Prevalence and Outcomes of Pericardial Effusion in Kidney Transplant Candidates

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Pericardial disease is a recognized manifestation of cardiovascular disease in the end-stage renal disease (ESRD) population, and can manifest as pericardial effusion, though the prognosis of pericardial disease in ESRD patients is unclear. In the modern era of renal replacement therapy, little is known about the prevalence and the implications of pericardial effusion in ESRD patients, its echocardiographic characteristics, and risk factors. We conducted a retrospective chart review on subjects > than 18 years of age with known ESRD who were undergoing outpatient evaluation for renal transplantation at Mayo Clinic Arizona between January 2001 and December 2015 and had baseline echocardiogram completed within 3 months of their initial evaluation. Patients with moderate sized pericardial effusions or larger were identified. The pericardial effusion cohort was age and gender matched with a cohort of patients with ESRD without pericardial effusion in a 1:2 fashion. 54 patients with moderate or greater sized pericardial effusion out of 2,820 patients that fit our inclusion criteria, corresponding to a prevalence of 1.9%. A total of 41 patients or 75.9%, had a moderate sized effusion. A total of 13 patients, or 24.1% had a large sized effusion, 7 of whom had tamponade physiology on echocardiography. The presence and size of the effusion was not predictive for worse outcomes. Hemodialysis duration was protective, but no other factors were predictive or protective in the development of moderate sized or larger pericardial effusions, including echocardiographic parameters. **(Am J Cardiol 2020;132:140−146)**

Cardiovascular related events are a common cause of morbidity and mortality in patients with chronic kidney disease and end stage renal disease (ESRD). Chronic kidney disease is an independent risk factor for the development of atherosclerotic coronary artery disease, arterial and vascular changes, structural heart disease, and dysrhythmias, which have been associated with increased morbidity and mortality.[1,2] Additionally, pericardial disease manifesting as effusion is a recognized manifestation of cardiovascular disease in the ESRD population. In ESRD patients undergoing dialysis, the reported prevalence of pericarditis in older literature (prior to 2001) has ranged from 2% to 21%, with one-third of all ESRD patients having a pericardial effusion of varying severity.[3] To our knowledge large population studies evaluating the long term cardiovascular outcomes in patients with ESRD and pericardial effusion are lacking in more recent studies. This study seeks to identify the prevalence of pericardial effusion in the ESRD population, whether it is associated with worse clinical outcomes, and what, if any, predictors, particularly echocardiographic predictors, there are for the development of pericardial effusion.

Methods

A retrospective chart review was conducted on all subjects greater than 18 years of age with ESRD who presented to Mayo Clinic Arizona between January 2001 and December 2015 for kidney transplant evaluation and had a baseline echocardiogram completed within 3 months of their initial evaluation.

The following patients were excluded from this study: those with (1) known prior history of pericardial disease before the diagnosis of end stage renal disease; (2) known malignancy; (3) systemic infection as the etiology for pericardial effusion; (4) known autoimmune disease at the time of the effusion; and (5) patients who developed a type I myocardial infarction within 30 days of the pericardial effusion (Figure 1).

A review of echocardiography data was then completed to assess which patients had moderate or larger sized pericardial effusion. Moderate pericardial effusion was defined as >1 cm wide during diastole, and large was defined as >2 cm during diastole based on standard American Society of Echocardiography (ASE) definitions of sizing.[4] Those with trivial or small sized pericardial effusion were not included in this study. Subjects with moderate or larger

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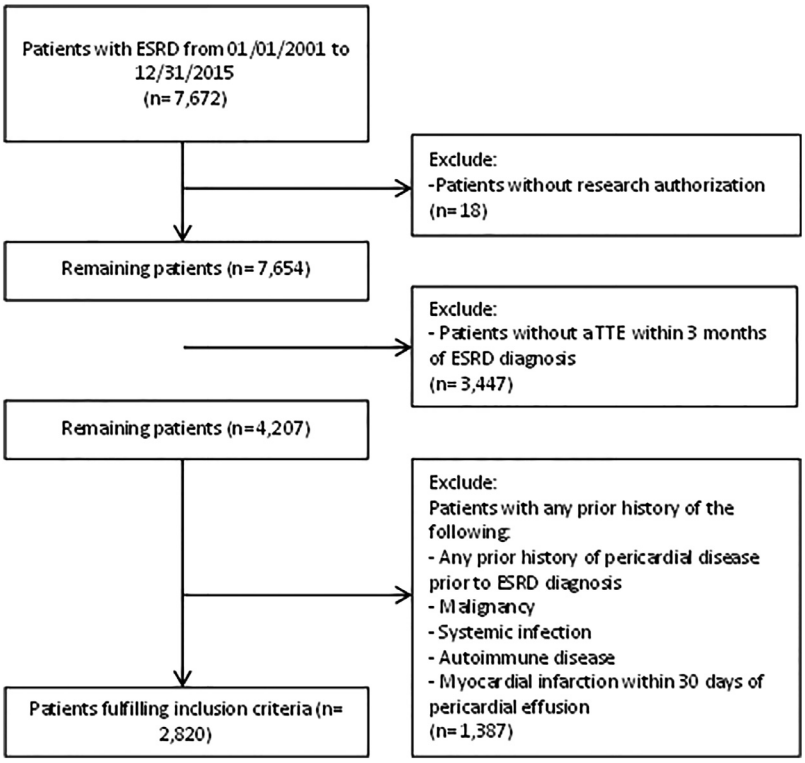

Figure 1. Patient inclusion and exclusion categorization flow diagram.

pericardial effusions were followed and had repeat echocardiography that allowed for the characterization of the effusion's evolution. The pericardial effusion cohort was age and gender match among a cohort of patients with ESRD in a 1:2 fashion randomly with 108 patients without pericardial effusion (Figure 2).

Statistical analysis was performed by using analysis of variance F-test for continuous variables. These are

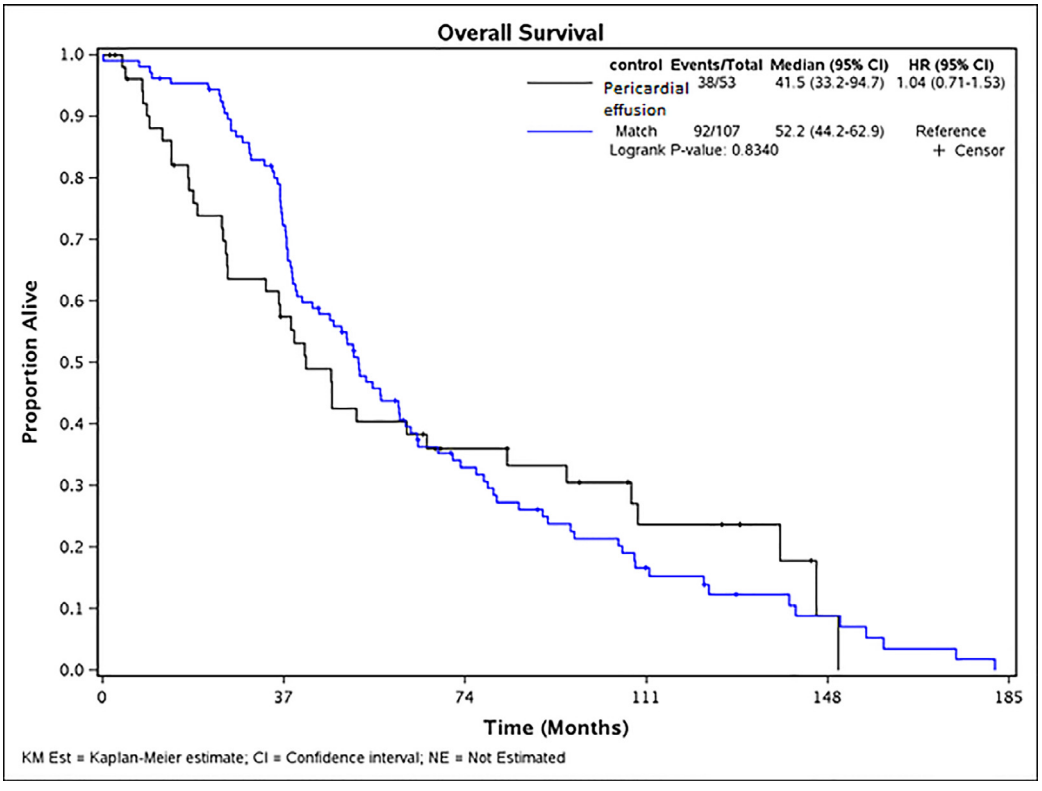

Figure 2. Overall Survival for pericardial effusion vs matched controls without pericardial effusion.

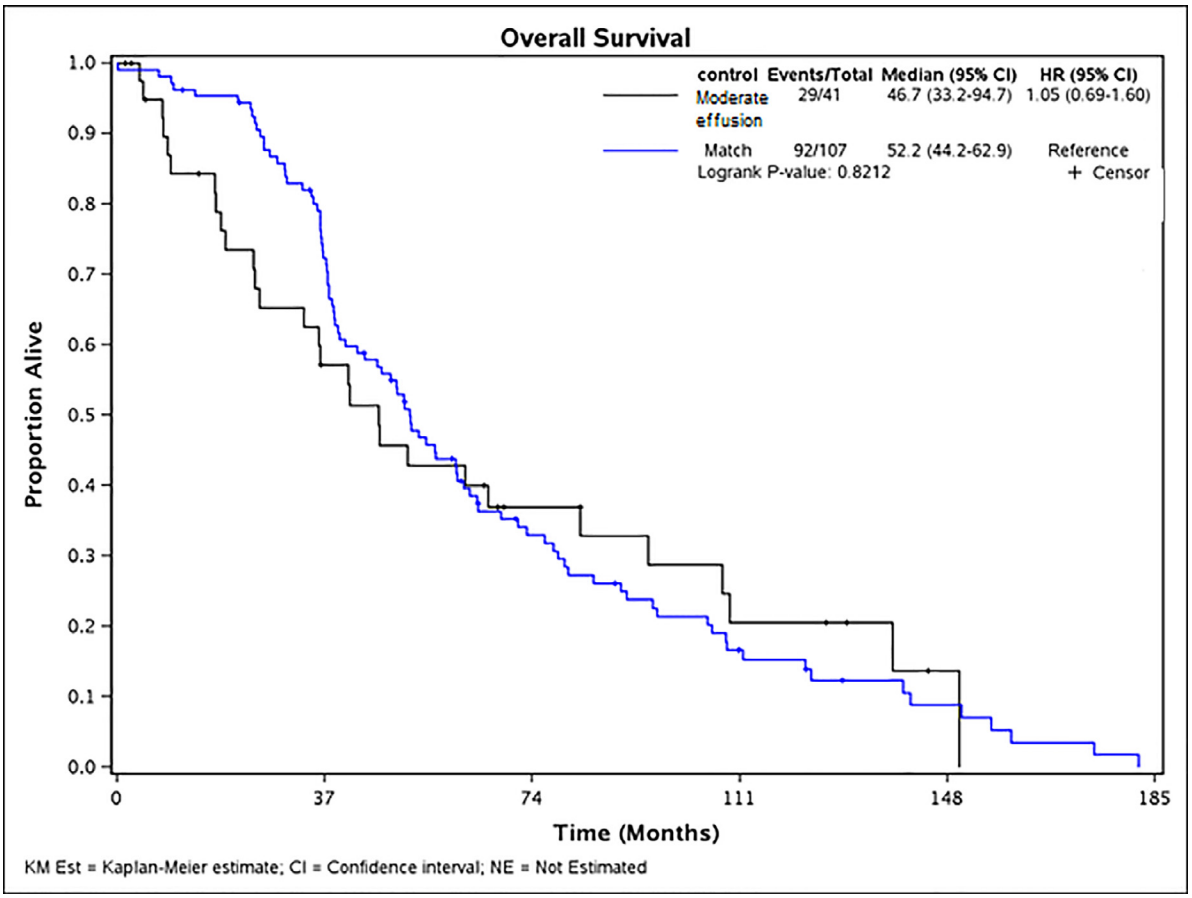

Figure 3. Overall survival for moderate sized pericardial effusion versus matched controls without pericardial effusion.

presented as a mean ± SD. For categorical and ordinal variables, the Chi-square test and Fisher's exact test was used and are presented as numbers and percentages. Kaplan-Meier estimates were used to generate survival curves with time-to-event analysis and were compared with the log-rank (Mantel-Cox) test (Figure 3).

Multivariable logistic regression analysis was performed to detect independent predictors for the development of pericardial effusion. Univariate clinical variables were chosen for analysis based on clinical relevance. Only univariate clinical variables with a p Value <0.05 were entered into a multivariable model. Results of the multivariable logistic regression analysis are presented as odds ratio with a 95% confidence interval. The C-statistic was used to verify the accuracy of the multivariable logistic regression model. A Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model. Statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc). The study was approved by the Institution Review Board at Mayo Clinic.

Results

A total of 2,820 patients with ESRD who fit our inclusion criteria were identified. Out of those 54 (1.9%) of patients were identified who had moderate size or greater pericardial effusion on initial echocardiography. The baseline demographic and laboratory characteristics of both the pericardial effusion cohort and matched controls are presented in Table 1. Basic demographic and clinical parameters were analyzed. Features of the pericardial effusion were also analyzed and are present in Table 2.

Out of the 54 patients we identified with moderate or larger pericardial effusion, 41 or 75.9%, had a moderate sized effusion. Thirteen, or 24.1% had a large sized effusion, and out of these 7 had tamponade physiology present on echocardiography. The 7 patients with tamponade physiology required hospitalization with procedural intervention for the effusion, with the rest treated with dialysis. Only 1 patient had a recurrence of a moderate sized effusion after documented resolution during follow-up (Figure 4).

After matching for age and gender, compared with those without pericardial effusion, those with pericardial effusion were noted to have a lower BSA, an increased rates of stroke, shorter dialysis vintage time, increased serum phosphorus and increased serum calcium. There was a trend towards more hyperparathyroidism. However, none of these, except for HD vintage, was predictive in the development of a moderate or larger sized effusion during multivariate analysis.

Multivariate analysis demonstrated that shorter hemodialysis (HD) vintage was independently a strong predictor of the development of a moderate or larger sized pericardial effusion (Table 3). Peritoneal dialysis (PD) vintage in contrast was not a predictor on either univariate or multivariate

Table 1
Patient demographics and characteristics

	Pericardial effusion		
Variable	Yes(n = 54)	No(n = 108)	p Value
Age (years)	52.8 ± 14.4	51.2 ± 14.8	0.55
Male	31 (57.4%)	62 (57.4%)	0.92
Female	23 (43.4%)	46 (42.6%)	
BMI (kg/m^2)	26.6 ± 5.7	28.2 ± 5.8	0.13
BSA (m^2)	1.5 ± 0.3	2.0 ± 0.3	<0.0001
Diabetes mellitus	25 (46.3%)	52 (49.1%)	0.74
Hypertension	49 (90.7%)	94 (89.5%)	0.81
Hyperlipidemia	26 (48.1%)	41 (39.0%)	0.27
Prior Stroke	8 (14.8%)	4 (3.8%)	0.02
Coronary Artery Disease	9 (16.7%)	17 (16.5%)	0.98
Etiology of ESRD			
DM	18 (33.3%)	51 (47.2%)	0.78
GN	15 (27.8%)	19 (17.6%)	0.15
Others	21 (38.9%)	38 (35.2%)	0.52
Dialysis (HD or PD)			
HD	38 (70.3%)	75 (69.4%)	0.78
PD	5 (9.2%)	11 (10.1%)	0.84
Kt/V (ml/min)*	2.4 ± 0.5	1.8 ± 0.5	0.17
HD Vintage (years)	1.1 ± 1.8	2.8 ± 2.1	<0.0001
PD Vintage (years)	0.2 ± 0.7	0.3 ± 1.0	0.42
Dialysis Access			
Fistula	40 (81.6%)	71 (81.6%)	1.00
Graft	1 (2.0%)	2 (2.3%)	
Catheter	8 (16.7%)	12 (16.0%)	
Eventual kidney transplant	54 (100%)	98 (90.7%)	0.87
Wait time for kidney transplant (years)	1.4 (4.7%)	1.9 (2.2%)	0.58
K (mEq/L)	4.4 ± 0.5	4.5 ± 0.5	0.63
P (mg/dL)	4.1 ± 1.6	3.4 ± 0.7	0.04
Ca (mg/dL)	10.5 ± 1.0	9.6 ± 0.9	0.02
Cr (mg/dL)	6.2 ± 3.9	7.3 ± 3.8	0.07
BUN (mg/dL)	66.0 ± 30.1	66.4 ± 26.3	0.93
Hb (g/dL)	9.1 ± 2.2	8.6 ± 1.9	0.17
PTH (pg/mL)	155.2 ± 110.8	121.8 ± 104.4	0.06
Albumin (g/dL)	3.5 ± 0.8	3.4 ± 0.6	0.81
CRP (mcg/mL)	18.4 ± 46.1	23.5 ± 53.6	0.31
ESR (mm/hr)	45.3 ± 20.3	32.7 ± 31.3	0.30
Troponin (ng/mL)	0.4 ± 2.5	0.4 ± 2.7	0.51
CKMB (units/L)	3.7 ± 1.7	4.6 ± 2.7	0.54

Values are mean ± SD or n (%).

BMI = body mass index, BSA = body surface area, BSA ESRD = end stage renal disease, DM = diabetes mellitus, GN = glomerulonephritis, HD = hemodialysis, PD= peritoneal dialysis.

* kt/v is a way of determining dialysis adequacy. K = dialyzer clearance in ml/min (which is the rate of blood passing through the dialyzer), t = time, and v = is the volume of water in the patient's body.

analysis. No echocardiographic parameter, nor any electrolyte or serum biomarker was found to be a statistically significant predictor of pericardial effusion.

The mean follow-up time was 39 months (ranging from 2 to 149 months). All of the 54 patients with pericardial effusion and 90.7% of the matched cohort (98/108) eventually underwent kidney transplant with no difference in wait times from initial transplant listing. Mortality for both the pericardial effusion and matched cohort was evaluated, and no difference was found over a 10-year period when comparing all patients. If further stratified based on effusion size, large sized effusions were still not associated with increased mortality compared with the matched groups. In general, overall 10-year mortality for the pericardial effusion group was 87%.

Table 2
Pericardial effusion characteristics and echocardiographic parameters

Characteristics of Pericardial effusion (n=54)	
Variable	
Pericardial Effusion Size	
Moderate	41 (75.9%)
Large	13 (24.1%)
Symptomatology	
Symptomatic	41 (75.9%)
Asymptomatic	13 (24.1%)
Duration, months	7.3 ± 8.7
Tamponade	7 (13.2%)
Intervention	7 (13.2%)
Recurrence	1 (1.9%)
Standard echocardiographic Characteristics	
Left ventricular ejection fraction	62.9 ± 10.1
E/A	1.29 ± 0.57
e' (medial)	0.06 ± 0.02
e' (lateral)	0.07 ± 0.02
E/e' (medial)	19.4 ± 7.29
E/e' (lateral)	16 ± 6.58
Grade II Diastolic Dysfunction	45 (83.3%)
Left atrial volume index (ml/m^2)	41.6 ± 12.6
Stroke volume index (ml/m^2)	50.2 ± 10.6
Cardiac index (L/min/m^2)	4.41 ± 3.3
Right atrial pressure (mmHg)	10.5 ± 6.2
Right ventricular systolic pressure (mmHg)	40.1 ± 14.4
Values are mean ± SD or n (%)	

Discussion

Only 54 out of a cohort of 2,820 patients with ESRD, or 1.9%, were found to have moderate sized or larger pericardial effusion. This is in the lower end of the range of 2% to 21%prevalence that most of the older studies demonstrated for pericardial effusion.[3] The lower prevalence in our population can be attributed to several possibilities: first 79.5% of our patients were on some form of dialysis at the time of echocardiography, which may have decreased the prevalence of larger sized pericardial effusions. Second, there may be a difference in the definition of pericardial effusion among various studies as we excluded trivial, small, and small to moderate sized effusions. Last, this cohort of patients is likely biased towards those who were deemed appropriate for kidney transplant evaluation. Therefore patients with poor dialysis adherence were likely not included in the study.

The mechanism of pericardial effusion development has clinical implications. Dialysis associated pericarditis is, postulated to be caused by inadequate dialysis and noncompliance, lower clearance (Kt/V), or decreased flow rates during dialysis.[5] Concordantly, some studies have shown that pericardial effusion can be reversed with dialysis and renal transplantation, although other studies have negated this finding.[6–8] In our 2 cohorts, there was no significant difference between the Kt/V, but there was a significant difference in HD vintage (1.1 vs 2.8 years, $p < 0.0001$). During multivariable analysis, this was found to be a very

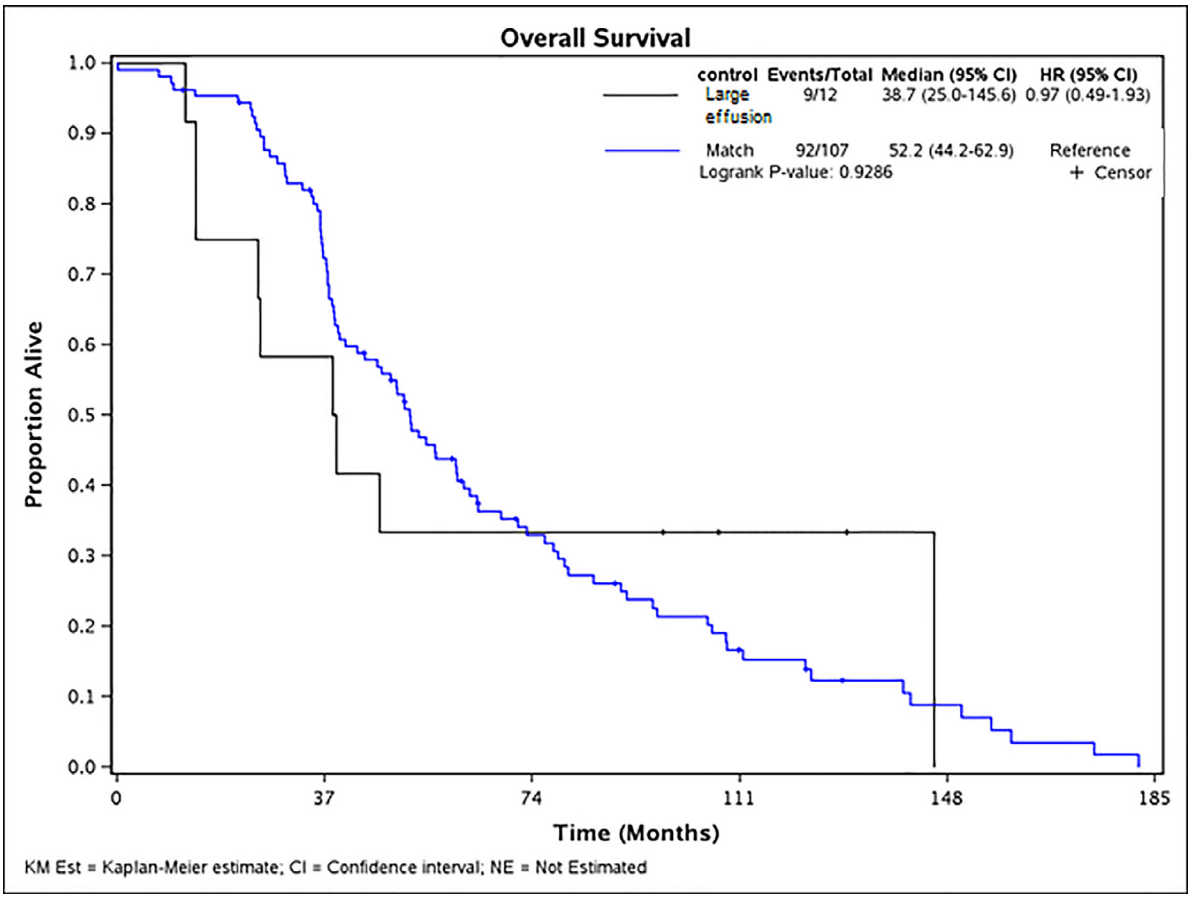

Figure 4. Overall survival for large pericardial effusion vs matched controls.

strong predictor of the development of pericardial effusion. This suggests that the important role that stable long-term dialysis can help prevent the formation of pericardial effusions. Dialysis clearance was not found to be a predictor, but this could be because of the small number of patients and the excellent clearance for most of the patients in both of the arms of the study.

Interestingly the finding of shorter HD vintages as predictors of effusion development was not found to be true of PD vintage, though this can be explained by the small number of patients in our cohort who were on PD, introducing the possibility of beta error. One study previously suggested that PD was actually superior to HD in preventing pericardial effusion.[9] Hence, further larger studies regarding the role of PD in the management and treatment of sizeable pericardial effusions are needed.

Stroke was found to be statistically significant on univariable analysis but not on multivariable analysis. Other co-morbidities such as diabetes and hypertension, which are the 2 leading causes of renal failure in the United States, nor laboratory results had any predictive value in our study.[10] Biomarkers and electrolytes were also not predictive, which is dissimilar from a recent study which found that serum potassium and calcium concentrations were predictive.[11]

Echocardiographic findings among patients with pericardial effusion reflect findings expected of chronic and long-standing renal insufficiency. Left ventricular systolic function was preserved in most patients, with elevated stroke volume index and cardiac index. This is unsurprising in the setting of ESRD patients of which the majority (70.3%) were on hemodialysis and the majority of whom had fistulas. Additionally, left ventricular filling pressures were elevated, as were right sided pressures, including right atrial pressures (RAP) and estimated systolic pulmonary artery pressures using right ventricular systolic pressure + RAP as an estimate. However, none of these were found to be predictors of pericardial effusion on multivariate regression. This may suggest that the normal mechanisms of pericardial effusion development may not apply in effusions in the ESRD population.

Clinical outcomes were not worse in the pericardial effusion cohort compared with their matched controls. Though pericardial effusion is not by itself life-threatening—barring extreme cases of tamponade, it can be symbolic of more severe systemic disease. However, this does not appear to be the case in ESRD patients, and this study confirms other studies.[11,12] A recent large scale study of 534 patients with small pericardial effusion found that these patients did have worse outcomes. However, only 4.3% of patients in that cohort had renal disease as the primary etiology of the effusion.[13] Additionally, the increased mortality was at 1-year, whereas our follow-up was over 10-years. In fact, pericardial effusion subjects did appear to have worse mortality

Table 3
Predictors of pericardial effusion in kidney transplant patients: univariate and multivariate analysis

Predictors of pericardial effusion in ESRD patients				
	Univariate analysis		Multivariate analysis	
Variable	Odds ratio(95% confidence interval)	p Value	Odds ratio(95% confidence interval)	p Value
Hypertension	1.15 (0.38-3.49)	0.81		
Hyperlipidemia	1.45 (0.75-2.81)	0.55		
Diabetes Mellitus	0.90 (0.46-1.73)	0.74		
Coronary Artery Disease	1.01 (0.42-2.45)	0.50		
Stroke	4.39 (1.26-15.33)	0.02	0.40 (0.08-1.99)	0.26
Smoking	0.83 (0.41-1.68)	0.60		
Alcoholism	1.04 (0.24-4.51)	0.96		
HD Vintage	0.61 (0.48-0.77)	<0.0001	0.62 (0.49-0.78)	<0.0001
PD Vintage	0.88 (0.55-1.40)	0.58		
Troponin	1.00 (0.98-1.03)	0.69		
Albumin	1.28 (0.74-2.21)	0.39		
Calcium	1.02 (0.97-1.08)	0.46		
Potassium	0.76 (0.39-1.46)	0.41		
Phosphorus	1.64 (1.16-2.32)	0.005		
PTH	1.003 (0.99-1.01)	0.12		
ESR	1.02 (0.98-1.06)	0.44		
CRP	1.00 (0.98-1.01)	0.74		
LVEF	0.63 (0.21-3.78)	0.86		
Concentric Left Ventricular Hypertrophy	1.88 (0.75-2.78)	0.42		
Concentric Left Ventricular Remodeling	1.65 (0.78-2.21)	0.74		
Left atrial volume index (ml/m^2)	0.99 (0.15-6.34)	0.55		
E	0.54 (0.38-0.88)	0.045	0.82 (0.04-15)	0.89
A	1.87 (1.24-2.58)	0.015	2.43 (0.33-17.6)	0.62
E/A	1.28 (0.89-2.78)	0.74		
e' (medial)	0.68 (0.57-1.09)	0.07		
e' (lateral)	0.79 (0.64-1.10)	0.06		
E/e' (medial)	0.78 (0.58-1.36)	0.86		
E/e' (lateral)	0.48 (0.28-2.38)	0.34		
Right atrial pressure (mmHg)	1.02 (0.79-1.24)	0.13		
Left ventricular filling pressure	3.67 (0.23-5.72)	0.64		
Stroke volume index (ml/m^2)	3.15 (2.48-5.87)	0.01	5.21 (0.57-47.2)	0.46
Cardiac Index (L/min/m^2)	2.48 (2.09-2.68)	<0.001	3.27 (0.09-11)	0.99

over the 4 years based on our survival curve, but the difference eventually diminished over time. Nevertheless, this lack of survival difference provides a growing body of evidence that outcomes in ESRD patients is determined primarily by other factors and co-morbidities.

The limitations of the study include its retrospective nature. It is a single center study and demonstrates the incidence of pericardial effusions in our center which is a high volume of tertiary cases and may therefore not be necessarily applicable to the larger population. The patients included in this study were evaluated for transplant, which can introduce bias into the study. Nevertheless, the complexity of patients seen at our center is higher than average, and this was reflected in the high mortality. Additionally, the predominance of HD as the mode of dialysis limits the findings largely to patients on HD.

In conclusion, the prevalence of moderate or larger sized pericardial effusion in ESRD patients is 1.9%. Whether this is a true decrease over time requires further study. The strongest predictor of the development of pericardial effusion was a short duration of hemodialysis. Stable long-term hemodialysis may therefore be an effective way of preventing pericardial effusions. Nevertheless neither the presence of pericardial effusion, nor the size of the effusion, appears to be associated with worse clinical outcomes.

Authors contribution

Hasan Ashraf: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Writing-Original Draft, Writing- Review & Editing Hong Lee: Investigation, Formal analysis, Resources Khang H. Tran: Conceptualization, Methodology, Investigation, Pradyumna Agasthi: Writing – Original Draft, Writing - Review & Editing, Visualization, Miral T. Keddis: Conceptualization, Methodology, Writing – Review & Editing, Samuel Unzek: Conceptualization, Methodology, Writing – Review & Editing, Hemalatha Naraynasamy: conceptualization, methodology, Writing – Review & Editing, Supervision Susan Wilkansky: conceptualization, methodology, Writing – Review & Editing, Supervision.

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