

Prevalence and Outcomes of Left-Sided Valvular Heart Disease Associated With Chronic Kidney Disease

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Background—Chronic kidney disease (CKD) is an adverse prognostic marker for valve intervention patients; however, the prevalence and related outcomes of valvular heart disease in CKD patients is unknown.

Methods and Results—Included patients underwent echocardiography (1999–2013), had serum creatinine values within 6 months before index echocardiogram, and had no history of valve surgery. CKD was defined as diagnosis based on the *International Classification of Diseases, Ninth Revision* or an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 . Qualitative assessment determined left heart stenotic and regurgitant valve lesions. Cox models assessed CKD and aortic stenosis (AS) interaction for subsequent mortality; analyses were repeated for mitral regurgitation (MR). Among 78 059 patients, 23 727 (30%) had CKD; of these, 1326 were on hemodialysis. CKD patients were older; female; had a higher prevalence of hypertension, hyperlipidemia, diabetes, history of coronary artery bypass grafting/percutaneous coronary intervention, atrial fibrillation, and heart failure \geq mild AS; and \geq mild MR (all $P<0.001$). Five-year survival estimates of mild, moderate, and severe AS for CKD patients were 40%, 34%, and 42%, respectively, and 69%, 54%, and 67% for non-CKD patients. Five-year survival estimates of mild, moderate, and severe MR for CKD patients were 51%, 38%, and 37%, respectively, and 75%, 66%, and 65% for non-CKD patients. Significant interaction occurred among CKD, AS/MR severity, and mortality in adjusted analyses; the CKD hazard ratio increased from 1.8 (non-AS patients) to 2.0 (severe AS) and from 1.7 (non-MR patients) to 2.6 (severe MR).

Conclusions—Prevalence of at least mild AS and MR is substantially higher and is associated with significantly lower survival among patients with versus without CKD. There is significant interaction among CKD, AS/MR severity, and mortality, with increasingly worse outcomes for CKD patients with increasing AS/MR severity. (*J Am Heart Assoc.* 2017;6:e006044. DOI: 10.1161/JAHA.117.006044.)

Key Words: aortic stenosis • chronic kidney disease • echocardiography • mitral regurgitation • mortality

Previous small studies have demonstrated an association between aortic stenosis (AS), mitral annular calcification, and end-stage renal disease.^{1–6} Thoracic surgery database studies and percutaneous valve intervention trials have shown that among patients undergoing valve surgery or intervention, the presence of chronic kidney disease (CKD) is associated

with a greater risk of death.^{7–9} However, there is a scarcity of longitudinal data examining the prevalence of valve disease and related outcomes among CKD patients. Expert consensus documents do not make specific recommendations regarding follow-up and management in CKD patients. Furthermore, the efficacy of traditional guideline-recommended approaches for treatment of the most common valve lesions requiring surgery (eg, AS and mitral regurgitation [MR]) are unknown.¹⁰

With the advent of safer percutaneous methods to treat valve disease,^{8,9,11} more treatment options exist for CKD patients. Consequently, a comprehensive evaluation of the natural history, treatment strategies, and outcomes associated with aortic and mitral valve disease in CKD patients is needed. Using a large echocardiographic registry, we sought to define (1) the echocardiographic characteristics of CKD patients and (2) the prevalence and outcomes of aortic and mitral valve disease among patients with versus without CKD. We hypothesized (1) that there is a higher prevalence of left-

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Clinical Perspective

What Is New?

- This study is the largest to date looking at the prevalence of left-sided valvular heart disease in patients with chronic kidney disease (CKD) compared with those without CKD.
- In addition, survival and rates of surgical intervention were compared between the groups.
- The prevalence of at least mild left-sided valvular disease in the CKD group was more than double than that in the non-CKD group.
- The 5-year mortality rate of patients with at least mild AS/MR was >50% greater in the CKD group than in the non-CKD group.

What Are the Clinical Implications?

- The presence of CKD should raise suspicion of significant valvular heart disease.
- Patients with CKD and valvular heart disease are at a high risk of mortality.
- Management of this complex cohort of patients requires informed, shared decision making between clinician and patient.
- Prospective trials targeting this population are needed to better define optimal management for these patients.

sided valve disease (specifically, AS and MR) in patients with CKD and (2) that AS and MR outcomes among patients with CKD or end-stage renal disease are worse, after accounting for differences in age and comorbid conditions.

Methods

Data Sources

The primary data source for this study was the Duke Echocardiography Laboratory Database (DELD), which has been described previously.^{12–14} DELD includes a prospectively maintained digital archive of all clinical echocardiography studies performed at Duke University Health System, linked to a corresponding searchable reporting database since 1995. Basic demographic information is included in DELD, and clinical data on patients are derived from the Duke Decision Support Repository (DSR) and Duke Databank for Cardiovascular Disease (DDCD).¹⁵ The DSR incorporates data from clinical and billing sources, including demographic information; *International Classification of Diseases, Ninth Revision* (ICD-9) codes; and Current Procedure Terminology codes. The DDCD comprises prospectively gathered clinical data and long-term follow-up information on all patients undergoing cardiac catheterization and/or cardiac surgery at Duke University Health System since 1969.¹⁶

Identification of the Study Population

The study population consisted of patients aged ≥ 18 years who had full clinical echocardiographic examinations (January 1, 1999–December 31, 2013) and serum creatinine values within 6 months before their echocardiogram. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2 , calculated from the median of creatinine values within 6 months before echocardiogram, or an ICD-9 diagnosis of CKD. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁷ Based on eGFR, patients were classified as *normal* (≥ 60 mL/min per 1.73 m^2), *mild CKD* (45–59 mL/min per 1.73 m^2), *moderate CKD* (30–44 mL/min per 1.73 m^2), or *severe CKD* (< 30 mL/min per 1.73 m^2). Patients with CKD on hemodialysis were identified using administrative data with ICD-9 diagnosis codes. Patients were excluded if they had a history of any prior valve intervention (surgical or percutaneous), congenital heart disease, cirrhosis, primary hyperparathyroidism, prior heart transplantation, or metastatic cancer at the time of the index echocardiogram.

Echocardiographic Data

Echocardiographic data were extracted from DELD. The date of the first echocardiogram served as the baseline date for study analyses. The presence of AS and MR was derived from the clinical report. MR was classified as *none*, *trivial*, *mild*, *moderate*, or *severe* mainly by visual assessment integrating color Doppler data from multiple acoustic windows, continuous wave Doppler MR signal, and pulmonary vein spectral Doppler profiles. In our laboratory compared with other semiquantitative and quantitative methods, visual estimation of MR has the best interobserver variability (intraclass correlation coefficient: 0.92).¹⁴ The severity of AS was graded by the reading physician with integration of information from (1) continuous wave Doppler aortic mean pressure gradient; (2) continuous wave Doppler aortic jet peak velocity; and (3) calculated aortic valve area, as recommended in the period-specific guidelines.¹⁰ Aortic regurgitation and mitral stenosis were classified as *none/trivial*, *mild*, *moderate*, or *severe*, according to guideline criteria.¹⁰ Left ventricular ejection fraction was obtained from the echocardiographic report and was visually estimated according to standard laboratory practice. Left ventricular hypertrophy was graded according to left ventricular septal thickness as *normal* (0.6–1.0 cm), *mild* (1.1–1.3 cm), *moderate* (1.4–1.6 cm), or *severe* (> 1.7 cm).¹⁸ Outcomes analyses focused on the 2 most commonly operated valve lesions: AS and MR.⁷ Left atrial/ventricular internal dimensions and estimated right ventricular systolic pressures recorded in DELD were obtained at the time of the echocardiographic examination, according to standard recommendations and laboratory practice.

Clinical Data

Information on past medical and cardiovascular history at baseline was obtained from DSR administration and billing resources, as well as the DDCD.^{12,15,16} For purposes of identifying comorbid conditions, all instances of myocardial infarction, coronary artery bypass grafting (CABG) surgery, and percutaneous coronary intervention (PCI) recorded before the index echocardiography were defined as prior cardiovascular events. DSR recordings were accepted as prior medical history if entered at any time before and up until 30 days after the index echocardiogram for conditions including hypertension, diabetes mellitus, hyperlipidemia, congestive heart failure, atrial fibrillation, peripheral artery disease, cerebral vascular disease, chronic obstructive pulmonary disease, and history of smoking. This time cutoff was chosen to allow for a delay in hospital coding.

DDCD records ongoing clinical follow-up of all patients at 6 months, 1 year, and annually thereafter through self-administered questionnaires and telephone follow-up for nonresponders. Patients who cannot be contacted through this mechanism have vital status determined through National Death Index and Social Security Death Index searches.¹⁹ The vital status of patients not followed in DDCD was queried through national death databases. Patients who were not followed by DDCD and not found in searches of national index death databases were censored at the last available contact date available in DSR. The outcome assessed was all-cause death; follow-up was administratively censored at 5 years after echocardiogram.

Data Analysis

Baseline clinical characteristics and echocardiographic findings were summarized according to CKD presence. Continuous data were expressed as median (interquartile range; 25th–75th percentiles); categorical variables were described as count (percentage). Comparisons between groups were made using the Pearson χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Multinomial logistic regression assessed the relationship between CKD status and increased severity of AS, adjusting for age; year of echo; race; sex; and history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, and prior CABG/PCI. An odds ratio (OR) and 95% confidence interval (CI) describe the increased odds of severe AS (as opposed to no AS) associated with CKD (versus no CKD) and end-stage renal disease on hemodialysis (versus no CKD).

The relationship of AS and CKD with subsequent mortality through 5 years after echocardiogram was assessed by Kaplan–Meier plots. Patients known to have undergone aortic valve surgery were censored at the time of the surgery. Cox proportional hazards models further assessed this

relationship using AS and CKD interaction status. Models were further adjusted for year of echocardiogram; age; sex; race; and history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, CABG, or PCI. Adjustment variables were determined to be possible confounders by clinical knowledge and univariable relationships. Adjustment covariates were assessed for linearity and proportional hazards assumptions, and transformations were applied, as needed. Using interaction test results, we reported the hazard ratios for CKD versus no CKD at each level of AS severity. The analysis was repeated using the same algorithm for MR. Finally, to assess the overall association of CKD with mortality among patients receiving echocardiography, a Cox model was created to assess for differences in mortality risk between CKD and non-CKD groups, adjusting for baseline clinical and echocardiographic covariates. All statistical computations were generated using SAS version 9.3 or higher (SAS Institute).

Ethics

This was a retrospective study, so patient consent was waived. This study was approved by the Duke institutional review board.

Role of Funding Source

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Results

Baseline Characteristics

Of 157 586 total patients in the echocardiographic database, 20 743 patients were excluded for being aged <18 years and for the presence of any of the following diagnoses on incident echocardiogram: heart transplant or ventricular assist device, cirrhosis, primary hyperparathyroidism, prior valve surgery, and metastatic cancer. Of the remaining 136 843 patients, 88 626 had at least 1 creatinine value within 6 months of the echocardiogram available for review; of these, 78 059 patients were seen between the years 1999–2013 and composed the final cohort.

Of the 78 059 patients in this study, 23 088 met the definition for CKD solely by eGFR criteria (10 533 with GFR 45.0–59.9 mL/min, and 12 555 with GFR <45 mL/min; Table 1), and 639 patients met the definition of CKD by ICD-9 diagnosis alone, for a total of 23 727 patients (30%;

Table 1. Baseline Clinical Characteristics Stratified by eGFR

Characteristic	Normal (eGFR ≥ 60) (n=54 971)	Mild (eGFR 45–59) (n=10 533)	Moderate (eGFR 30–44) (n=6480)	Severe (eGFR <30) (n=6075)	P Value
Age, y					<0.001
n	54 971	10 533	6480	6075	
Median (25th–75th)	56 (44–67)	72 (63–79)	74 (65–81)	67 (56–77)	
Sex					0.036
Male	26 900/54 971 (48.9)	5153/10 533 (48.9)	3051/6480 (47.1)	2990/6075 (49.2)	
Female	28 071/54 971 (51.1)	5380/10 533 (51.1)	3429/6480 (52.9)	3085/6075 (50.8)	
Race					<0.001
White	34 830/53 432 (65.2)	7417/10 250 (72.4)	4441/6315 (70.3)	3071/5910 (52.0)	
Black	15 771/53 432 (29.5)	2454/10 250 (23.9)	1621/6315 (25.7)	2563/5910 (43.4)	
Other	2831/53 432 (5.3)	379/10 250 (3.7)	253/6315 (4.0)	276/5910 (4.7)	
History of hyperlipidemia	24 366/54 971 (44.3)	5917/10 533 (56.2)	3594/6480 (55.5)	2893/6075 (47.6)	<0.001
History of hypertension	35 261/54 971 (64.1)	8608/10 533 (81.7)	5455/6480 (84.2)	5355/6075 (88.1)	<0.001
History of CHF	13 492/54 971 (24.5)	4637/10 533 (44.0)	3370/6480 (52.0)	3273/6075 (53.9)	<0.001
History of diabetes mellitus	14 707/54 971 (26.8)	3934/10 533 (37.3)	2839/6480 (43.8)	3177/6075 (52.3)	<0.001
History of CABG/PCI	6698/54 971 (12.2)	2051/10 533 (19.5)	1276/6480 (19.7)	946/6075 (15.6)	<0.001
History of atrial fibrillation	11 096/54 044 (20.5)	3527/10 362 (34.0)	2360/6413 (36.8)	1840/6034 (30.5)	<0.001

Data shown as count/total (percentage) unless otherwise noted. CABG indicates coronary artery bypass graft surgery; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; PCI, percutaneous intervention.

Table 2) who had CKD; of these, 1326 were on hemodialysis. Patients with CKD were older (median age: 72 years) and more frequently female (51% versus 49%), but those on hemodialysis were younger (median age: 59 years) and more frequently male. CKD patients were predominantly white, but those on hemodialysis were predominantly black. A higher prevalence of hypertension (83.4% versus 63.9%), hyperlipidemia (53.1% versus 44.1%), diabetes mellitus (41.7% versus 26.5%), history of CABG/PCI (18.7% versus 12.1%), congestive heart failure (47.7% versus 24.3%), and atrial fibrillation (33.8% versus 20.4%) was found among those with CKD compared with those without CKD (all $P<0.001$; Tables 1 and 2). The echocardiographic findings of CKD patients included significantly higher left atrial and left ventricular dimensions, lower left ventricular systolic function, higher prevalence of left ventricular hypertrophy, diastolic dysfunction, and estimated right ventricular systolic pressure $\geq 35\%$ (Tables 3 and 4).

Prevalence of Valve Disease Among Patients With Versus Without CKD

Patients with CKD more frequently had \geq mild AS compared with patients without CKD (9.5% versus 3.5%), as well as at least mild MR (42.9% versus 23.8%). Similar trends were noted for other valve lesions like mitral stenosis (2.2% versus

1.1%) and aortic regurgitation (19.1% versus 10.1%) $P<0.001$. The prevalence of AS, aortic regurgitation, mitral stenosis, and MR stratified by eGFR groups is presented in Figure 1.

After adjusting for age, year of echocardiogram, race, sex, history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, and prior CABG or PCI, patients with CKD had higher odds of having mild AS (OR: 1.30; 95% CI, 1.18–1.43) and moderate AS (OR: 1.22; 95% CI, 1.07–1.4) but not severe AS (OR: 1.08; 95% CI, 0.93–1.25) compared with patients without CKD ($P<0.001$). Patients on hemodialysis had higher odds of having mild AS (OR: 2.51; 95% CI, 1.90–3.32) and moderate AS (OR: 2.06; 95% CI, 1.39–3.05) but not severe AS (OR: 1.27; 95% CI, 0.73–2.21) compared with patients without CKD ($P<0.001$). There was a sex \times CKD interaction for AS ($P<0.001$). The corresponding CKD estimates for women are OR 1.38 (95% CI, 1.21–1.59) for mild AS, OR 1.35 (95% CI, 1.10–1.65) for moderate AS, and OR 1.16 (95% CI, 0.93–1.43) for severe AS; the estimates for men are OR 1.23 (95% CI, 1.08–1.41) for mild AS, OR 1.14 (95% CI, 0.96–1.37) for moderate AS, and OR 1.02 (95% CI, 0.83–1.26) for severe AS.

Using the same adjustment variables as noted, patients with CKD had higher odds of having mild MR (OR: 1.32; 95% CI, 1.27–1.38), moderate MR (OR: 1.81; 95% CI, 1.68–1.95), and severe MR (OR: 1.82; 95% CI, 1.61–2.06) compared with patients without CKD ($P<0.0001$). These associations were

Table 2. Clinical Characteristics Stratified by No CKD, ESRD on HD, and CKD

Characteristic	Non-CKD (n=54 332)	ESRD on HD (n=1326)	CKD (n=22 401)	P Value
Age, y				<0.001
n	54 332	1326	22 401	
Median (25th–75th)	56 (44–67)	59 (48–68)	72 (62–80)	
Sex				0.004
Male	26 467/54 332 (48.7)	707/1326 (53.3)	10 920/22 401 (48.7)	
Female	27 865/54 332 (51.3)	619/1326 (46.7)	11 481/22 401 (51.3)	
Race				<0.001
White	34 533/52 795 (65.4)	392/1322 (29.7)	14 834/21 790 (68.1)	
Black	15 453/52 795 (29.3)	877/1322 (66.3)	6079/21 790 (27.9)	
Other	2809/52 795 (5.3)	53/1322 (4.0)	877/21 790 (4.0)	
History of hyperlipidemia	23 979/54 332 (44.1)	888/1326 (67.0)	11 903/22 401 (53.1)	<0.001
History of hypertension	34 691/54 332 (63.9)	1300/1326 (98.0)	18 688/22 401 (83.4)	<0.001
History of CHF	13 208/54 332 (24.3)	871/1326 (65.7)	10 693/22 401 (47.7)	<0.001
History of diabetes mellitus	14 398/54 332 (26.5)	910/1326 (68.6)	9349/22 401 (41.7)	<0.001
History of CABG/PCI	6553/54 332 (12.1)	231/1326 (17.4)	4187/22 401 (18.7)	<0.001
History of atrial fibrillation	10 912/53 405 (20.4)	436/1326 (32.9)	7475/22 122 (33.8)	<0.001

Data shown as count/total (percentage) unless otherwise noted. CABG indicates coronary artery bypass grafting; CHF, congestive heart failure; CKD, chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysis; PCI, percutaneous coronary intervention.

more pronounced among CKD patients on hemodialysis (mild MR: OR: 1.79 [95% CI, 1.57–2.04]; moderate MR: OR: 2.35 [95% CI, 1.91–2.87]; severe MR: OR: 1.66 [95% CI, 1.16–2.39]). There was a sex×CKD interaction for MR ($P<0.001$). The corresponding CKD estimates for women are OR 1.28 (95% CI, 1.21–1.36) for mild MR, OR 1.78 (95% CI, 1.60–1.96) for moderate MR, and OR 1.87 (95% CI, 1.56–2.24) for severe MR; the estimates for men are OR 1.36 (95% CI, 1.28–1.45) for mild MR, OR 1.84 (95% CI, 1.66–2.05) for moderate MR, and OR 1.75 (95% CI, 1.48–2.08) for severe MR.

Survival of Patients With AS, MR, and CKD

The median follow-up among the 78 059 patients was 3.05 years (interquartile range: 0.97–5.00), which amounts to 238 080 person-years. On follow-up, 416 of 2203 patients (18.8%) with at least mild AS and CKD, and 526 of 1925 patients (27.3%) with at least mild AS without CKD underwent aortic valve replacement. The survival estimates at 1, 3, and 5 years for all degrees of AS and MR severity were significantly worse for patients with versus without CKD. The 5-year survival estimates of patients with mild, moderate, and severe AS and CKD were 40%, 34%, and 42%, respectively, compared with 69%, 54%, and 67% for mild, moderate, and severe AS without CKD, respectively. Kaplan–Meier survival plots stratified by AS severity and CKD presence

are displayed in Figure 2A. Kaplan–Meier plots stratified by AS severity and CKD presence with censoring at aortic valve surgery are presented in Figure 2B.

A total of 469 of 10 001 patients (4.7%) with at least mild MR and CKD and 625 of 13 106 patients (4.8%) with at least mild MR without CKD underwent mitral valve surgery within 5 years of the index echocardiographic study. The 5-year survival estimates of patients with mild, moderate, and severe MR and CKD were 51%, 38%, and 37%, respectively, compared with 75%, 66%, and 65% for mild, moderate, and severe MR without CKD, respectively. Kaplan–Meier survival plots stratified by MR severity and presence of CKD are displayed in Figure 3A and with censoring at mitral valve surgery in Figure 3B.

Survival of Patients With CKD

Survival rates at 1, 3, and 5 years were markedly lower among patients with versus without CKD (Figure 4). After adjustment for clinical and echocardiographic characteristics, CKD presence was independently associated with mortality (hazard ratio: 1.83; 95% CI, 1.77–1.89). In a multivariable model, there was a significant interaction between CKD and AS/MR in terms of mortality. The relationship of CKD and mortality was more pronounced among patients with increasing severity of MR and AS (Table 5).

Table 3. Baseline Echocardiographic Characteristics Stratified by eGFR

Characteristic	Normal (eGFR ≥ 60) (n=54 971)	Mild (eGFR 45–59) (n=10 533)	Moderate (eGFR 30–44) (n=6480)	Severe (eGFR <30) (n=6075)	P Value
Echocardiographic characteristics					
Mitral regurgitation					<0.001
No/trivial	41 865/54 971 (76.2)	6252/10 533 (59.4)	3551/6480 (54.8)	3284/6075 (54.1)	
Mild	10 357/54 971 (18.8)	3115/10 533 (29.6)	2074/6480 (32.0)	1877/6075 (30.9)	
Moderate	2061/54 971 (3.7)	920/10 533 (8.7)	652/6480 (10.1)	691/6075 (11.4)	
Severe	688/54 971 (1.3)	246/10 533 (2.3)	203/6480 (3.1)	223/6075 (3.7)	
Mitral stenosis					<0.001
No/trivial	54 381/54 971 (98.9)	10 313/10 533 (97.9)	6308/6480 (97.3)	5943/6075 (97.8)	
Mild	241/54 971 (0.4)	124/10 533 (1.2)	105/6480 (1.6)	83/6075 (1.4)	
Moderate	221/54 971 (0.4)	70/10 533 (0.7)	48/6480 (0.7)	34/6075 (0.6)	
Severe	128/54 971 (0.2)	26/10 533 (0.2)	19/6480 (0.3)	15/6075 (0.2)	
Aortic regurgitation					<0.001
No/trivial	49 434/54 971 (89.9)	8497/10 533 (80.7)	5165/6480 (79.7)	5006/6075 (82.4)	
Mild	4493/54 971 (8.2)	1716/10 533 (16.3)	1106/6480 (17.1)	842/6075 (13.9)	
Moderate	853/54 971 (1.6)	275/10 533 (2.6)	189/6480 (2.9)	180/6075 (3.0)	
Severe	191/54 971 (0.3)	45/10 533 (0.4)	20/6480 (0.3)	47/6075 (0.8)	
Aortic stenosis					<0.001
No/trivial	53 045/54 970 (96.5)	9561/10 533 (90.8)	5822/6480 (89.8)	5502/6075 (90.6)	
Mild	1033/54 970 (1.9)	465/10 533 (4.4)	333/6480 (5.1)	317/6075 (5.2)	
Moderate	488/54 970 (0.9)	265/10 533 (2.5)	180/6480 (2.8)	157/6075 (2.6)	
Severe	404/54 970 (0.7)	242/10 533 (2.3)	145/6480 (2.2)	99/6075 (1.6)	
Mitral annular calcification	4216/54 971 (7.7)	2001/10 533 (19.0)	1475/6480 (22.8)	1451/6075 (23.9)	<0.001
LV ejection fraction					<0.001
n	54 869	10 496	6449	6055	
Median (25th–75th)	55 (55–55)	55 (45–55)	55 (45–55)	55 (40–55)	
Increased LV wall thickness					<0.001
None	30 133/54 122 (55.7)	4091/10 296 (39.7)	2296/6307 (36.4)	1862/5918 (31.5)	
Mild	17 912/54 122 (33.1)	4191/10 296 (40.7)	2615/6307 (41.5)	2381/5918 (40.2)	
Moderate	5317/54 122 (9.8)	1699/10 296 (16.5)	1174/6307 (18.6)	1340/5918 (22.6)	
Severe	760/54 122 (1.4)	315/10 296 (3.1)	222/6307 (3.5)	335/5918 (5.7)	
RVSP, mm Hg					<0.001
<35	10 336/17 188 (60.1)	2051/4619 (44.4)	1136/3095 (36.7)	777/2736 (28.4)	
≥ 35	6852/17 188 (39.9)	2568/4619 (55.6)	1959/3095 (63.3)	1959/2736 (71.6)	
Diastolic dysfunction					<0.001
Grade 1	14 428/27 241 (53.0)	3419/4569 (74.8)	1955/2609 (74.9)	1555/2295 (67.8)	
Grade 2	2752/27 241 (10.1)	513/4569 (11.2)	303/2609 (11.6)	320/2295 (13.9)	
Grade 3–4	316/27 241 (1.2)	107/4569 (2.3)	98/2609 (3.8)	98/2295 (4.3)	
Normal	9745/27 241 (35.8)	530/4569 (11.6)	253/2609 (9.7)	322/2295 (14.0)	
LV size					<0.001
Normal	50 123/54 924 (91.3)	9162/10 514 (87.1)	5539/6461 (85.7)	5178/6064 (85.4)	
Small	1293/54 924 (2.4)	375/10 514 (3.6)	254/6461 (3.9)	219/6064 (3.6)	
Mildly enlarged	2150/54 924 (3.9)	584/10 514 (5.6)	404/6461 (6.3)	440/6064 (7.3)	

Continued

Table 3. Continued

Characteristic	Normal (eGFR ≥ 60) (n=54 971)	Mild (eGFR 45–59) (n=10 533)	Moderate (eGFR 30–44) (n=6480)	Severe (eGFR <30) (n=6075)	P Value
Moderately enlarged	772/54 924 (1.4)	224/10 514 (2.1)	146/6461 (2.3)	144/6064 (2.4)	
Severely enlarged	586/54 924 (1.1)	169/10 514 (1.6)	118/6461 (1.8)	83/6064 (1.4)	
LA diameter, cm	47 460	8653	5248	4957	<0.001
n (median, 25th–75th)	3.7 (3.2–4.1)	3.9 (3.5–4.5)	4.0 (3.5–4.5)	4.1 (3.6–4.6)	
LV end-diastolic dimension, cm	48 420	8887	5389	5083	<0.001
n (median, 25th–75th)	4.5 (4.1–5.0)	4.5 (4.0–5.1)	4.5 (4.0–5.1)	4.7 (4.2–5.2)	
LV end-systolic dimension, cm	48 235	8847	5355	5055	<0.001
n (median, 25th–75th)	3.0 (2.6–3.5)	3.0 (2.5–3.7)	3.1 (2.5–3.8)	3.2 (2.7–4.0)	

Data shown as count/total (percentage) unless otherwise noted. eGFR indicates estimated glomerular filtration rate; LA, left atrial; LV, left ventricular; RVSP, right ventricular systolic pressure.

Discussion

The main findings of this large observational echocardiographic study demonstrate that CKD is associated with worse echocardiographic characteristics and clinical outcomes and that left-sided valve disease is highly prevalent and associated with higher mortality among CKD patients. CKD patients are more likely to die of cardiovascular events than of kidney failure.²⁰ Observational registries, prospective community cohort studies, and substudies of large randomized trials have previously established the poor prognosis associated with CKD presence. Also well recognized is the fact that cardiovascular disease is the leading cause of morbidity and mortality in this group of patients,^{21–23} yet there is a lack of large imaging registries, so the cardiac morphologic characteristics associated with CKD and hemodialysis have not been described comprehensively. As with clinical risk factors, the present study found a higher prevalence of known echocardiographic poor prognostic markers of both the left and right ventricle among CKD patients. Left ventricular hypertrophy, as well as left ventricular systolic and diastolic dysfunction, were found to be more prevalent among patients with CKD and end-stage renal disease on hemodialysis compared with those without CKD. Along with enlarged left atrial/ventricular dimensions, CKD patients were also much more likely to have elevated estimated right ventricular systolic pressures. Although these morphologic characteristics may largely reflect left ventricular end-organ damage from diabetes mellitus and hypertension (which are known CKD risk factors), they may also represent compensatory changes in response to pressure/volume overload in CKD patients not yet on hemodialysis. Several small studies previously documented the prognostic impact of left ventricular, systolic, and diastolic dysfunction, as well as higher left ventricular mass, in hemodialysis and prehemodialysis groups of patients.^{24–27}

Nonetheless, these cardiac morphologic characteristics may represent end-organ damage or compensatory responses, but they herald poor outcomes as prognostic indicators. Whether these imaging markers can serve as triggers for specific intervention or alter the timing of such intervention to ultimately affect outcomes in a salutary fashion is unknown.

The present study confirms previously reported findings of the high burden of clinical cardiovascular risk factors among patients with kidney disease. This clustering and high prevalence of cardiovascular risk factors likely represents shared disease pathways in kidney and cardiovascular disease.²⁸ The same risk factors most likely also contribute to poor cardiovascular outcomes among CKD patients; however, whether the tight control of these risk factors has the same beneficial effect in terms of disease progression or cardiovascular event reduction in CKD versus non-CKD patients is unclear and needs further investigation.^{29–33} Notably, the prevalence of coronary artery disease (CAD) risk factors in the present study was far greater than what was reported in prior investigations, which may be due to the nature of this observational cohort that included patients who underwent clinically ordered echocardiography, thereby representing a sicker patient group. The prevalence of these risk factors and the hazard associated with CKD were similar to findings from the VALIANT (Valsartan in Acute Myocardial Infarction) trial that enrolled post-myocardial infarction patients with evidence of heart failure.²¹

This investigation represents the largest-to-date inquiry into the prevalence of valve pathology among patients with CKD. This study found higher odds of AS and MR (after adjusting for age and comorbid conditions) among those with versus without CKD; this finding highlights the fact that although CKD may be a poor prognostic marker in valve

Table 4. Echocardiographic Characteristics Stratified by CKD, ESRD on HD, and No CKD

Echocardiographic Characteristics	Non-CKD (n=54 332)	ESRD (n=1326)	CKD (n=22 401)	P Value
Mitral regurgitation				<0.001
No/trivial	41 407/54 332 (76.2)	759/1326 (57.2)	12 786/22 401 (57.1)	
Mild	10 227/54 332 (18.8)	403/1326 (30.4)	6793/22 401 (30.3)	
Moderate	2024/54 332 (3.7)	129/1326 (9.7)	2171/22 401 (9.7)	
Severe	674/54 332 (1.2)	35/1326 (2.6)	651/22 401 (2.9)	
Mitral stenosis				<0.001
No/trivial	53 750/54 332 (98.9)	1289/1326 (97.2)	21 906/22 401 (97.8)	
Mild	236/54 332 (0.4)	19/1326 (1.4)	298/22 401 (1.3)	
Moderate	219/54 332 (0.4)	11/1326 (0.8)	143/22 401 (0.6)	
Severe	127/54 332 (0.2)	7/1326 (0.5)	54/22 401 (0.2)	
Aortic regurgitation				<0.001
No/trivial	48 864/54 332 (89.9)	1119/1326 (84.4)	18 119/22 401 (80.9)	
Mild	4440/54 332 (8.2)	160/1326 (12.1)	3557/22 401 (15.9)	
Moderate	839/54 332 (1.5)	33/1326 (2.5)	625/22 401 (2.8)	
Severe	189/54 332 (0.3)	14/1326 (1.1)	100/22 401 (0.4)	
Aortic stenosis				<0.001
No/trivial	52 433/54 331 (96.5)	1223/1326 (92.2)	20 274/22 401 (90.5)	
Mild	1024/54 331 (1.9)	60/1326 (4.5)	1064/22 401 (4.7)	
Moderate	478/54 331 (0.9)	29/1326 (2.2)	583/22 401 (2.6)	
Severe	396/54 331 (0.7)	14/1326 (1.1)	480/22 401 (2.1)	
LA and LV dimensions				<0.001
LA diameter cm median (IQR)	3.7 (3.2–4.1) 46 875	4.1 (3.6–4.6) 1170	4.0 (3.5–4.5) 18 273	
LVIDD, cm, median (IQR)				
LVISD, cm, median (IQR)				
LVEF%, median (IQR), n	55 (55–55) 54 231	55 (45–55) 1323	55 (45–55) 22 315	<0.001
Increased LV wall thickness				<0.001
None	29 901/53 491 (55.9)	301/1312 (22.9)	8180/21 840 (37.5)	
Mild	17 651/53 491 (33.0)	518/1312 (39.5)	8930/21 840 (40.9)	
Moderate	5197/53 491 (9.7)	398/1312 (30.3)	3935/21 840 (18.0)	
Severe	742/53 491 (1.4)	95/1312 (7.2)	795/21 840 (3.6)	
RVSP, mm Hg				<0.001
<35	10 227/16 960 (60.3)	168/536 (31.3)	3905/10 142 (38.5)	
≥35	6733/16 960 (39.7)	368/536 (68.7)	6237/10 142 (61.5)	
Diastolic dysfunction				<0.001
Normal	9650/26 829 (36.0)	126/633 (19.9)	1074/9252 (11.6)	
Grade 1	14 175/26 829 (52.8)	371/633 (58.6)	6811/9252 (73.6)	
Grade 2	2696/26 829 (10.0)	107/633 (16.9)	1085/9252 (11.7)	
Grade 3–4	308/26 829 (1.1)	29/633 (4.6)	282/9252 (3.0)	

CKD indicates chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysis; IQR, interquartile range; LA, left atrial; LVEF, left ventricular ejection fraction; LV, left ventricular; LVIDD, left ventricular internal diastolic dimension; LVISD, left ventricular internal systolic dimension; RVSP, right ventricular systolic pressure.

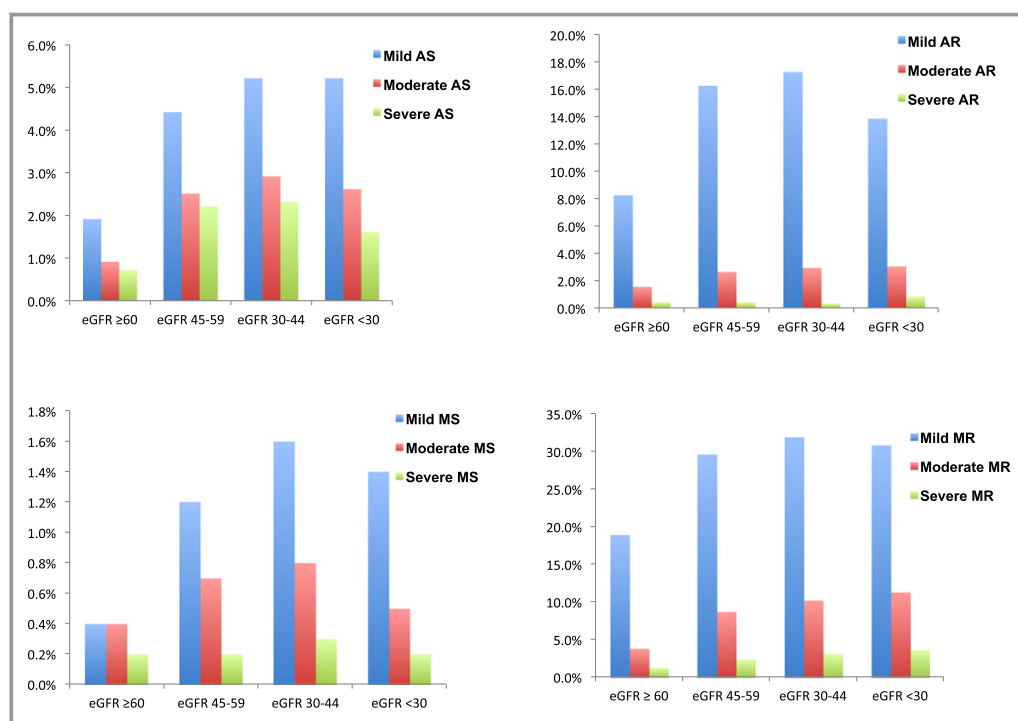


Figure 1. Prevalence of left-sided valve disease. Prevalence of left-sided valve disease stratified by eGFR. AR indicates aortic regurgitation; AS, aortic stenosis; eGFR, estimated glomerular filtration rate; MR, mitral regurgitation; MS, mitral stenosis.

disease, CKD patients suffer more from valve disease. A higher prevalence of MR likely reflects structural changes in the mitral valve apparatus: restricted motion of the annulus, leaflets, or chordae caused by calcification and reduced left ventricular wall motion related to CAD among CKD patients. The higher prevalence of AS in patients undergoing hemodialysis is well known and previously thought to be related to progressive valve calcification of the cardiac skeleton and valve leaflets—a result of altered or deranged calcium–phosphate metabolism and hypertension in end-stage renal disease.^{34,35} The present data extend the previous literature by demonstrating the increased prevalence of valve disease, even among patients with lesser degrees of renal dysfunction. This finding is unique and suggests the calcification process tied to declining GFR may start early and may be cumulative, thus providing a rationale for the higher frequency of AS in older adults.

Risk factors for CAD and known CAD were significantly more common in CKD patients.³⁵ Many studies have highlighted risk factors common to both CAD and valvular calcifications; the available data suggest that the metabolic milieu in CKD patients promotes early aging, atherosclerosis, and early calcification, thereby leading to disease pathologies with shared risk factor profiles like valvular heart disease, CAD, and CKD. Even for patients with mild valve disease and CKD, poor outcomes may be

related to concomitant CAD. The higher mortality among CKD patients with moderate and severe AS noted in our cohort may be a reflection of this phenomenon. In addition, worse outcomes among those with moderate AS could be explained by faster progression to severe AS on follow-up.¹² Although the unadjusted 5-year survival of patients with moderate AS appeared worse than those with severe AS, this difference was not significant after adjustment for other risk factors.

There was a significant association between CKD and mortality at each level of severity for AS after adjusting for other risk factors. Increasing severity of MR was associated with increasing mortality in those with CKD. The presence of AS increased the hazard for death among CKD patients, but the relationship of increasing hazard and increasing AS severity was not linear. At every level of AS and MR severity, CKD patients had worse outcomes than those with AS and MR but without CKD.

Our study provides significant evidence that CKD patients are at higher risk of valve disease and have worse outcomes across severity of valve disease than patients without CKD; however, this evidence is based on associations observed in this retrospective study. Despite our efforts to adjust for other risk factors, our conclusions are subject to effects of potential, unaccounted for, or unmeasured factors or biases caused by selection of our study cohort that might provide

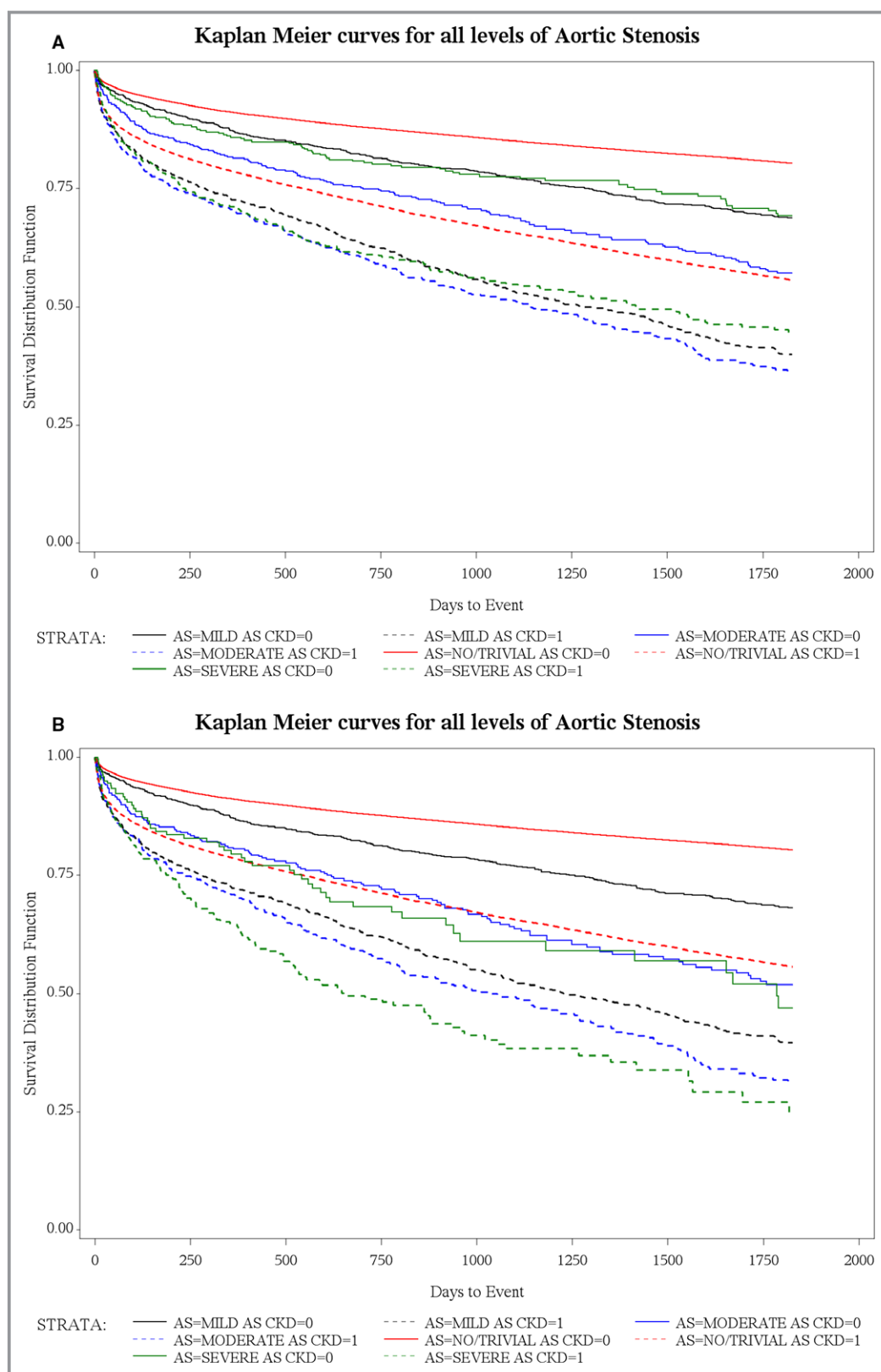


Figure 2. AS severity and presence of CKD. Kaplan–Meier survival plots stratified by (A) AS severity and presence of CKD and (B) AS severity and presence of CKD with censoring at aortic valve surgery. AS indicates aortic stenosis; CKD, chronic kidney disease.

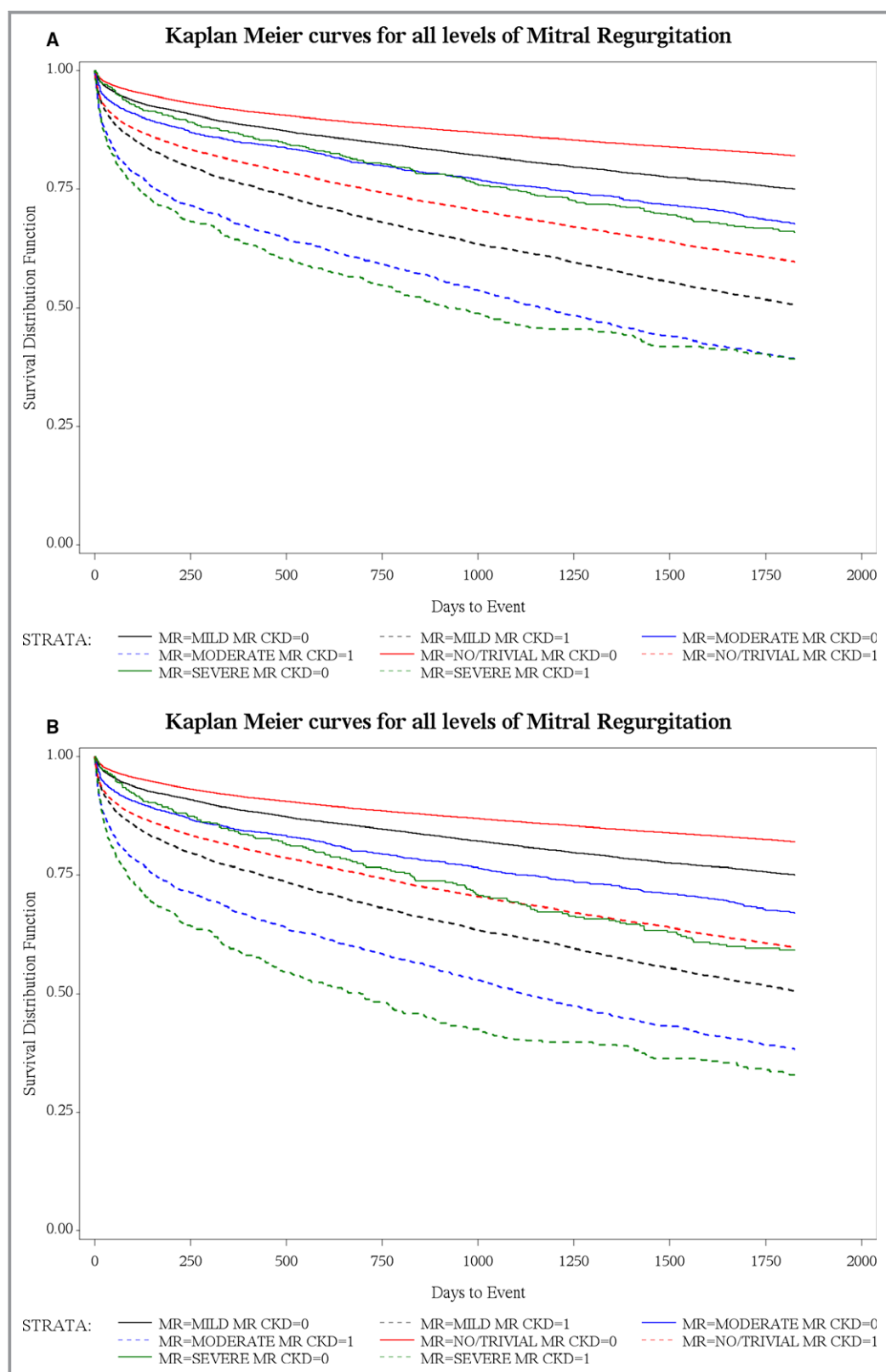


Figure 3. MR severity and presence of CKD. Kaplan–Meier survival plots stratified by (A) MR severity and presence of CKD and (B) MR severity and presence of CKD with censoring at mitral valve surgery. CKD indicates chronic kidney disease; MR, mitral regurgitation.

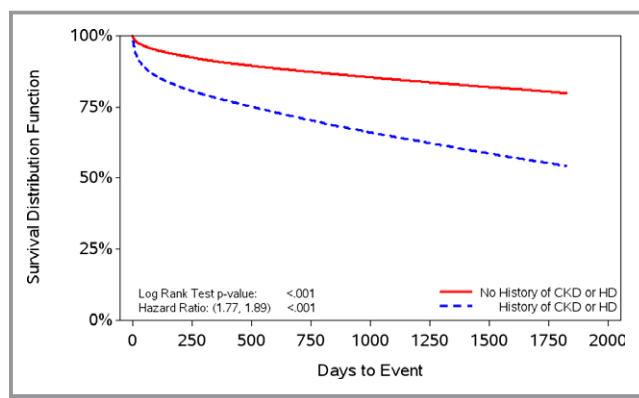


Figure 4. Presence of CKD. Kaplan–Meier survival plots stratified by presence of CKD. CKD indicates chronic kidney disease; HD, hemodialysis.

alternative explanations for these associations. Consequently, we have not established these relationships as causative, although we have speculated on potential mechanistic explanations.

These data suggest that CKD patients represent both a high-prevalence and a high-risk group for valve disease. Previous investigations have consistently shown CKD to be a poor prognostic marker among those receiving surgical or percutaneous intervention for valve disease. In a study of >400 000 valve surgeries included in the Society of Thoracic Surgery database, CKD was noted to be an important risk factor for operative mortality.⁷ Similarly, Smith found CKD to be an independent risk factor for poor outcomes among patients undergoing transcatheter aortic valve replacement for AS.^{36,37} The present study's findings, coupled with what we know about intervention outcomes in CKD patients, highlight a particularly difficult management dilemma faced by clinicians and patients. These data underscore a critical gap in expert consensus documents that, at present, do not make

specific recommendations regarding follow-up and management in CKD patients.^{10,38} Future research should be directed toward identifying methods to reduce surgical risk, exploring new methods for safer interventions, and testing novel therapies with the aim of retarding valve disease progression.

Clinical Implications

A high prevalence of echocardiographic abnormalities that are poor prognostic markers in CKD patients makes screening an important decision. Further investigation is needed to determine whether these abnormalities can serve as triggers for interventions or more aggressive therapy. Patients with CKD have higher prevalence of valve disease and worse outcomes and represent a higher surgical risk group. Prospective research and trials need to target this patient population to evaluate effectiveness of standard treatment approaches and to test novel therapies with the aim of retarding valve disease progression.

Limitations

This was a single-center observational study and, consequently, was subject to inherent limitations related to sampling and recruitment biases affecting generalizability of results. The potential for residual confounding remains despite multivariable adjustment of models. Because the echocardiography studies were clinically ordered, the sample that was examined likely represents a sicker group of patients; as a result, prevalence patterns may be higher than they are in the general population. One should expect that this disease enrichment could also have affected the non-CKD group. MR grades were based on clinical reports, which also formed the basis for clinical decision making. MR was primarily assessed through visual estimation. Compared with

Table 5. Adjusted* Association of CKD and Mortality at Levels of AS and MR

Severity of Valve Lesion/Presence of CKD	Aortic Stenosis, HR (95% CI)	P Value	Mitral Regurgitation, HR (95% CI)	P Value
None/CKD	1.832 (1.773–1.894)	<0.001	1.796 (1.725–1.87)	<0.001
Mild/CKD	2.193 (2.013–2.388)	<0.001	1.996 (1.904–2.093)	<0.001
Moderate/CKD	2.318 (2.068–2.599)	<0.001	2.567 (2.406–2.74)	<0.001
Severe/CKD	2.063 (1.794–2.371)	<0.001	2.687 (2.414–2.989)	<0.001
Mild/No CKD	1.156 (1.028–1.299)	0.015	1.117 (1.064–1.172)	<0.001
Moderate/No CKD	1.542 (1.326–1.793)	<0.001	1.372 (1.26–1.495)	<0.001
Severe/No CKD	1.069 (0.873–1.31)	0.518	1.405 (1.22–1.618)	<0.001

P<0.001 for interaction among valve lesion severity, CKD, and mortality. AS indicates aortic stenosis; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MR, mitral regurgitation.

*Adjusted for: age, year of echocardiogram, race, sex, history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, and prior coronary artery bypass grafting or percutaneous coronary intervention.

other semiquantitative and quantitative methods, visual estimation in our laboratory has the best reproducibility. Semiquantitative measurement of MR, although done as part of an integrated approach to grading MR, is not routinely captured in our reports and thus was not evaluated in this study. Despite these limitations, this study represents the largest inquiry to date into cardiac morphologic characteristics and valve pathology in CKD patients and raises important questions that will drive future research.

Conclusions

CKD is associated with worse echocardiographic characteristics and clinical outcomes. Left-sided valve disease is highly prevalent and associated with higher mortality among patients with CKD. There is a critical need for research directed toward the pathophysiology and management implications of valve disease in CKD patients.

Author Contributions

Dr Samad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr Samad obtained funding (NIH 1P30DK096493-01), contributed to the conception and design of the study, the data analysis, the data interpretation, the article drafting, and the critical revision of the article. Dr Sivak contributed to the data analysis, the data interpretation, the article drafting, and the critical revision of the article. Dr Phelan contributed to the data analysis, the data interpretation, the article drafting, and the critical revision of the article. Dr Schulte contributed to the data analysis, the data interpretation, the article drafting, and the critical revision of the article. Dr Patel contributed to the data analysis, the data interpretation, the article drafting, and the critical revision of the article. Dr Velazquez contributed to the conception and design of the study, data acquisition, analysis and interpretation, provided discretionary funds to complete the project, the article drafting, critical revision of the article.

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