 (18)	116 (20)
Hemodialysis start year				
<2005	198 (37)	209 (32)	39 (45)	170 (30)#
≥2005	335 (63)	445 (68)	48 (55)	397 (70)
ECHO time period				
Days from dialysis start to ECHO examination	-	0.0 (−4.0 to 9.0)	2.0 (−3.0 to 36.0)	0.0 (−4.0 to 8.0)*
K-M mortality estimate (number of events)				
6 months	8% (41)	17% (108)	16% (14)	17% (94)
3 yrs	38% (190)	46% (286)	45% (38)	46% (248)
5 yrs	54% (253)	62% (363)	56% (46)	63% (317)

Values are mean ± SD, median (interquartile range), or n (%), unless otherwise indicated. Data compare baseline patient characteristics and ECHO findings for patients without ECHO (No ECHO), with ECHO and no SHD (ECHO-No SHD), and with ECHO and SHD (ECHO-SHD) among incident HD patients. Statistical comparison of Echo-No SHD and Echo-SHD groups. *$p < 0.001$. #$p < 0.05$ for ≥1 SHD versus No SHD.

AVF = arteriovenous fistula; AVG = arteriovenous graft; Charlson score = Charlson comorbidity index score; ECHO = echocardiogram; HF = heart failure; ICU = intensive care unit; K-M = Kaplan-Meier; RRT = renal replacement therapy; SD = standard deviation; SHD = structural heart disease.

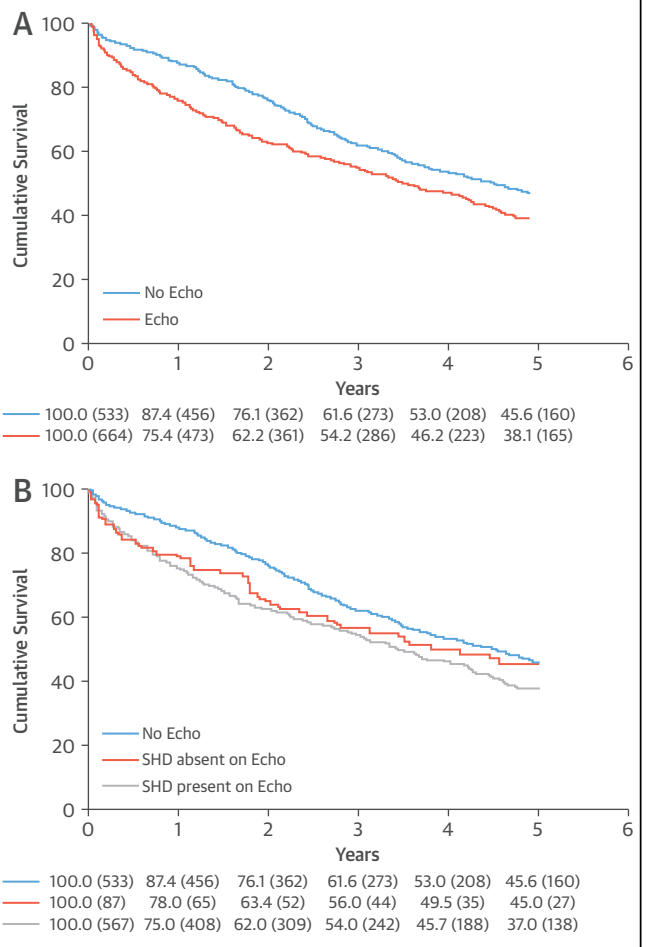
patients with SHD, the most common abnormalities were LA volume index ≥34 ml/m^2 (81%), diastolic dysfunction ≥grade 2 (78%), LVH by g/m^2 (49%) and by g/m$^{2.7}$ (71%), and RWMA (50%). Of patients with valvular SHD (16%), mitral regurgitation was the most common (13%), followed by aortic stenosis (3%). RV systolic dysfunction was present in 34% of patients by semiquantitative assessment and 28% by S′ criteria.

OVERALL SURVIVAL. Over a median follow-up of 2.4 years (IQR: 0.9 to 4.9 years), 239 subjects were censored, of whom 61 (26%) underwent kidney transplantation, 46 (19%) were transferred to an outside dialysis unit, 32 (13%) had renal recovery, 4 (2%) were transitioned to home HD or PD, and 96 (40%) were alive at the end of the study. Overall, 415 patients died; 108 (26%) of these deaths occurred within 6 months. Cumulative death rates were 17%,

38%, and 62% at 6 months, 2 years, and 5 years, respectively. Causes of death were sudden cardiac arrest (29%), dialysis withdrawal (inpatient or outpatient) leading to death (25%), other causes (10%), sepsis (7%), trauma (0.2%), and unknown causes (28%). In unadjusted analysis, compared to patients with 0 to 1 SHD abnormalities, survival was reduced by the presence of >1 abnormality at baseline ($p = 0.002$). However, this association was no longer significant following adjustment for age and sex (0 to 1 SHD vs. 2 to 3 SHD, $p = 0.75$; 0 to 1 SHD vs. >3 SHD, $p = 0.13$; and 2 to 3 SHD vs. >3 SHD, $p = 0.05$, with p trend = 0.12). The 2 age- and sex-adjusted SHD variables significantly associated with mortality were LVEF ≤45% (hazard ratio [HR]: 1.48; confidence interval [CI]: 1.20 to 1.83; $p < 0.001$) and RV systolic dysfunction (HR: 1.68; CI: 1.35 to 2.07, $p < 0.001$) (**Table 3**). RV systolic dysfunction was an important predictor of mortality, with the absence of RV dysfunction among SHD patients conferring no evident difference in survival to patients with no SHD at baseline (**Central Illustration**). In age- and sex-adjusted analyses using patients with no SHD as the reference group, patients with SHD but without RV dysfunction experienced no difference in survival (HR: 0.84; CI: 0.61 to 1.14, $p = 0.25$), whereas SHD patients with RV dysfunction had reduced survival (HR: 1.41; CI: 1.01 to 1.96, $p = 0.04$). The combination of RV and LV systolic dysfunction was also a strong determinant of survival. Age- and sex-adjusted relationships among RV systolic function, LVEF, and survival were further explored (**Figure 2**, **Table 4**). Patients with impaired LV function (LVEF: ≤45%) and RV systolic dysfunction had an increased risk of death (HR: 2.0; CI: 1.6 to 2.7, $p < 0.001$) compared to patients with LVEF ≥45% and normal RV systolic function. The combination of these 2 SHD factors was simply additive (test for interaction, $p = 0.53$). We further assessed RV systolic dysfunction in a model with age, sex, race, diabetic kidney disease, and AV fistula access. RV dysfunction remained associated with death by study end (HR: 1.66; CI: 1.34 to 2.06; $p < 0.001$).

Sensitivity analyses examined whether our findings were supported among patients who started dialysis prior to ECHO ($n = 358$). In that cohort, Cox regression analyses revealed 3 important SHD predictors of death, including moderate diastolic dysfunction (HR: 1.49; CI: 1.03 to 2.17, $p = 0.04$), RV dysfunction (HR: 1.75; CI: 1.30 to 2.36, $p < 0.001$), and LV systolic dysfunction (HR: 1.74; CI: 1.29 to 2.33, $p < 0.001$). Analyses were further limited to patients undergoing dialysis treatments ≤24 h prior to their ECHO ($n = 190$) and revealed similar findings to the original study cohort wherein both RV and LV systolic dysfunction remained the only predictors of death. Separate analyses examined the relationship between pulmonary hypertension and death. Among those with measured pulmonary artery systolic pressure ($n = 530$), the mean pressure was 46.8 ± 14.8 mm Hg, and 75% of patients had evidence of pulmonary hypertension (pulmonary artery systolic pressure >35 mm Hg). Compared to those without any SHD, those

FIGURE 1 Survival According to ECHO at Incident Dialysis



(A) Cumulative survival among incident hemodialysis patients by patients undergoing ECHO during the 1 month prior to or 3 months after dialysis initiation (ECHO group) and patients not undergoing echocardiograms (No ECHO group) ($p = 0.003$). Numbers below figure represent survival estimate (n at risk) at each time point. **(B)** Survival according to performance of ECHO and presence of SHD at incident dialysis. Cumulative survival among incident HD patients by patients with ECHO evidence of SHD (SHD present on ECHO group), patients without evidence of SHD (SHD absent from ECHO group), and patients without ECHO (no ECHO group); no ECHO versus SHD absent on ECHO ($p = 0.97$); no ECHO versus SHD present on ECHO ($p < 0.001$); SHD absent on ECHO versus SHD present on ECHO ($p = 0.08$). Numbers below figure represent survival estimate (n at risk) at each time point. ECHO = echocardiography; SD = standard deviation; SHD = structural heart disease.

TABLE 2 ECHO Findings Among Incident HD Patients (N = 567) With SHD Based on ECHO Criteria Proposed by the Acute Dialysis Quality Initiative

Time to ECHO	
Prior to HD initiation, days (n = 330)	3 (1-9)
Following HD initiation, days (n = 237)	15 (3-48)
Absolute time between dialysis initiation and ECHO	0 (−4 to 8)
SHD subgroups	
LV size (n = 497)	
LV hypertrophy present by LVM/m^2 measurement	242 (49)
LVM/m^2 overall, g/m^2	118 (99-144)
LVM/m^2 women, g/m^2	115 (95-136)
LVM/m^2 men, g/m^2	123 (103-148)
LV hypertrophy present by LVM/height$^{2.7}$ measurement	351 (71)
LVM/height$^{2.7}$ overall, g/$m^{2.7}$	57 (47-68)
LVM/height$^{2.7}$ women, g/$m^{2.7}$	59 (48-71)
LVM/height$^{2.7}$ men, g/$m^{2.7}$	55 (46-67)
LV volume index (n = 71)	
LV volume index diastole >86 or systole >37 ml/m^2	51 (72)
LV volume index diastole, ml/m^2	76 (62-96)
LV volume index systole, ml/m^2	48 (33-67)
LA size (n = 444)	
LA enlargement present	359 (81)
LA volume index, ml/m^2	43 (34-54)
Diastolic function (n = 448)	
Diastolic dysfunction present	350 (78)
Valvular heart disease (n = 531)	
≥Moderate mitral or aortic valve dysfunction present	86 (16)
≥Moderate mitral valve dysfunction present	70 (13)
≥Moderate mitral stenosis	3 (1)
≥Moderate mitral regurgitation	68 (13)
≥Moderate aortic valve dysfunction present	21 (4)
≥Moderate aortic stenosis	15 (3)
≥Moderate aortic regurgitation	6 (1)
Quantitaive RV systolic function (n = 186)	
S′ <9.5 cm/s	52 (28)
S′, cm/s	12 (9-16)
Semiquantitative RV systolic function (n = 533)	
RV systolic dysfunction present	180 (34)
LVEF (n = 562)	
LVEF ≤45%	180 (32)
Regional wall motion of LV (n = 483)	
RWMA present	242 (50)
Number of SHD variables present	3.0 ± 1.7
	3 (2-4)
≥3 SHD abnormalities present	306 (54)

Values are median (interquartile range), n (%), or mean ± SD. LV hypertrophy is calculated by 2 measurements: LV mass index >110 g/m^2 for women and >130 g/m^2 for men or LV mass index >47 g/$m^{2.7}$ for women and >50 g/$m^{2.7}$ for men.

HD = hemodialysis; IQR = interquartile range; LA = left atrial; LV = left ventricle; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; RV = right ventricle; RWMA = regional wall motion abnormality abnormality; S′ = systolic lateral tricuspid annulus velocity (S′) was measured by tissue Doppler in the apical four-chamber view; SHD = structural heart disease.

with ≥1 SHD abnormality had higher pulmonary artery systolic pressure (47.9 ± 14.7 vs. 35.0 ± 10.3, respectively, $p < 0.001$) and higher prevalence of pulmonary hypertension (78% vs. 44%, respectively, $p < 0.001$). Pulmonary hypertension was associated with reduced survival after adjusting for age and sex (HR: 1.41; CI: 1.08 to 1.84, $p = 0.01$) but was not independently associated with overall survival when adjusted for RV systolic dysfunction and LVEF ≤45% (HR: 1.26; CI: 0.96 to 1.66, $p = 0.09$).

DISCUSSION

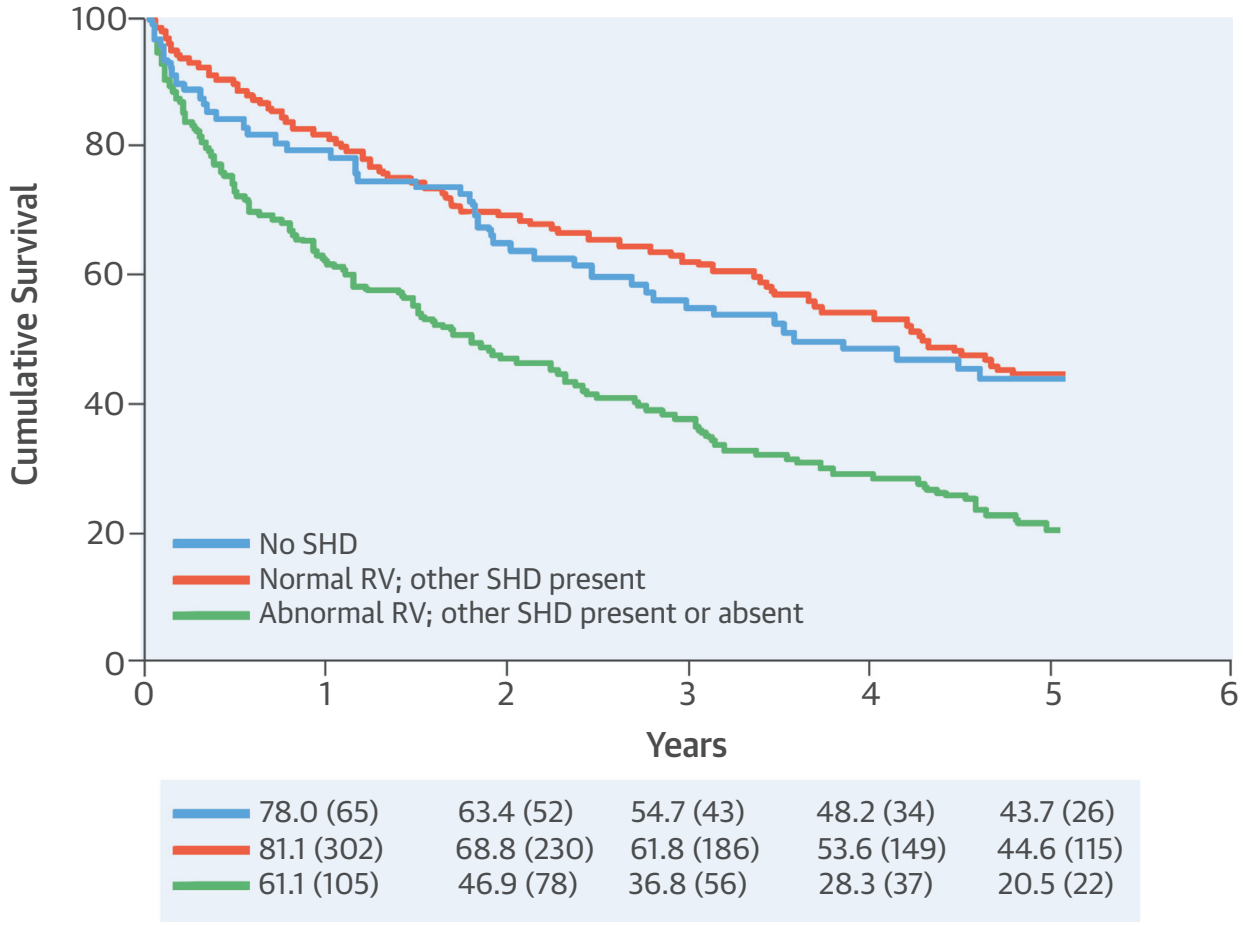
In our study cohort, SHD was common, with a substantial majority of the patients having ≥1 baseline ECHO abnormality and more than one-half having ≥3. The presence of SHD was also associated with more comorbidities. Patients with impaired LVEF and RV dysfunction had a 2-fold increased risk of death compared to patients with LVEF >45% and normal RV function. Overall, RV dysfunction appeared to have the strongest association with mortality in this cohort.

The prevalence of underlying SHD is influenced by patient demographics and associated comorbidities, such as higher prevalence of LVH in patients with long-standing or poorly controlled hypertension, either contributing to or a result of their kidney disease. Patients with ESRD have a demonstrated substrate for rapid progression of many SHD subtypes (e.g., calcific valvular lesions) and known risks for ischemic cardiac dysfunction (16).

LEFT VENTRICLE AND MORTALITY. Several studies have shown impaired LVEF, diastolic dysfunction, and LVH as predictors of mortality in dialysis patients (17-25). Yamada et al. (23) found that, in 1,254 incident HD patients of similar age to those in the present study (62 ± 14 years) and who were followed for 7 years, reduced LVEF was present in 13% and was a strong predictor of death from cardiovascular events as well as all-cause mortality. Progressive decline of LVEF was associated with increasing risk of death. We also found LV dysfunction was prevalent and associated with higher risk of mortality.

Diastolic dysfunction of grade 2 or higher was not independently associated with excess mortality in the age- and sex-adjusted analyses of our entire study cohort. However, an association with diastolic dysfunction and mortality was seen in patients who initiated dialysis before an ECHO was performed. Barberato et al. (20) examined a somewhat younger patient group (52 ± 16 years) with no previous cardiovascular disease such as HF, myocardial infarction, or valvular disease. That study found that advanced diastolic dysfunction was independently and significantly predictive of cardiovascular events (including sudden death, acute myocardial infarction, and decompensated HF requiring

CENTRAL ILLUSTRATION **Structural Heart Disease in Dialysis Patients: Survival**



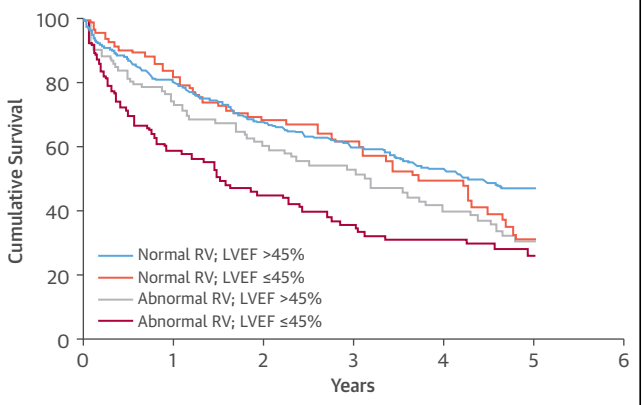
Hickson, L.J. et al. J Am Coll Cardiol. 2016; 67(10):1173–82.

Cumulative survival according to the presence or absence of SHD and RV function at incident dialysis ($p < 0.001$). Numbers below figures represent survival estimate (n at risk) at each time point. RV = right ventricle; SHD = structural heart disease.

hospitalization), as well as increased mortality compared to those with normal diastolic function or mild diastolic dysfunction. Han et al. (21) found a strong impact of diastolic dysfunction on cardiovascular events in dialysis patients, although that study included only patients with preserved LV systolic function and defined diastolic dysfunction based on Doppler criteria (mitral early inflow velocity to early mitral annular velocity ratio of E:E′ >15). Dubin et al. (26) demonstrated in a study of 40 patients that E:E′ but not conventional measures of diastolic dysfunction (i.e., classification into impaired relaxation, pseudonormal, and restrictive filling patterns) was associated with elevated N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin. This suggests that Doppler-based data may have greater utility in evaluating cardiac function in the ESRD population. The aforementioned discordant findings may be explained by different patient populations and suggest that further evaluation of how to define diastolic function in ESRD and its impact on patient outcomes is needed.

Silberberg et al. (25) found that LVH (LV mass index >125 g/m^2) upon HD initiation was an independent determinant of all-cause mortality in 91 patients (55 ± 15 years of age) followed for ≤5 years. However, that study excluded patients with pre-existing malignancy and those with valvular disease. Paoletti et al. (24) also showed LVH to be predictive of subsequent sudden cardiac death in 123 patients

FIGURE 2 Survival According to LV and RV Function at Incident Dialysis



Age- and sex-adjusted survival by LV and RV systolic function groupings (p <0 .001). LV = left ventricle; LVEF = left ventricular ejection fraction; RV = right ventricle.

(range: 29 to 79 years of age) who were on HD therapy for at least 6 months and followed for more than 10 years. Our study confirmed the link between impaired LV systolic function but not LVH or diastolic dysfunction and poor outcome.

RIGHT VENTRICLE AND MORTALITY. In this study, RV systolic dysfunction was relatively common (27%), and a minority of patients (10%) had moderate to severe dysfunction. RV systolic dysfunction was independently associated with poor survival even when modeled with age, sex, diabetes, ESRD cause, and AV fistula access in a multivariate analysis. RV dysfunction in HD patients is thought to result from chronic volume overload and is exacerbated by AV fistula access, especially in the brachial position (27,28). RV dysfunction in turn leads to an impaired LV. This was shown by Paneni et al. (27) in 120 patients undergoing chronic dialysis, who had preserved LVEF (>50%) in which RV systolic dysfunction correlated with indices of LV systolic and diastolic function and was independently associated with reduced LVEF. The RV-to-LV interdependence and impact of RV dysfunction are known in several cardiac diseases (29–35): RV systolic dysfunction is associated with poor outcomes in severe native aortic valve stenosis (29), is an independent predictor of short- and long-term mortality in patients with HF (31), predicts transplant-free survival in patients with dilated cardiomyopathy (32), is predictive of outcomes in patients who have undergone primary percutaneous coronary intervention for acute myocardial infarction (34), and is associated with clinical and ECHO evidence of more advanced HF predictive of poorer outcomes (36). Our study supports the interdependent relationship between RV and LV, as biventricular failure was associated with a significantly increased risk of death.

TABLE 3 Association of Age- and Sex-Adjusted Structural Heart Disease Variables With Overall Mortality

Structural Heart Disease Variable	Hazard Ratio for Overall Mortality (95% CI)	p Value
Left atrial volume index ≥34 ml/m^2	1.26 (0.94–1.69)	0.12
Diastolic dysfunction ≥grade 2	1.16 (0.89–1.52)	0.28
Left ventricular hypertrophy	0.93 (0.75–1.15)	0.50
Regional wall motion abnormality	1.24 (1.00–1.55)	0.05
Left ventricular ejection fraction ≤45%	1.48 (1.20–1.83)	<0.001
Right ventricular systolic dysfunction, any	1.68 (1.35–2.07)	<0.001
≥Moderate aortic/mitral valvular heart disease	1.14 (0.87–1.49)	0.34
Left ventricular volume index >86 ml/m^2	0.80 (0.41–1.53)	0.48

Left ventricular hypertrophy measurement included LVMI >110 g/m^2 for women and >130 g/m^2 for men. Additional results for LVH by height was defined as LVMI height >47 g/m$^{2.7}$ for women and >50 g/m$^{2.7}$ for men where HR: 0.96 (CI 0.77 to 1.20), p = 0.72.

CI = confidence interval; LVH = left ventricular hypertrophy; LVMI = Left ventricular mass index.

TABLE 4 Association Between Death and Left and Right Systolic Ventricular Function Structural Heart Disease Subgroups at Baseline Examination

	Hazard Ratio for Overall Mortality (95% CI)	p Value
LVEF and RV function		
LVEF >45%, normal RV	1.00 (ref)	
LVEF ≤45%, normal RV	1.24 (0.92–1.66)	0.15
LVEF >45%, abnormal RV	1.43 (1.07–1.91)	0.02
LVEF ≤45%, abnormal RV	2.04 (1.57–2.67)	<0.001

Abbreviations as in Tables 2 and 3.

STUDY LIMITATIONS. This was a retrospective study of ECHO examinations performed over a several-year timeframe in which practice patterns and guidelines changed, including the recommendation for more quantitative RV functional assessment (37,38). However, while semiquantitative RV assessment has limitations (31,37,39), it does afford useful information about RV size and function, provided the ECHO is sufficiently detailed (40,41). Semiquantitative RV assessment correlated well with quantitative assessment in our study. Referral for ECHO <1 month prior to or ≤3 months after HD initiation was not systematic, as shown by the different survivorship between those who had an ECHO and those that did not. Our study nonetheless provides insight into the need for a standardized approach to SHD assessment,

emphasizing the position of the ADQI to adopt consistent methodology for collection and documentation of ECHO data in dialysis patients. The predominantly white population of our study may limit generalizability, and a lack of data regarding dialysis-specific factors (adequacy, bone and mineral metabolism, anemia, hypoalbuminemia, and AV fistula duration) may have affected the association of SHD with mortality.

CONCLUSIONS

SHD is common among incident HD patients. Both the impaired LV and RV systolic functions were associated with poor outcomes and death. RV systolic dysfunction appears to have important prognostic implications, however additional studies are needed to confirm these findings. Implementation of a standardized comprehensive screening ECHO examination to completely evaluate all SHD variables may help identify HD patients at highest risk of death, inform the need for early intervention to improve patient outcomes, and generate critical conversations with patients related to their prognosis.

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PERSPECTIVES

COMPETENCY IN PRACTICE-BASED LEARNING: Guidelines recommend screening ECHO to evaluate cardiac structure and function in patients with end-stage renal disease after initiating dialysis.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with end-stage renal disease and RV dysfunction, as assessed by ECHO, are at higher risk of death during the first 6 months after dialysis was initiated than patients with normal RV function.

TRANSLATIONAL OUTLOOK: Additional research is needed to understand the prevalence of SHD and identify predictors of early mortality in patients who start dialysis.

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APPENDIX For an expanded Methods section and supplemental tables, please see the online version of this article.