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The combination of left ventricular ejection fraction and end-diastolic diameter and outcomes in peritoneal dialysis patients: a multicenter retrospective study

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ABSTRACT

End-stage renal disease (ESRD) is often complicated by left ventricular dysfunction, which is associated with a poor prognosis. This study aims to investigate the association between baseline left ventricular ejection fraction (LVEF) plus left ventricular end-diastolic diameter (LVEDD) with outcomes in peritoneal dialysis (PD) patients. In this multicenter retrospective study, 1,511 incident Chinese patients on PD between 1 January 2005 and 31 December 2021 were enrolled. Restricted cubic splines (RCS) were used to explore the non-linear associations between LVEF+LVEDD and the risk of mortality. Parametric models for interval-censored survival-time data (stintreg) were used to examine the association between LVEF+LVEDD quartiles and the outcomes. During 6,451.11 person-years of follow-up [median 4.81 (IQR 3.61–6.81) years], 247 (17.8%) patients died, including 88 cardiovascular deaths. RCS showed a U-shaped association between LVEF+LVEDD and the risks of all-cause and CV mortality. According to the quartiles, the optimal range of LVEF+LVEDD associated with the lowest risk of all-cause and CV mortality was 103–107, which was set as the reference range. Both higher (≥115) and lower (<103) levels of LVEF+LVEDD were associated with increased risks of all-cause mortality (hazard ratio [HR] 2.20, 95% confidence interval [CI] 1.58–3.07; HR 1.68, 95% CI 1.19–2.36) and cardiovascular mortality (HR 2.51, 95% CI 1.33–4.75; HR 1.86, 95% CI 0.96–3.61). Low and high levels of baseline LVEF+LVEDD were associated with increased risks of all-cause and cardiovascular mortality in PD patients.

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1. Introduction

Cardiovascular (CV) deaths are the most common causes of death in patients with end-stage renal disease (ESRD) who are maintained on dialysis [1,2]. Of these, canonical coronary events account for a relatively small percentage of CV deaths, with the most common causes being sudden cardiac death and heart failure due to left ventricular (LV) remodeling [3–5]. Peritoneal dialysis (PD) is a common renal replacement therapy for patients with ESRD. According to estimates, over 272,000 patients worldwide undergo PD, accounting for approximately 11% of dialysis patients globally [6]. A recent meta-analysis found that PD patients had a higher CV mortality rate than those on hemodialysis (HD) [7]. Therefore, it is of great significance to identify potential risk factors for mortality in PD patients.

Observational studies showed that around 50–75% and 60–65% of patients with ESRD undergoing maintenance dialysis had left ventricular dysfunction and left ventricular hypertrophy, which are thought to be the result of uremic cardiomyopathy [8,9]. Echocardiography is a useful tool for evaluating cardiac systolic and diastolic function, specifically left ventricular dimensions and left ventricular ejection fraction (LVEF). Several echocardiographic parameters are associated

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with mortality and adverse outcomes in patients undergoing PD. For instance, left ventricular mass index progression was associated with all-cause mortality and CV outcomes in PD patients [10]. In addition, both low LVEF and larger left ventricular end-diastolic diameter (LVEDD) were associated with increased risk of mortality and CV events in PD patients [11,12]. As we know, the left ventricle has an intrinsic and limited range of possible volumes at end diastole. The Frank-Starling mechanism showed that, the larger the resting left ventricular end diastolic volumes, the lower the preload reserve. Further increase of the preload on a maximally enlarged left ventricle will result in minor or no increase in stroke volume, indicating a low LVEF [13]. A recent study of a large cohort demonstrated a U-shaped relationship between LVEF and mortality. The study found that the nadir of risk occurred at an LVEF of 60–65% [14]. Therefore, we propose the concept of combining LVEF and LVEDD, referred to as LVEF+LVEDD, to enhance the predictive value of these parameters. To the best of our knowledge, no previous studies have evaluated these associations. In this retrospective study, we investigate the associations between LVEF+LVEDD and mortality as well as CV events in PD patients.

2. Methods

2.1. Study design and population

The study adhered to STROBE guidelines. This was a retrospective cohort study of 1,556 consecutive incident patients who used continuous ambulatory peritoneal dialysis (CAPD) as the first renal replacement therapy in 8 tertiary hospitals in China from 1 January 2005 to 31 December 2021. According to our previous study [15], patients aged < 18 years, with < 3-month follow up, missing of echocardiographic parameters, missing other covariables and loss to follow up were excluded. The study protocol was approved by each Clinical Research Ethics Committee, and adhered to the tenets of the declaration of Helsinki. The data were anonymous and the need for informed consent was waived.

2.2. Clinical and biochemical measurements

The decision to initiate dialysis was made at the discretion of the attending physicians from each participating center. All patients' demographic characteristics, comorbidities and laboratory data were recorded, including age, sex, body mass index (BMI), diabetes mellitus (DM), hypertension, estimated glomerular filtration rate (eGFR), lipid profiles and serum electrolytes, among others. All tests were measured in the biochemical laboratory of each participating center.

2.3. Echocardiography measurements

Transthoracic echocardiography was performed at baseline by experienced technicians using a standard ultrasound device (Philips EPIQ CVx), according to recommendations [16]. Systolic and diastolic left ventricular dimensions and ventricular wall thickness were measured on two-dimensional gray-scale images along the parasternal long axis view. LVEF was calculated using the biplane Simpson's method. The echocardiographic data was stored anonymously and analyzed offline. All measurements from three end-expiratory cycles were averaged at a sweep speed of 100 mm/s [16].

2.4. Follow up and outcomes

Patients were connected by monthly face-to-face interviews or telephone interviews by healthcare providers, in order to assess the patients' overall conditions and medication adherence. Additionally, quarterly readmission to each center was required for an overall medical assessment. The patients were followed up for 12 years, or from the date of enrollment to the date of death, transferring to hemodialysis, undergoing renal transplantation, loss of follow up, transferring to other centers, or the end of follow up (31 December 2021). Patients lost to follow up were censored at the date of the last assessment.

The outcomes were all-cause mortality, CV mortality and CV events (acute coronary and cerebral vascular events, decompensating heart failure requiring hospital admission and life-threatening arrhythmias). The cause of death was determined from the medical records when available. If the patient died outside the hospital, the cause of death was ascertained from signs and symptoms and circumstances preceding death through interviewing family members. CV deaths was defined as deaths associated with acute coronary syndrome, heart failure, ischemic or hemorrhagic stroke, life-threatening arrhythmia, and sudden cardiac death based on the definition provided by the literature [17].

2.5. Statistical analysis

Continuous variables were expressed as means and standard deviations for normally distributed data and as medians and interquartile ranges (IQR) for skewed data. We did multiple imputations to impute missing data on covariates assuming a missing-at-random mechanism, and chained equations were used to generate 20 imputed datafiles. Linear regression models were used for imputing continuous variables and logistic regression for binary variables.

To examine the association between LVEF+LVEDD quartiles and the outcomes, we performed parametric models for interval-censored survival-time data (stintreg) taking left-censored data into account. The models were adjusted for age, sex, BMI, DM, hypertension, albumin, eGFR, cholesterol, calcium, potassium, sodium and centers. The results were presented as hazard ratios (HRs) and 95% confidence interval (CI). Subgroup analyses were performed according to confounders such as age (<60 or ≥60 years old), sex (men or women), DM (with or without), hypertension (with or without) and malnutrition (with, albumin <36.0 or without, albumin ≥36.0 g/L). Restricted cubic splines (xblc) were used to explore the non-linear association between LVEF+LVEDD as a continuous variable and the risk of outcomes. Statistical

analyses were performed using Stata 17.0 statistical software (StataCorp, College Station, TX), and a p value < 0.05 was considered significant.

3. Results

3.1. Baseline characteristics

We excluded 13 patients < 18 years of age, 32 patients with less than 3-month follow up. Therefore, a total of 1,511 patients were finally enrolled into the analysis (Figure 1).

Of the 1,511 patients, the mean age was 53.2 ± 14.4 years, 56% were male, and 27.7% and 76.2% had diabetes and hypertension, respectively. The median LVEF+LVEDD was 108.2 [interquartile range (IQR): 103–115.4]. We chose the nadir as the reference point based on the results of restricted cubic spline analysis, in which HRs were 1.0. Based on restricted cubic spline plots for the all-cause and CV mortality, we further treated the value of LVEF+LVEDD as quartiles, and selected the second quartile (103–107) as the reference category for LVEF+LVEDD. Table 1 presented the baseline characteristics of patients according to quartiles of LVEF+LVEDD.

3.2. LVEF+LVEDD and outcomes

During 6,451.11 person-years of follow-up [median 4.81 (IQR 3.61–6.81) years], 247 (17.8%) patients died, 162 (11.7%) patients transferred to hemodialysis, 66 (4.75%) patients received renal transplantation and 11 (0.79%) patients transferred to other dialysis centers. Of 247 deaths, 88 (35.6%) deaths were caused by CV diseases. All-cause deaths occurred

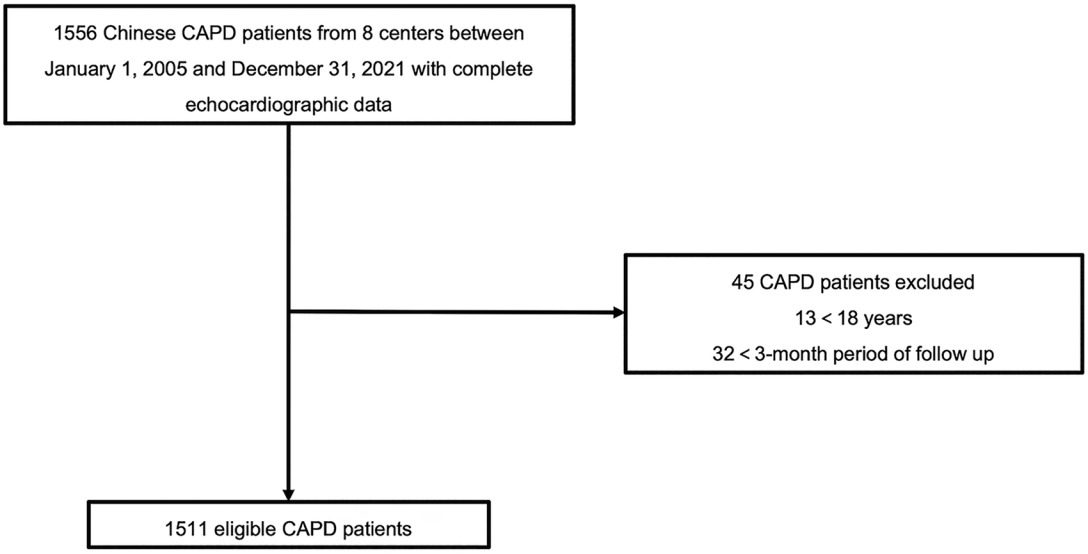

Figure 1. Flow-chart of eligible and ineligible patients. The numbers of potential and eligible patients were shown on the left side, and the reasons for in ineligibility and the numbers of ineligible patients were shown on the right side. CAPD, continuous ambulatory peritoneal dialysis.

Table 1. Baseline characteristics.

Variable	Total	Q1 (<103)	Q2 (103–107)	Q3 (108–114)	Q4 (≥115)	Missing data, n	p-Value
N	1,511	365	331	398	417		
Age, year	53.2 ± 14.4	54.7 ± 15.1	52 ± 14	52.3 ± 14.9	53.9 ± 13.5	0	0.027
Men, *n* (%)	845 (56.0)	183 (50.1)	171 (51.7)	230 (57.8)	261 (62.7)	1	0.001
BMI, kg/m^2	23.1 ± 8.0	22.7 ± 8.3	22.5 ± 3.2	23.8 ± 12.4	23.1 ± 3.6	82	0.124
DM, *n* (%)	406 (27.7)	101 (28.5)	75 (23.2)	113 (29)	117 (29.3)	43	0.247
Hypertension, *n* (%)	977 (76.2)	199 (67.7)	220 (71.7)	277 (76.3)	281 (88.4)	229	<0.001
Albumin, g/L	34.1 ± 6.5	33.6 ± 5.3	33.3 ± 4.9	33.4 ± 5.5	35.7 ± 8.6	114	<0.001
eGFR, mL/min/1.73 m^2	5.32 (3.89, 7.30)	5.46 (4.17, 7.94)	4.83 (3.82, 6.80)	5.28 (3.72, 7.10)	5.43 (4.03, 7.59)	83	0.005
Cholesterol, mmol/L	4.5 (3.74, 5.34)	4.38 (3.84, 5.19)	4.42 (3.62, 5.23)	4.48 (3.68, 5.33)	4.75 (3.88, 5.6)	337	0.008
Calcium, mmol/L	2.13 (1.96, 2.29)	2.12 (2.00, 2.27)	2.06 (1.89, 2.21)	2.11 (1.96, 2.24)	2.2 (2.05, 2.33)	301	<0.001
Potassium, mmol/L	4.03 (3.57, 4.54)	4.02 (3.53, 4.57)	3.9 (3.54, 4.43)	4.05 (3.59, 4.62)	4.1 (3.62, 4.54)	84	0.151
Sodium, mmol/L	141 (138.9, 143)	141 (138.5, 143)	141 (139, 143.45)	140.95 (138.4, 143)	141 (139, 143)	90	0.269
Centers						0	<0.001
1	190 (12.6)	34 (9.3)	31 (9.4)	62 (15.6)	63 (15.1)		
2	94 (6.2)	6 (1.6)	10 (3.0)	29 (7.3)	49 (11.8)		
3	703 (46.5)	201 (55.1)	241 (72.8)	212 (53.3)	49 (11.8)		
4	16 (1.1)	3 (0.8)	4 (1.2)	2 (0.5)	7 (1.7)		
5	385 (25.5)	115 (31.5)	31 (9.4)	67 (16.8)	172 (41.3)		
6	123 (8.1)	6 (1.6)	14 (4.2)	26 (6.5)	77 (18.5)		
7	190 (12.6)	34 (9.3)	31 (9.4)	62 (15.6)	63 (15.1)		
8	94 (6.2)	6 (1.6)	10 (3)	29 (7.3)	49 (11.8)		

in 64 (40.7/1000 person-years), 42 (26.5/1000 person-years), 69 (38.1/1000 person-years), and 72 (48.3/1000 person-years) patients from the first to the fourth quartiles of LVEF+LVEDD, respectively; CV deaths occurred in 22 (14.0/1000 person-years), 9 (5.6/1000 person-years), 30 (16.5 person-years), and 27 (18.1/1000 person-years), respectively (Table 2). Cumulative all-cause mortality and CV mortality were significantly lower in the second quartile (Figure 2). Cumulative CV events were not significantly different across quartiles (Figure 3).

Of the 797 patients with complete data on covariates, the unadjusted HRs (Model 1) for all-cause mortality were 1.89 (95% CI, 1.23–2.89), 1.41 (95% CI, 0.93–2.14), 2.13 (95% CI, 1.43–3.16) for the first, third and fourth quartiles, respectively, compared with the second quartile. After adjustments for

Table 2. Incidence rate of outcomes according to quartiles of EF+LVEDD (excluding left-censor cases).

Outcomes	Overall	Q1 (<1.33)	Q2 (1.34–1.37)	Q3 (1.38–1.42)	Q4 (>1.42)
All-cause mortality					
No. of patients	1,390	324	321	385	360
Person-years	6,451.1	1,573.5	1,579.2	1,808.8	1,490.0
Events	247	64	42	69	72
Events per 1000 person-years	38.2	40.7	26.5	38.1	48.3
Cardiovascular mortality					
No. of patients	1,390	324	321	385	360
Person-years	6,451.1	1,573.5	1,579.2	1,808.8	1,490.0
Events	88	22	9	30	27
Events per 1000 person-years	13.6	14.0	5.6	16.5	18.1
Cardiovascular event					
No. of patients	1,459	350	329	389	391
Person-years	6,626.1	1,670.5	1,581.3	1,760.5	1,613.7
Events	106	28	26	28	24
Events per 1000 person-years	16.0	16.7	16.4	15.9	14.9

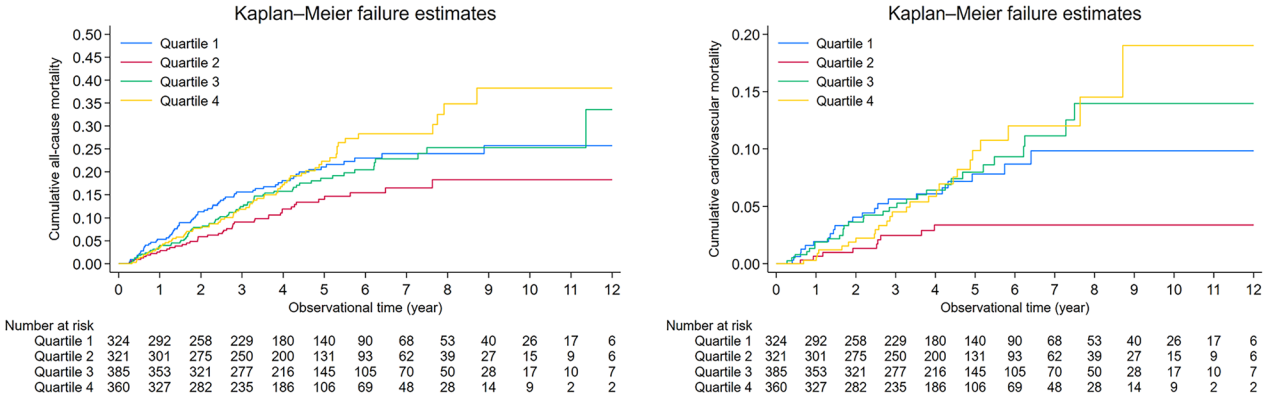

Figure 2. Cumulative all-cause and cardiovascular mortality according to EF+LVEDD quartiles. *p* Value for log-rank test were 0.028 and 0.016, respectively.

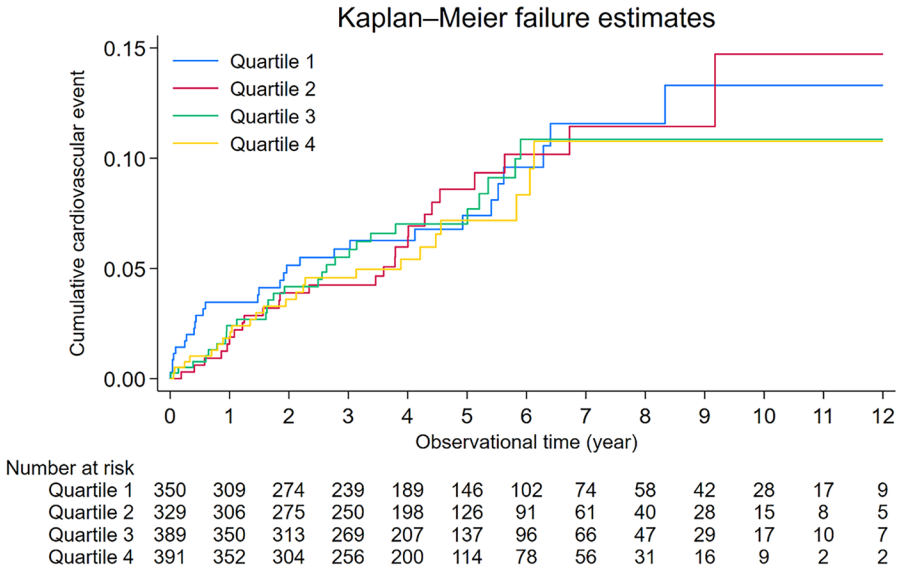

Figure 3. Cumulative cardiovascular event according to EF+LVEDD quartiles. *p* Value for log-rank test was 0.937.

demographics and comorbidities in Model 2, the HRs for all-cause mortality in the first, third and fourth quartiles were 1.49 (95% CI, 0.97–2.30), 1.25 (95% CI, 0.82–1.90) and 1.88 (95% CI, 1.26–2.80), respectively. After further adjustments with covariables in the final model (Model 3), the HRs for all-cause mortality in the first, third and fourth quartiles were 1.49 (95% CI, 0.96–2.31), 1.24 (95% CI, 0.81–1.90) and 1.70 (95% CI, 1.12–2.56), respectively. The association between LVEF+LVEDD and CV mortality showed a similar pattern, in which the adjusted HRs for CV mortality (Model 3) in the first, third and fourth quartiles were 2.27 (95% CI, 0.92–5.64), 2.42 (95% CI, 1.02–5.74) and 2.38 (95% CI, 1.00–5.66), respectively. However, there were no significant associations between LVEF+LVEDD and CV events, even after adjustments (Table 3).

Table 3. Association between EF+LVEDD and mortality using parametric models for interval-censored survival-time data based on complete data ($n = 797$).

	Model 1	*p*-Value	Model 2	*p*-Value	Model 3	*p*-Value
All-cause mortality						
Q1 (<103)	1.89 (1.23–2.89)	0.003	1.49 (0.97–2.30)	0.068	1.49 (0.96–2.31)	0.075
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	1.41 (0.93–2.14)	0.108	1.25 (0.82–1.90)	0.305	1.24 (0.81–1.90)	0.317
Q4 (≥115)	2.13 (1.43–3.16)	<0.001	1.88 (1.26–2.80)	0.002	1.70 (1.12–2.56)	0.012
Cardiovascular mortality						
Q1 (<103)	2.87 (1.18–6.97)	0.020	2.21 (0.90–5.42)	0.084	2.27 (0.92–5.64)	0.076
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	2.77 (1.18–6.52)	0.020	2.36 (1.00–5.57)	0.050	2.42 (1.02–5.74)	0.046
Q4 (≥115)	3.44 (1.49–7.97)	0.004	2.78 (1.19–6.48)	0.018	2.38 (1.00–5.66)	0.049
Cardiovascular event						
Q1 (<103)	1.66 (0.89–3.07)	0.109	1.52 (0.82–2.83)	0.186	1.62 (0.86–3.02)	0.133
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	1.20 (0.65–2.21)	0.560	1.04 (0.56–1.93)	0.898	0.99 (0.53–1.84)	0.981
Q4 (≥115)	1.61 (0.90–2.86)	0.108	1.34 (0.74–2.41)	0.334	1.30 (0.71–2.38)	0.387

Model 1: unadjusted crude HR. Model 2: adjusted for age, sex, BMI, DM, and hypertension. Model 3: model 2 plus albumin, eGFR, cholesterol, calcium, potassium, sodium and centers. Q, quartile; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazards ratio; CI, confidence interval.

Table 4. Association between EF+LVEDD and mortality using parametric models for interval-censored survival-time data based on imputed data ($n = 1511$).

	Model 1	*p*-Value	Model 2	*p*-Value	Model 3	*P*-value
All-cause mortality						
Q1 (<103)	1.92 (1.37–2.67)	<0.001	1.69 (1.21–2.36)	0.002	1.68 (1.19–2.36)	0.003
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	1.38 (0.98–1.96)	0.068	1.35 (0.95–1.91)	0.095	1.33 (0.94–1.89)	0.112
Q4 (≥115)	2.45 (1.78–3.39)	<0.001	2.28 (1.64–3.16)	<0.001	2.20 (1.58–3.07)	<0.001
Cardiovascular mortality						
Q1 (<103)	2.06 (1.08–3.95)	0.029	1.79 (0.93–3.45)	0.080	1.86 (0.96–3.61)	0.066
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	2.22 (1.17–4.22)	0.015	2.11 (1.11–4.02)	0.023	2.07 (1.08–3.95)	0.028
Q4 (≥115)	2.98 (1.60–5.57)	0.001	2.55 (1.36–4.79)	0.004	2.51 (1.33–4.75)	0.005
Cardiovascular event						
Q1 (<103)	1.40 (0.87–2.26)	0.169	1.30 (0.80–2.09)	0.291	1.47 (0.90–2.39)	0.122
Q2 (103–107)	Reference	–	Reference	–	Reference	–
Q3 (108–114)	1.16 (0.71–1.90)	0.544	1.11 (0.68–1.82)	0.670	1.10 (0.67–1.81)	0.698
Q4 (≥115)	1.60 (1.01–2.55)	0.047	1.42 (0.89–2.27)	0.146	1.53 (0.95–2.47)	0.080

Model 1: unadjusted crude HR. Model 2: adjusted for age, sex, BMI, DM, and hypertension. Model 3: model 2 plus albumin, eGFR, cholesterol, calcium, potassium, sodium and centers. Q, quartile; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazards ratio; CI, confidence interval.

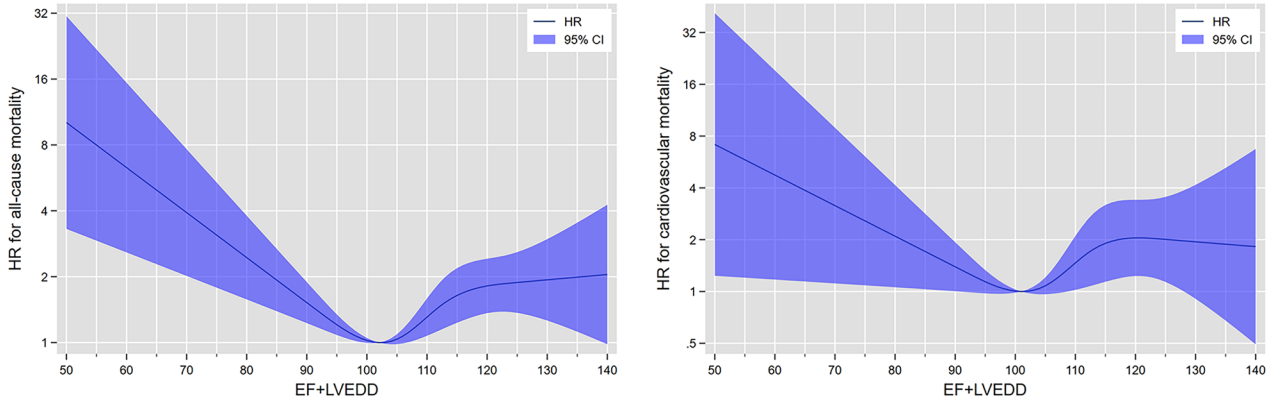

Figure 4. Association between EF+LVEDD and all-cause and cardiovascular mortality (p for non-linear trend were < 0.001 and 0.016, respectively) based on model 3. The cutoff were 102 and 101.

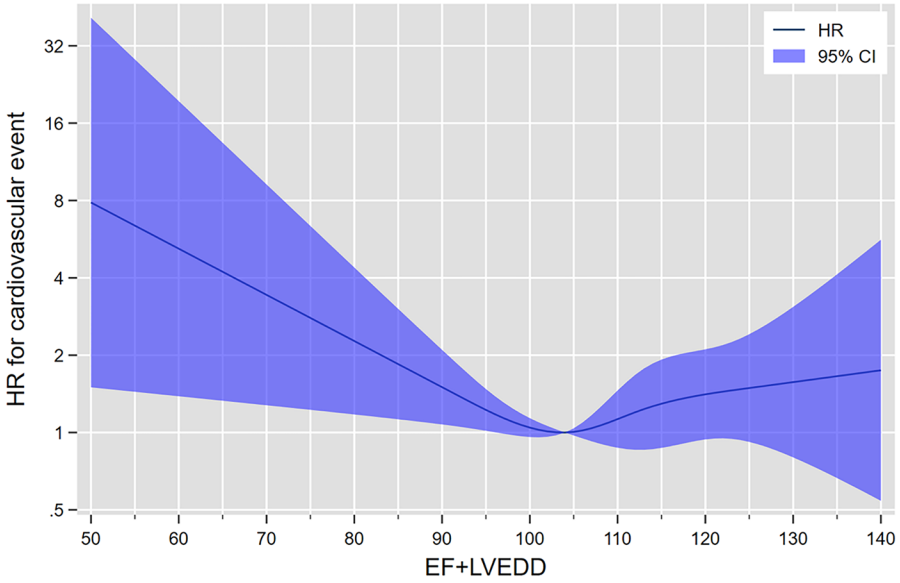

Figure 5. Association between EF+LVEDD and cardiovascular event based on model 3 (p for non-linear trend = 0.037). The cutoff was 104.

Table 5. Sensitivity analyses of association between quartiles of EF+LVEDD and outcomes.

Outcomes	Number of participants	HR (95% CI) for EF+LVEDD quartiles			
		Q1 (<103)	Q2 (103–107)	Q3 (108–114)	Q4 (≥115)
All-cause mortality					
Patients without prior cardiovascular disease	644	1.49 (0.87–2.55)	Reference	1.01 (0.57–1.76)	1.40 (0.85–2.29)
Patients without deaths during the first 2 year of follow-up	1,403	1.60 (1.05–2.44)	Reference	1.32 (0.86–2.05)	2.77 (1.85–4.15)
Patients with follow-up period ≥ 24 months	1,257	1.61 (1.05–2.45)	Reference	1.33 (0.86–2.05)	2.78 (1.86–4.16)
Cardiovascular mortality					
Patients without prior cardiovascular disease	644	1.14 (0.39–3.28)	Reference	0.95 (0.32–2.80)	1.49 (0.58–3.80)
Patients without deaths during the first 2 year of follow-up	1,403	1.49 (0.65–3.38)	Reference	1.80 (0.81–3.99)	3.13 (1.47–6.68)
Patients with follow-up period ≥ 24 months	1,257	1.49 (0.65–3.38)	Reference	1.80 (0.81–3.99)	3.14 (1.47–6.69)
Cardiovascular event					
Patients without prior cardiovascular disease	644	2.06 (0.82–5.13)	Reference	1.08 (0.44–2.67)	1.03 (0.43–2.46)
Patients without deaths during the first 2 year of follow-up	1,401	1.29 (0.78–2.13)	Reference	1.04 (0.63–1.72)	1.50 (0.93–2.43)
Patients with follow-up period ≥ 24 months	1,255	1.47 (0.87–2.50)	Reference	1.22 (0.72–2.06)	1.69 (1.02–2.82)

Models were adjusted for age, sex, BMI, DM, and hypertension. Model 3: model 2 plus albumin, eGFR, cholesterol, calcium, potassium, sodium and centers.
Q, quartile; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazards ratio; CI, confidence interval.

Due to missing time of death in 121 patients, who were treated as left-censored data, we further used parametric models for interval-censored survival-time data (stintreg) to confirm our analysis. Based on 1,511 patients with imputed data, we observed similar results regarding the associations between LVEF+LVEDD and all-cause and CV mortality, in which the adjusted HRs for all-cause mortality were 1.68 (95% CI, 1.19–2.36), 1.33 (95% CI, 0.94–1.89) and 2.20 (95% CI, 1.58–3.07); the adjusted HRs for CV mortality were 1.86 (95% CI, 0.96–3.61), 2.07 (95% CI, 1.08–3.95) and 2.51 (95% CI, 1.33–4.75) for the first, third and fourth quartile, respectively. Similarly, there was no significant associations between LVEF+LVEDD and CV events, even after adjustments (Table 4).

When analyzing LVEF+LVEDD as a continuous variable in the restricted cubic spline models, a U-shaped association was found between LVEF+LVEDD and all-cause mortality and CV mortality. Both lower and higher levels of LVEF+LVEDD were associated with an increased risk of all-cause mortality and CV mortality, as shown in Figure 4. However, similar trends were not significant between LVEF+LVEDD and CV events, as shown in Figure 5.

3.3. Sensitivity analysis

Sensitivity analysis was performed in patients without prior CV diseases, without deaths during the first 2 years of follow-up, the follow-up period ≥ 24 months, respectively. Similar results were observed in patients without deaths during the first 2 years of follow-up and in patients with follow-up period ≥ 24 months (Table 5).

3.4. Subgroup analysis

The associations between left ventricular ejection fraction (LVEF) and left ventricular end-diastolic diameter (LVEDD) and outcomes exhibited a similar pattern in various subgroups. Patients had a higher risk of all-cause mortality if they had hypertension in both lower and higher quartiles of LVEF and LVEDD. For cardiovascular (CV) mortality, patients had a higher risk if they were older than or equal to 60 years, female, had no diabetes, or had hypertension. No associations were found for CV events across all subgroups (refer to Table 6).

Table 6. Subgroup analysis of association between EF+LVEDD and mortality using parametric models for interval-censored survival-time data based on imputed data.

	Number	Q1 (<103)	Q2 (103–107)	Q3 (108–114)	Q4 (≥115)
All-cause mortality					
Age at study entry <60 years	952	2.00 (1.13–3.54)	Reference	1.43 (0.78–2.61)	2.74 (1.57–4.78)
Age at study entry ≥60 years	559	1.65 (1.08–2.52)	Reference	1.13 (0.73–1.75)	1.81 (1.19–2.77)
Men	845	1.46 (0.87–2.42)	Reference	1.12 (0.66–1.89)	2.40 (1.49–3.86)
Women	665	1.89 (1.19–2.99)	Reference	1.54 (0.96–2.47)	1.96 (1.22–3.14)
Without diabetes	1,089	1.93 (1.23–3.01)	Reference	1.28 (0.79–2.06)	2.45 (1.56–3.83)
With diabetes	413	1.36 (0.79–2.34)	Reference	1.32 (0.76–2.28)	1.80 (1.06–3.05)
Without hypertension	343	2.16 (0.92–5.08)	Reference	0.97 (0.36–2.62)	1.68 (0.51–5.55)
With hypertension	1,138	1.52 (1.02–2.26)	Reference	1.36 (0.93–2.00)	2.22 (1.54–3.18)
Without malnutrition	467	1.24 (0.58–2.67)	Reference	1.00 (0.45–2.18)	2.35 (1.20–4.61)
With malnutrition	903	1.97 (1.31–2.96)	Reference	1.44 (0.94–2.18)	1.95 (1.28–2.98)
Cardiovascular mortality					
Age at study entry <60 years	952	0.86 (0.29–2.53)	Reference	1.77 (0.70–4.50)	2.17 (0.87–5.46)
Age at study entry ≥60 years	559	3.16 (1.27–7.90)	Reference	2.14 (0.85–5.39)	2.70 (1.08–6.79)
Men	845	1.18 (0.48–2.94)	Reference	1.54 (0.65–3.64)	1.81 (0.78–4.22)
Women	665	3.05 (1.11–8.40)	Reference	2.89 (1.05–7.91)	3.83 (1.41–10.42)
Without diabetes	1,089	1.84 (0.77–4.41)	Reference	1.76 (0.74–4.18)	2.84 (1.23–6.54)
With diabetes	413	1.96 (0.68–5.69)	Reference	2.35 (0.84–6.61)	2.03 (0.70–5.84)
Without hypertension	343	1.27 (0.19–8.30)	Reference	1.92 (0.32–11.37)	2.82 (0.35–22.57)
With hypertension	1,138	1.97 (0.95–4.10)	Reference	2.10 (1.03–4.26)	2.55 (1.28–5.11)
Without malnutrition	467	2.62 (0.28–24.47)	Reference	5.30 (0.63–44.76)	12.2 (1.55–95.8)
With malnutrition	903	2.44 (1.11–5.35)	Reference	2.23 (1.03–4.84)	2.10 (0.93–4.71)
Cardiovascular event					
Age at study entry <60 years	952	1.48 (0.76–2.90)	Reference	1.05 (0.53–2.07)	1.34 (0.69–2.61)
Age at study entry ≥60 years	559	1.60 (0.78–3.29)	Reference	1.07 (0.51–2.21)	1.73 (0.86–3.48)
Men	845	1.22 (0.64–2.34)	Reference	1.12 (0.61–2.09)	1.27 (0.69–2.35)
Women	665	1.86 (0.88–3.92)	Reference	0.91 (0.39–2.12)	1.86 (0.87–4.01)
Without diabetes	1,089	1.19 (0.64–2.22)	Reference	1.11 (0.61–2.03)	1.60 (0.89–2.87)
With diabetes	413	2.02 (0.87–4.69)	Reference	0.97 (0.39–2.39)	1.36 (0.58–3.2)
Without hypertension	343	2.05 (0.61–6.89)	Reference	1.55 (0.44–5.47)	1.93 (0.46–8.18)
With hypertension	1,138	1.36 (0.79–2.35)	Reference	0.98 (0.57–1.69)	1.42 (0.85–2.36)
Without malnutrition	467	0.85 (0.26–2.71)	Reference	0.82 (0.27–2.48)	1.80 (0.71–4.54)
With malnutrition	903	1.77 (0.99–3.16)	Reference	1.17 (0.65–2.14)	1.41 (0.76–2.63)

Models were adjusted for age, sex, BMI, DM, hypertension, albumin, eGFR, cholesterol, calcium, potassium, sodium and centers, except for variable of subgroup. Q, quartile; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazards ratio; CI, confidence interval.

4. Discussion

In this multicenter retrospective cohort study, we first reported a U-shaped association between LVEF+LVEDD and the risks of all-cause and CV mortality, with low and high values associated with increased mortality. The study found that the optimal range of LVEF+LVEDD associated with the lowest risk of all-cause and CV mortality was 103–107, according to the quartiles. The results remained consistent after adjustments and imputations, which strengthens the validity of the findings.

Globally, PD accounts for 11% of all dialysis and 9% of all kidney replacement therapies. In patients receiving PD, CVD is the leading cause of death, accounting for 52.7% of all deaths [18]. Furthermore, patients receiving dialysis are estimated to have a 10- to 20-fold higher CVD mortality risk than the general population [19]. Recent studies have shown that patients with PD have a higher risk of emergency hospitalization and mortality associated with CVDs compared to hemodialysis patients [7,20]. According to observational studies, more than half of the patients with ESRD receiving maintenance dialysis had left ventricular hypertrophy and left ventricular dysfunction, as previously mentioned. Echocardiography is a convenient and feasible tool for assessing cardiac function and chamber sizes. Studies showed that echocardiographic parameters were associated with mortality and adverse outcomes in patients undergoing PD. For example, baseline left ventricular hypertrophy and left ventricular mass index were independently associated with increased risk of mortality and CV outcomes in PD patients [10,21,22]. Interventricular septum end-diastolic thickness and LVEDD were found to be associated with increased risk of all-cause mortality in PD patients [12]. Furthermore, left ventricular diastolic dysfunction and right ventricular dysfunction were also independent predictors of adverse outcomes and mortality in PD patients [23,24]. Reciprocally, patients with PD developed left ventricular dysfunction and myocardial systolic dyssynchrony earlier compare with healthy controls [25]. Based on administrative data and limited echocardiographic studies, approximately 20% of hemodialysis patients and 10–20% of peritoneal dialysis patients have heart failure with reduced ejection fraction (HFrEF) [11,26,27]. Compared to patients without heart failure, dialysis patients with heart failure have a lower 2-year survival rate [28]. A study of a large cohort has recently demonstrated a U-shaped relationship between LVEF and mortality [14]. In this study, we investigate the associations between LVEF+LVEDD with the outcomes in patients with PD. We found a U-shaped association between LVEF and LVEDD with all-cause and cardiovascular mortality in PD patients.

In the early nineteenth century, experiments on skeletal muscle demonstrated that progressive stretching of a resting muscle before contraction increases not only resting

tension but also tension development and energy production during contraction [29]. This finding highlights the importance of pre-contraction stretching in muscle performance. This principle, as known as the Frank-Starling Law, also applies to cardiac muscle. Whenever extra blood enters the heart chambers, the stretched cardiac muscle contracts with a greatly increased force, thereby pumping the extra blood into the arteries automatically [30]. An acute reduction in stroke volume due to reduced contractility or increased afterload may be compensated by an increase in LVEDV and consequent activation of the Frank-Starling mechanism. In addition, LVEDV may compensate for chronic reductions in contractility in patients with heart failure, but in this case, increased LVEDV may also reflect positive remodeling independent of chamber stretch. There must be a range of possible volumes of the left ventricle, ranging from a LVEDV at zero transmural left ventricular end-diastolic pressure (LVEDP) to that at which there is a high LVEDP. LVEDV and LVEDP exhibit a curvilinear relationship, with the curve steepening as volume increases. The normal left ventricle operates in a volume ranging well within these limits, but in the presence of cardiac pathology such as heart failure, it could be operating near its maximum LVEDV [31]. A preload reserve is considered exhausted when attempts to increase LVEDV result in small or absent increases in both LVEDV and stroke volume, and large increases in LVEDP [31]. Our present study can be explained by these mechanisms. Our results showed a U-shaped association of LVEF+LVEDD and all-cause and CV mortality, indicating that both higher and lower LVEF+LVEDD values were associated with increased mortality. Higher LVEF+LVEDD values typically represent a combination of relatively preserved LVEF and an extremely enlarged left ventricle, indicating a state of preload reserve exhaustion. Lower LVEF+LVEDD values, on the other hand, usually represent a combination of extremely low LVEF and an already enlarged left ventricle, indicating a state of severe pump failure combined with preload reserve exhaustion. Both of these conditions can significantly increase the risk of mortality.

Our study has several limitations. First, due to the retrospective and observational nature of our study, we cannot rule out the residual or unmeasured confoundings, and cannot draw conclusions regarding the causality between LVEF+LVEDD and mortality. Second, the echocardiography in our study was measured at baseline and the patients were followed up for long periods. Thus we did not investigate and cannot rule out the effects of medical therapy on mortality and outcomes. Third, our results may not be generalizable to other populations due to the inclusion and exclusion criteria. Further large scale prospective studies are warranted to confirm our findings and mechanistic studies are needed to fully explain the results of our study.

5. Conclusions

Both low and high levels of baseline LVEF+LVEDD were associated with increased risks of all-cause and cardiovascular mortality in PD patients. As echocardiography is part of routine clinical screening, our findings could potentially be translated into clinical settings to identify high-risk patients on PD.

Ethics approval

The study protocol adhered to the declaration of Helsinki and was approved by each Clinical Research Ethics Committee.

Informed consent

The data were anonymous and the need for informed consent was waived.

Authors contributions

JY, XW and NW contributed to the conception of the research, statistical analysis, drafting, revision and approval of the manuscript. NS, XF, FP, QX, XZ, YW, XW and NT contributed to the interpretation of results, revised the manuscript and approved the final version. JY and XW have accessed and verified the data. NW is the guarantor of this study and takes responsibility for the integrity of the data and the accuracy of the analysis.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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