Research Article

Serum Prealbumin and Echocardiography Parameters Predict Mortality in Peritoneal Dialysis Patients

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Keywords

Echocardiography · Prealbumin · Peritoneal dialysis

Abstract

Aim: Protein-energy malnutrition and cardiovascular (CV) disease predisposes patients with end-stage renal disease (ESRD) on dialysis to a high risk of early death, but the prognostic value of prealbumin (PAB) and echocardiographic indices in ESRD patients treated with maintenance peritoneal dialysis (PD) remains unclear. **Methods:** A total of 211 PD patients (mean age 49.2 ± 15.4 years, 51.7% male) were prospectively studied. PAB and echocardiography parameters were recorded at baseline. Follow-up (mean $\pm$ SD: 33.7 ± 17.3 months) was conducted based on hospital records, clinic visits, and telephone reviews, to record death events and their causes. **Results:** In the Cox proportional hazards model, PAB and the echocardiographic parameters listed below were found to be optimal predictors of all-cause mortality: PAB ($p = 0.003$), aortic root diameter (ARD) ($p = 0.004$), interventricular septum end-diastolic thickness (IVSd) ($p = 0.046$), and left ventricular end-diastolic diameter index (LVEDDI) ($p = 0.029$). Of the above-mentioned factors, PAB ($p = 0.018$), ARD ($p = 0.031$), and IVSd ($p = 0.037$) were independent predictors of CV mortality in PD patients. Of note, malnutrition, degradation of the aorta, and myocardial hypertrophy are also known death risk factors in the general population. The all-cause mortality and CV death rate significantly increased as the number of risk factors increased, reaching values as high as 40 and 22% in patients who had all of the risk factors, i.e., abnormal PAB, ARD, and IVSd ($p < 0.001$ and $p = 0.011$). **Conclusion:** In PD patients, low serum PAB and abnormal echocardiographic parameters together were sig-

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nificantly associated with all-cause mortality and CV death, independently of other risk factors. These risk factors for death in PD are similar to those in the general population. Noticeably, the combination of echocardiographic parameters and PAB could provide additional predictive value for mortality in PD patients. In light of these findings, more studies in an optimal model containing PAB and echocardiographic parameters for the prediction of outcomes in ESRD are required.

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Introduction

Patients with end-stage renal disease (ESRD) on dialysis experience a poor quality of life with a high risk of early death, which is particularly driven by protein-energy malnutrition and an increased incidence of cardiovascular (CV) events [1–4]. In response to the high mortality and the low quality and great cost of health care, a better risk stratification strategy to improve patients' outcomes is one of the most important goals before the implementation of preventive therapies. Echocardiography and nutritional biomarkers are commonly used in PD patients, but they have been neither correlated nor evaluated in prediction of the risk of all-cause mortality and CV death. Therefore, the purpose of this prospective study was to investigate the association of echocardiography and serum prealbumin (PAB) with all-cause and CV mortality in patients treated with PD.

In recent years, it has been suggested that more attention should be paid to the association between nutrition and clinical outcomes in ESRD patients, especially in dialysis patients [5]. Previous studies have shown that a poor nutrient intake is significantly associated with a higher mortality in dialysis patients, independently of preexisting comorbidities and other confounders [1, 6]. PAB, known as the earliest and most sensitive laboratory indicator of nutritional status, has emerged as the preferred biochemical marker for detecting malnutrition during dialysis [7]. Moreover, it has been proven that PAB is independently correlated with patient outcomes in various diseases, including ESRD [8–12]. In echocardiographic studies, the assessment of left ventricular (LV) structure and myocardial systolic and diastolic functions using tissue Doppler imaging has been established as a common approach to detect subclinical CV impairment in ESRD patients [13–16]. Multiple studies have confirmed the predictive value of echocardiography and tissue Doppler imaging for CV events and mortality in CKD patients [17–19]. LV hypertrophy (LVH) and LV dysfunction are reliable markers for adverse outcomes among patients with ESRD [20–22]. However, the combined value of nutritional biomarkers and echocardiography in prediction of the mortality risk in ESRD patients remained unclear.

As mentioned above, nutritional status and cardiac abnormalities are both well-recognized risk factors for mortality in ESRD patients. Therefore, we hypothesized that combined nutritional biomarkers and echocardiographic parameters might be useful indicators of the mortality risk in PD patients and that, if true, it could be used to identify patients at risk for all-cause and CV mortality. We aimed to analyze whether the combination of PAB and echocardiography could provide complementary predictive information on all-cause and CV mortality.

Materials and Methods

Patients

This prospective study included 211 adult patients with ESRD treated with continuous ambulatory peritoneal dialysis (PD) for more than 3 months. The patients were enrolled into

a single PD center at The First Affiliated Hospital of Sun Yat-sen University between July 2013 and April 2014. The inclusion criteria were blood tests including serum PAB and echocardiography. Patients with recent acute coronary syndrome, cardiomyopathy, significant arrhythmias, severe mitral valve disease, pericardial disease, or congenital heart disease were excluded. Clinical parameters, including demographic data, systolic/diastolic blood pressure, a prior medical history (such as hypertension, diabetes, and etiology of CKD), and risk factors for CV disease (both traditional and uremia-related risk factors), were recorded. BMI was calculated as: weight (kg)/height (m)².

Laboratory Tests

Biochemical parameters were collected 3 months after the initiation of PD. All parameters, including serum PAB, phosphorus, calcium, albumin, cholesterol, creatinine, pro-brain natriuretic peptide, and hemoglobin, were tested at the central laboratory of The First Affiliated Hospital of Sun Yat-sen University. Analytic coefficients of variation were <5%.

Echocardiography

Transthoracic 2-dimensional echocardiography examinations were performed at the times when blood samples were taken for the test of serum PAB, using a commercially available ultrasound system (Vivid 7; GE Health Medical, Milwaukee, WI, USA) equipped with a multifrequency transducer (M3S 1.7/3.4 MHz). Echocardiographic measurements, including aortic root diameter (ARD), left atrium diameter (LAD), LV wall thickness, and LV dimension, were taken according to guidelines advocated by the American Society of Echocardiography (ASE) [23] by an echocardiologist who was unaware of the laboratory results. The ARD (at the maximal diameter of the sinuses of Valsalva) was obtained from the parasternal long-axis view, by using the leading edge-to-leading edge (L-L) convention. The anteroposterior diameter of the left atrium was measured in the parasternal long-axis view perpendicular to the LA posterior wall, and the LV internal dimensions (LV end-diastolic diameter [LVEDD] and LV end-systolic diameter) were obtained with a 2-dimensional echocardiography-guided M-mode approach, with the electronic calipers positioned on the interface between the myocardial wall and cavity. They were further indexed to body surface area (LV end-diastolic diameter index [LVEDDI] and LV end-systolic diameter). As for LV wall thickness (interventricular septum end-diastolic thickness, [IVSd] and left ventricular posterior wall end-diastolic thickness), the electronic calipers were positioned on the interface between the wall and the pericardium. LV mass (LVM) was calculated according to the ASE-recommended cube formula from linear dimensions and indexed to body surface area (left ventricular max index; LVMI). Regional wall thickness was measured as follows: $2 \times \text{LV posterior wall thickness (mm)}/\text{LV end-diastolic dimension (mm)}$. LV geometry was divided into 4 categories based on the ASE guideline. LVH was defined as LVMI >115 g/m² for men and >95 g/m² for women. The LV ejection fraction was taken in the parasternal long axis view using the Teichholz method.

Transmitral inflow was taken in an apical 4-chamber view using pulsed-wave Doppler recordings at the tip of mitral leaflets. Peak early (E) and late (A) diastolic velocities, and the E/A ratio, were measured. Early (e') diastolic mitral annular velocities were measured on the lateral side of the mitral annulus in an apical 4-chamber view using the tissue Doppler technique with a Nyquist limit of 15 cm/s. The E/A and E/e' ratios for the LV filling index were calculated in accordance with the ASE guideline [23]. An LV ejection fraction >55% was defined as normal ventricle systolic function.

Patient Follow-Up

Patients were followed up quarterly in the PD center at our hospital by means of retrieval of medical records, clinical visits or telephone contacts. The primary outcome of interest was

all-cause mortality, and the secondary outcome of interest was CV mortality. Death from all causes was confirmed by active follow-up through outpatient dialysis clinics, as well as passive follow-up using the patient's medical records in our center database. All patients were followed up until death, transfer to hemodialysis, kidney transplantation, or censoring on April 4, 2018.

Statistical Analysis

Normally distributed continuous variables are presented as means $\pm$ SD and were compared using analysis of variance (ANOVA) and 2-sample *t* tests (or nonparametric equivalents, i.e., Mann-Whitney test and signed-rank Wilcoxon test). Categorical variables are reported as absolute value (%) and were compared using the χ^2 test. All-cause mortality and the CV death rate were compared among different LV geometry patterns. Survival probabilities were calculated and compared using the Kaplan-Meier method plotted in survival graphs and the log-rank test, respectively. Cox proportional hazards models were constructed to identify the associations between PAB, echocardiographic parameters, and all-cause mortality and CV death. In Cox regression models, the time at risk was from study entry until death, transfer to hemodialysis therapy, kidney transplantation, or the end of the study on April 4, 2018. Percentages of all-cause mortality and CV mortality in relation to the number of baseline risk factors were compared. A two-sided *p* < 0.05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS), version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of the Patients

Two hundred eleven patients were enrolled into this prospective study. The mean ($\pm$ SD) age was 49.2 ± 15.4 years, and there were 109 (51.7%) males and 102 (48.3%) females. All-cause mortality in 47 (22.3%) and CV death in (13.8%) subjects were observed during the 4.7-year follow-up. Baseline demographic and clinical data of the study patients are detailed in Table 1. Patients who died during the follow-up period were more likely to be older and have a higher BMI and a lower diastolic blood pressure. Patients with diabetes or hypertension have an increased mortality risk in comparison to those without. In addition, 22 (46.8%) patients in the all-cause mortality group and 16 (55.2%) in the CV mortality group had clinical evidence of diabetes mellitus; this was significantly higher than the proportion of diabetes mellitus in survivors (*p* = 0.002 and *p* = 0.001, respectively). The serum PAB values of the all-cause mortality group (329.3 ± 92.3 g/L) and the CV mortality group (338.3 ± 102.6 g/L) were significantly lower in comparison to those of the survivors (388.2 ± 84.8 g/L) (*p* < 0.001). The median (IQR) hsCRP value was 2.77 mg/dL (1.18–8.57) in the all-cause mortality group and 2.77 mg/dL (1.14–11.22) in CV mortality group; this was significantly higher than the values of the survivors, i.e., 1.41 mg/dL (0.39, 4.09). An ROC curve was drawn to determine the utility of PAB and more widely available nutritional measures, including cholesterol and albumin levels, in predicting mortality in the study patients (Fig. 1). The area under the ROC curve for PAB, cholesterol, and albumin to predict all-cause mortality was 0.69 (95% CI 0.61–0.77), 0.55 (95% CI 0.46–0.63), and 0.59 (95% CI 0.50–0.67), respectively. The area under ROC curve for PAB, cholesterol, and albumin to predict CV mortality was 0.61 (95% CI 0.50–0.73), 0.52 (95% CI 0.42–0.63), and 0.55 (95% CI 0.44–0.66), respectively. These findings indicate that PAB had better performance in prediction of all-cause and CV mortality in PD patients.

Baseline echocardiographic parameters are shown in Table 2. The ARD of the all-cause mortality group and the CV mortality group were significantly larger than that of survivors

Table 1. Clinical characteristics of the study patients

Variable	Overall (n = 211)	Survivors (n = 164)	All-cause mortality (n = 47)	CV mortality (n = 29)
Demographics				
Males	109 (51.7)	82 (50)	27 (57.4)	18 (62.1)
Age, years	49.2±15.4	45.9±14.3	60.5±13.9*	59.1±14.2*
BMI	22.1±3.1	21.9±3.0	22.8±3.4	23.2±3.2*
Body surface area, m ²	1.6±0.2	1.6±0.2	1.6±0.1	1.7±0.1
Dialysis duration, months	30.0 (16.0–47.0)	30.5 (15.2–47.7)	29.0 (16.0–45.0)	25.0 (14.0–45.0)
Etiology of ESRD				
Glomerulonephritis	119 (56.4)	99 (60.4)	20 (42.6)	11 (37.9)
Diabetes	43 (20.3)	27 (16.5)	16 (34.0)*	11 (37.9)*
Hypertension	15 (7.1)	9 (5.5)	6 (12.8)*	4 (13.8)*
Other	34 (16.1)	29 (17.7)	5 (10.6)	3 (10.3)
Prevalent diabetes	60 (28.6)	39 (23.8)	22 (46.8)*	16 (55.2)*
Prevalent hypertension	207 (98.1)	160 (97.6)	47 (100)	29 (100)
Systolic BP, mmHg	142.2±19.6	142.4±19.7	141.3±19.7	137.8±19.2
Diastolic BP, mmHg	84.1±13.0	85.8±12.8	78.3±12.2*	77.8±10.8*
Laboratory values				
Creatinine, μmol/L	1021.0±311.9	1059.1±305.3	888.0±300.9*	939.7±320.3
eGFR, ml/min/1.73 m ²	3.97 (3.38–4.94)	3.86 (3.22–4.69)	4.34 (3.61–6.08)*	4.08 (3.36–5.42)
Triglycerides, mmol/L	1.27 (0.91–1.82)	1.25 (0.88–1.79)	1.38 (1.05–2.31)	1.25 (0.98–1.99)
TCHO, mmol/L	4.90 (4.20–5.70)	4.90 (4.20–5.80)	4.80 (3.90–5.40)	5.00 (4.10–5.45)
HDL-C, mmol/L	1.1±0.3	1.1±0.3	1.0±0.3*	1.1±0.3
LDL-C, mmol/L	2.8±0.9	2.8±0.9	2.6±0.9	2.7±0.9
Phosphorus, mmol/L	1.66±0.48	1.67±0.46	1.62±0.58	1.65±0.58
Calcium ^a , mmol/L	2.37±0.20	2.37±0.19	2.37±0.21	2.39±0.23
iPTH, pg/mL	408.2 (240.6–702.8)	411.4 (228.5–710.8)	399.2 (272.4–656.9)	399.6 (288.3–673.4)
Uric acid, mmol/L	403.6±78.1	406.3±77.0	393.9±81.7	386.6±91.0
Albumin, g/L	37.8±3.6	38.0±3.5	37.2±4.0	37.6±4.3
PAB, g/L	375.0±89.7	388.2±84.8	329.3±92.3*	338.3±102.6*
Hb, g/L	108.0±19.1	107.3±20.0	110.6±15.7	109.6±14.7
hsCRP, mg/	1.59 (0.57–4.45)	1.41 (0.39–4.09)	2.77 (1.18–8.57)*	2.77 (1.14–11.22)*
ProBNP, pg/mL	4,147.0 (1,619.5–14,041.0)	4,734.5 (1,635.2–14,737.2)	2,815.0 (1,341.0–11,644.0)	3,306.5 (2,088.7–15,342.0)

Data are presented as means ± SD or medians (IQR) for continuous variables according to their distribution or as numbers (%) for categorical variables. BP, blood pressure; iPTH, intact parathyroid hormone; TCHO, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hb, hemoglobin; hsCRP, high-sensitivity C reactive protein; ProBNP, B-type natriuretic peptide. **p* < 0.05 compared with survivors. ^aCorrected for serum albumin concentration.

Fig. 1. ROC curve showing the sensitivity and specificity of prealbumin, total cholesterol (TCHO), and albumin in predicting all-cause mortality (A) and CV mortality (B) in PD patients.

(34.6 ± 3.9 and 34.7 ± 4.2 vs. 32.9 ± 3.6 mm; $p = 0.004$). Compared with the survivors, patients in the all-cause mortality group and the CV mortality group had a smaller LVEDDI (32.9 ± 4.5 vs. 31.3 ± 3.8 and 31.0 ± 4.1 mm/m²; $p = 0.029$) and higher IVSd (13.1 ± 1.5 and 13.3 ± 1.7 vs. 12.4 ± 2.2 mm; $p = 0.017$). However, patients who survived or died during the follow-up period showed no significant difference in LVM (253.9 ± 69.1 and 266.8 ± 73.3 vs. 259.7 ± 89.6 g; $p = 0.690$) or LVMI (153.0 ± 36.7 and 158.1 ± 38.9 vs. 158.5 ± 49.3 g/m²; $p = 0.408$).

In addition, in comparison with the patients who survived, it was found that the early diastolic mitral inflow velocity was lower and the late diastolic mitral inflow velocity was higher ($p = 0.004$ and $p = 0.044$, respectively) in patients who died during the follow-up period. The E/A ratio was lower in the mortality groups than in the survivors ($p = 0.002$ and $p = 0.043$, respectively). In tissue Doppler analysis, the early diastolic lateral mitral annular velocity was lower in those who died of all causes than in survivors ($p = 0.036$). The E/e' ratio also showed an increasing trend in patients in the mortality group in comparison to the survivors, although it did not show a statistical significance.

Correlation analysis of serum PAB and echocardiographic data was also conducted in this PD cohort (Table 3). LAD and LVEDD were significantly correlated to PAB, but this effect disappeared after adjusting for potential clinical confounders. In addition, ARD has a borderline correlation with serum PAB after correction for confounders (Fig. 2). No statistically significant associations were found between PAB and other echocardiographic parameters after adjustments.

During the mean follow-up of 33.7 ± 17.3 months, 47 patients (22.3%) died (27 men and 20 women). Seventy-eight patients (36.9%) continued with PD treatment, 39 (18.5%) patients received a kidney transplant, and 45 (21.3%) patients changed to long-term hemodialysis.

Mortality and LV Geometry

To further assess the influence of LV remodeling on all-cause mortality and CV death, patients were divided into 4 groups on the basis of LV geometry (Fig. 3). The patients with concentric remodeling or hypertrophy had a relatively higher all-cause death rate (27.3 and 27.8%, respectively) in comparison with those with normal geometry or eccentric hypertrophy (15.8 and 16.7%, respectively). Similarly, the CV mortality rate was also higher in patients with concentric remodeling or hypertrophy (18.2 and 19.8%, respectively) than those with normal geometry or eccentric hypertrophy (5.3 and 8.3%, respectively).

Table 2. Echocardiographic characteristics of the study patients

Variable	Overall (n = 211)	Survivor (n = 164)	All-cause mortality (n = 47)	CV mortality (n = 29)
ARD, mm	33.4±3.7	32.9±3.6	34.6±3.9*	34.7±4.2*
LAD, mm	39.8±6.2	39.7±6.6	39.5±4.9	40.0±5.2
LVEDD, mm	52.9±7.1	53.2±7.3	51.4±6.4	51.9±7.1
LVESD, mm	33.8±6.9	34.2±7.1	32.4±6.3	33.5±7.0
LVEDDI, mm/m ²	32.5±4.4	32.9±4.5	31.3±3.8*	31.0±4.1*
LVESDI, mm/m ²	20.8±4.3	21.1±4.4	19.7±3.6*	20.0±4.1
IVSd, mm	12.6±2.1	12.4±2.2	13.1±1.5*	13.3±1.7*
LVPWd, mm	11.2±1.9	11.1±1.9	11.3±1.9	11.6±2.0
LVEF, %	64.8±9.5	64.5±9.7	65.7±8.5	64.6±8.7
LVM, g	259.4±85.6	259.7±89.6	253.9±69.1	266.8±73.3
LVMI, g/m ²	157.8±46.8	158.5±49.3	153.0±36.7	158.1±38.9
<i>Pulsed wave Doppler</i>				
E, cm/s	83.4±28.8	86.2±30.3	74.4±20.9*	75.7±21.7
A, cm/s	92.5±24.6	90.3±22.7	98.8±29.8*	101.0±31.9
E/A ratio	0.8 (0.7–1.1)	0.9 (0.7–1.2)	0.7 (0.6–0.9)*	0.8 (0.6–1.0)*
<i>Tissue Doppler</i>				
e', cm/s	10.0 (7.8–13.3)	8.0 (6.0–9.0)	7.0 (6.0–8.0)*	7.0 (6.0–8.0)
E/e' ratio	11.5±5.5	11.5±5.4	11.6±5.4	12.0±6.5

Data are presented as means ± SD or medians (IQR) for continuous variables according to their distribution. LVESD, LV end-systolic diameter; LVESDI, LV end-systolic diameter index; LVPWd, LV posterior wall end-diastolic thickness; LVEF, LV ejection fraction. * $p < 0.05$ compared with survivors.

Table 3. Correlation analysis of serum PAB and echocardiographic data in the study patients

	Unadjusted correlation coefficient	<i>p</i> value	Adjusted correlation coefficient ^a	<i>p</i> value
ARD (mm)	0.07	0.300	0.15	0.051
LAD (mm)	–0.13	0.05	–0.09	0.222
LVEDD (mm)	0.16	0.021	0.10	0.200
IVSd (mm)	0.02	0.743	–0.01	0.952
LVPWd (mm)	0.05	0.436	0.03	0.717
LVEF	–0.08	0.228	–0.10	0.194
LVM (g)	0.12	0.084	0.09	0.271
E/e' ratio	–0.04	0.629	0.02	0.767

LVPWd, LV posterior wall end-diastolic thickness. ^a Adjusted for: age, gender, dialysis duration, BMI, prevalent diabetes, and prevalent hypertension.

PAB, Echocardiography, and Survival

Using the log-rank test, it was noticed that patients in the lower tertile of PAB had higher all-cause mortality ($p = 0.001$) and CV mortality ($p = 0.039$) than those in the upper tertile. Patients with ARD in the upper tertile had higher all-cause death ($p = 0.017$) and CV mortality ($p = 0.037$) than those in the lower tertile. Also, a significant increase in all-cause mortality

($p = 0.012$) and CV death ($p = 0.014$) was observed with increased IVSd. All-cause mortality ($p = 0.007$) and CV death ($p = 0.023$) were higher in patients with lower LVEDDI (Fig. 4) compared to patients with a higher LVEDDI.

In univariate as well as multivariate Cox models, PAB was highly significant and an independent predictor of both overall and CV death (Table 4). In the Cox proportional hazards model, the optimal echocardiographic parameters to predict all-cause mortality or CV death consisted of the following (continuous predictors): ARD (HR = 1.18; 95% CI 1.05–1.32; HR = 1.13; 95% CI 1.01–1.27), IVSd (HR = 1.21; 95% CI 1.00–1.45; HR = 1.24; 95% CI 1.01–1.53),

Fig. 2. Scatterplots showing the correlations between serum prealbumin and ARD (A), LAD (B), and LVEDD (C) after adjustments in PD patients.

Fig. 3. Percentage of all-cause mortality and CV mortality in relation to LV geometry in the study patients. NG, normal geometry; CR, concentric remodeling; CH, concentric hypertrophy; EH, eccentric hypertrophy.

Fig. 4. Kaplan-Meier survival analysis of cumulative all-cause mortality (A–D) and CV mortality (E–H) in subgroups of patients according to tertiles of prealbumin or echocardiographic parameters (including ARD, IVS, and LVEDDI). **A, E** Prealbumin: I tertile, <336 g/L; II tertile, ≥336 g/L but <410 g/L; and III tertile, ≥410 g/L. **B, F** ARD: I tertile, <32 mm; II tertile, ≥32 mm but <35 mm; III tertile, ≥35 mm. **C, G** IVS: I tertile, <12 mm; II tertile, ≥12 mm but <13 mm; III tertile, ≥13 mm. **D, H** LVEDDI: I tertile, <30.38 mm/m²; II tertile, ≥30.38 mm/m² but <33.75 mm/m²; and III tertile, ≥33.75 mm/m².

(For figure see next page.)

Table 4. Univariate and multivariate Cox regression analysis of factors associated with all-cause and CV mortality in the study patients

Parameters	Univariate			Multivariate ^a		
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
All-cause mortality						
PAB	0.99	0.99–1.00	<0.001	0.99	0.98–0.99	0.003
ARD (mm)	1.10	1.02–1.18	0.011	1.18	1.05–1.32	0.004
IVSd (mm)	1.14	1.00–1.30	0.045	1.21	1.00–1.45	0.046
LVEDDI (mm/m ²)	0.93	0.87–0.99	0.027	0.91	0.83–0.99	0.029
CV mortality						
PAB	0.99	0.99–1.00	0.015	0.99	0.98–0.99	0.018
ARD (mm)	1.10	1.01–1.21	0.038	1.13	1.01–1.27	0.031
IVSd (mm)	1.20	1.01–1.41	0.033	1.24	1.01–1.53	0.037
LVEDDI (mm/m ²)	0.91	0.84–0.99	0.039	0.92	0.83–1.03	0.142

^a Adjusted for: age, gender, BMI (except for LVEDDI), etiology of ESRD, diabetes and hypertension, systolic and diastolic blood pressure, serum albumin, total cholesterol, hsCRP, and eGFR.

and LVEDDI (HR = 0.91; 95% CI 0.83–0.99; HR = 0.92; 95% CI 0.83–1.03). However, after adjustment for clinical characteristics, the prediction value of LVEDDI for CV death showed no statistical significance (Table 4).

Mortality Regarding PAB and Echocardiographic Parameters at Baseline

In order to explore the predictive value of the combination of PAB and echocardiographic parameters in all-cause mortality and CV death, the patients were divided into 4 groups on the basis of the existence of: abnormal PAB, abnormal echocardiographic parameters, and both of the risk factors, i.e., a lower PAB (as denoted by PAB ≤bottom tertile, i.e., 336 mmol/L), a larger ARD (as denoted by ARD ≥top tertile, i.e., 35 mm), a thicker IVSd (as denoted by IVSd ≥top tertile, i.e., 13 mm), and a relatively small LVEDDI (as denoted by LVEDDI ≤bottom tertile, i.e., 30.35 mm/m²). Of the 211 patients, 21 (10.0%) had abnormal serum PAB alone, 79 (37.4%) had abnormal echocardiographic parameters alone, and 50 (23.7%) had both of the risk factors. We examined the survival rate in relation to the presence of abnormal PAB alone, abnormal echocardiographic parameters alone, and both abnormal PAB and echocardiographic parameters at the study baseline and noted a significant increase in all-cause mortality and CV death in patients with all of the above mentioned risk factors compared to those with none of the risk factors (*p* < 0.001 and *p* < 0.011; Fig. 5). Noticeably, patients with abnormal serum PAB alone had a higher mortality risk than those with abnormal echocardiographic parameters alone. Patients with both abnormal PAB and echocardiographic parameters had a higher mortality rate than those with abnormal serum PAB alone.

Discussion

Malnutrition and cardiac remodeling are well-known independent predictors of survival in ESRD patients. Our study investigated the relationship between the combined PAB and echocardiographic parameters and all-cause mortality and CV mortality in ESRD patients

Fig. 5. Percentage of all-cause mortality and CV mortality in relation to the number of risk factors present at the study baseline, i.e., a lower PAB (as denoted by $\text{PAB} \leq \text{bottom tertile}$, i.e., 336 mmol/L), a larger ARD (as denoted by $\text{ARD} \geq \text{top tertile}$, i.e., 35 mm), a thicker IVSd (as denoted by $\text{IVSd} \geq \text{top tertile}$, i.e., 13 mm), and a relatively small LVEDDI (as denoted by $\text{LVEDDI} \leq \text{bottom tertile}$, i.e., 30.35 mm/m²).

treated with PD. This study has confirmed that PAB is a strong predictor of mortality in patients with ESRD on PD. It has demonstrated that PAB acts as a significant outcome predictor even after adjustment for other nutritional parameters (serum albumin, cholesterol, and BMI) and eGFR. Adjusted HR per 1-g/L decrease in serum PAB were 0.99 (95% CI 0.98–0.99; $p = 0.002$) for all-cause mortality and 0.99 (95% CI 0.99–1.00; $p = 0.048$) for CV mortality. Moreover, all-cause and CV mortalities were significantly higher in patients in the lowest tertile (tertile 3) of serum PAB compared to those in the highest tertile (tertile 1). These findings are in accordance with previous prospective cohort studies which tested the serum PAB concentration among CKD nondialysis and dialysis patients [8–10]. Goldwasser et al. [24] proposed that a PAB value lower than 15 mg/dL was an independent predictor of mortality risk in hemodialysis patients. Avram et al. [24] demonstrated that a serum PAB value lower than 30 mg/dL was associated with increased mortality compared to higher PAB values in continuous ambulatory PD patients [25]. In the study conducted by Sreedhara et al. [26] it was further demonstrated that serum PAB appeared to be the single best nutritional predictor of survival in ESRD patients. Of note, these studies did not investigate CV mortality specifically or the echocardiographic parameters were excluded in the mortality risk prediction. In present study, we discovered a significant trend, i.e., that a low serum PAB was correlated with an increasing risk of CV death, even after adjustment for echocardiographic parameters.

Whether the serum PAB concentration is a more accurate indicator of nutritional status and an independent mortality predictor compared to previous markers, i.e., albumin and BMI, has been a matter of debate. This controversy persists with respect to the general population [27–29] and patients with various conditions [26, 30–32]. In present study, when other nutritional markers (albumin, cholesterol, and BMI) were included into Cox regression models, no difference was found in the association between serum PAB and overall mortality. In addition, the present study showed no significant difference in cholesterol or albumin between patients who survived or died during the follow-up period. This indicates that the prognostic value of PAB is independent of the above-mentioned markers. Although there was a significant

difference in BMI and hsCRP between the survivors and patients who died of CV or other causes, the relationship between PAB and mortality remained significant after adjustment. This indicates that the effect of PAB on mortality was at least partly independent of the inflammatory status.

In this study, we further noticed that the mortality risk could be predicted by echocardiographic indices in both univariable and multivariable analyses after adjustment for conventional clinical risk factors and renal function. ARD and septal wall thickness remained independent predictors of all-cause and CV mortality after adjustment of PAB. A relatively small, hypertrophic left ventricle was found to be a significant predictor of all-cause mortality in the PD cohort. The mechanisms underlying the linkage of echocardiographic data and increased mortality in PD patients may be multifactorial. In the present study, ARD was positively associated with all-cause mortality and CV death in PD patients. Enlargement of the ARD is thought to be correlated with tissue remodeling of the aortic wall (including increased collagen deposition, fatigue and fracture of elastin, and increased calcification), which contributed to the progression of aortic artery stiffness. Thus, we speculate that the resultant functional degradation of the aorta might contribute to the relationship between ARD and mortality observed in the present study. Previous studies have shown that the prevalence of concentric LVH is higher than that of eccentric LVH in chronic uremia [33]. Moreover, the prognostic value of LVH progression in CKD and dialysis patients has been clearly demonstrated [34]. However, most previous echocardiography studies in CKD patients have focused on the impact of LVM on outcomes and have not included IVS or LV diameter in the multivariate regression analysis. In our study, IVS and LVEDDI were found to be significant echocardiographic predictors of all-cause mortality, while LVMI and LV dysfunction were not significantly different between the survivors and patients who died during follow-up. This finding suggests that IVS together with LVEDDI might have a better prognostic value than LVMI and LV functional parameters in PD patients. Of note, although echocardiography is most readily available and widely utilized in routine clinical practice, the interpretation of these results needs to take into account the reproducibility of echocardiographic measurements. Further research with a larger sample size may be needed to validate the consistency of these findings in a PD population.

Results from this study showed that the all-cause mortality and CV death rates were 6.6 and 3.3%, respectively, in patients with none of the aforementioned risk factors. Patients with either of the two risk factors showed a significant increased risk of both all-cause and CV mortality compared to those without the 2 risk factors. Moreover, the combination of both abnormal PAB and echocardiographic parameters conveyed the greatest mortality risk. These findings support the value of combining PAB, ARD, IVS, and LVEDDI for improvement of the mortality risk stratification in PD patients. Furthermore, the mortality risk associated with a lower PAB, aortic dilatation, interventricular septal thickening, and a relatively small left ventricle was independent of CRP, blood pressure, and diabetes. This suggests that abnormal PAB, ARD, IVS, and LVEDDI may mediate increased mortality via mechanisms independent of inflammation and those risk factors.

To the best of our knowledge, the studies focusing on the combination value of nutritional markers and echocardiography for mortality risk stratification are limited, and therefore the prediction value of combining PAB and echocardiographic parameters has not yet been examined. This study particularly links the changes in PAB and echocardiography together to provide a noninvasive assessment of all-cause and CV mortality risk in patients treated with PD. It has been demonstrated that, in PD patients, together with PAB, multiple and easily determined echocardiographic indices including ARD, septal wall thickness, and LVEDDI would provide an incremental prognostic value versus a single-parameter evaluation.

There are several limitations in present study. First, small sample sizes limited the statistical power. Second, the follow-up periods were relatively short. Thus, a large-scale prospective cohort study among different ethnic groups is needed to eliminate the possibility of chance findings regarding especially echocardiographic parameters. Second, the present findings should be qualified given the observational nature of our study design. Also, additional evaluation is required, including comparisons with normal control patients in further studies, to further confirm the prediction value of serum PAB and the above-mentioned echocardiographic indices in a PD population. In addition, residual confounding might dampen or enhance the mortality risks described here. More precise estimates of the risks associated with serum PAB and echocardiographic indices might be obtained with additional adjustment for comorbidity and use of medications, although these would be unlikely to extinguish the associations described. Finally, the study sample was restricted to PD patients, so the results of this study might not apply to hemodialysis patients or to patients with less severe chronic kidney disease.

Conclusions

In present study, it was found that the combination of echocardiography and PAB would provide incremental prognostic value in PD patients, independently of each other and of other CV risk factors. Combining PAB and the above-mentioned echocardiography parameters in a simple prognosis model could further assist in the clinical management of patients undergoing PD treatment. Large-scale prospective studies are required to further prove an optimal model which contains PAB and echocardiographic indices for prediction of the mortality risk.

Statement of Ethics

This study complies with the Declaration of Helsinki, and ethical approval was obtained from the Ethical Review Committee of The First affiliated Hospital of Sun Yat-sen University. Informed consent was obtained from all of the enrolled patients before study entry.

Conflict of Interest Statement

The authors declare that no conflict of interests exists.

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Author Contributions

Conception and design of this study: M.Y., J.L., F.Y., and H.H. Acquisition of data: M.Y., J.L., Y.L., W.H., H.L., R.F., C.L., W.L., and J.Z. Data analysis, literature search, and generation of figures: M.Y., Y.L., and W.H. Data interpretation: M.Y., J.L., F.Y., and H.H. Drafting of this article: M.Y. and J.L. Critical revision of this paper for important intellectual content: F.Y. and H.H. Final approval of the version to be submitted: all authors.

References

- 1 Avram MM, Sreedhara R, Fein P, Oo KK, Chattopadhyay J, Mittman N. Survival on hemodialysis and peritoneal dialysis over 12 years with emphasis on nutritional parameters. *Am J Kidney Dis*. 2001 Jan;37(1 Suppl 2):S77–80.
- 2 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004 Sep;351(13):1296–305.
- 3 Kovesdy CP, George SM, Anderson JE, Kalantar-Zadeh K. Outcome predictability of biomarkers of protein-energy wasting and inflammation in moderate and advanced chronic kidney disease. *Am J Clin Nutr*. 2009 Aug;90(2):407–14.
- 4 Kovesdy CP, Shinaberger CS, Kalantar-Zadeh K. Epidemiology of dietary nutrient intake in ESRD. *Semin Dial*. 2010 Jul-Aug;23(4):353–8.
- 5 Chan M, Kelly J, Batterham M, Tapsell L. Malnutrition (subjective global assessment) scores and serum albumin levels, but not body mass index values, at initiation of dialysis are independent predictors of mortality: a 10-year clinical cohort study. *J Ren Nutr*. 2012 Nov;22(6):547–57.
- 6 Dai L, Mukai H, Lindholm B, Heimbürger O, Barany P, Stenvinkel P, et al. Clinical global assessment of nutritional status as predictor of mortality in chronic kidney disease patients. *PLoS One*. 2017 Dec;12(12):e0186659.
- 7 Chertow GM, Ackert K, Lew NL, Lazarus JM, Lowrie EG. Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. *Kidney Int*. 2000 Dec;58(6):2512–7.
- 8 Holland DC, Meers C, Lawlor ME, Lam M. Serial prealbumin levels as predictors of outcomes in a retrospective cohort of peritoneal and hemodialysis patients. *J Ren Nutr*. 2001 Jul;11(3):129–38.
- 9 Mittman N, Avram MM, Oo KK, Chattopadhyay J. Serum prealbumin predicts survival in hemodialysis and peritoneal dialysis: 10 years of prospective observation. *Am J Kidney Dis*. 2001 Dec;38(6):1358–64.
- 10 Chertow GM, Goldstein-Fuchs DJ, Lazarus JM, Kaysen GA. Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients. *Kidney Int*. 2005 Dec;68(6):2794–800.
- 11 Devakonda A, George L, Raoof S, Esan A, Saleh A, Bernstein LH. Transthyretin as a marker to predict outcome in critically ill patients. *Clin Biochem*. 2008 Oct;41(14–15):1126–30.
- 12 Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. *Am J Clin Nutr*. 2008 Dec;88(6):1485–94.
- 13 Park M, Hsu CY, Li Y, Mishra RK, Keane M, Rosas SE, et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Associations between kidney function and subclinical cardiac abnormalities in CKD. *J Am Soc Nephrol*. 2012 Oct;23(10):1725–34.
- 14 Chen R, Wu X, Shen LJ, Wang B, Ma MM, Yang Y, et al. Left ventricular myocardial function in hemodialysis and nondialysis uremia patients: a three-dimensional speckle-tracking echocardiography study. *PLoS One*. 2014 Jun;9(6):e100265.
- 15 Poulidakos D, Ross L, Recio-Mayoral A, Cole D, Andoh J, Chitalia N, et al. Left ventricular hypertrophy and endothelial dysfunction in chronic kidney disease. *Eur Heart J Cardiovasc Imaging*. 2014 Jan;15(1):56–61.
- 16 van Huis M, Schoenmaker NJ, Groothoff JW, van der Lee JH, van Dyk M, Gewillig M, et al. Impaired longitudinal deformation measured by speckle-tracking echocardiography in children with end-stage renal disease. *Pediatr Nephrol*. 2016 Sep;31(9):1499–508.
- 17 Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, et al. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol*. 2007 Feb;99(3):393–8.
- 18 Wu IW, Hung MJ, Chen YC, Hsu HJ, Cherg WJ, Chang CJ, et al. Ventricular function and all-cause mortality in chronic kidney disease patients with angiographic coronary artery disease. *J Nephrol*. 2010 Mar-Apr;23(2):181–8.
- 19 Payne J, Sharma S, De Leon D, Lu JL, Alemu F, Balogun RA, et al. Association of echocardiographic abnormalities with mortality in men with non-dialysis-dependent chronic kidney disease. *Nephrol Dial Transplant*. 2012 Feb;27(2):694–700.
- 20 Chen SC, Chang JM, Liu WC, Huang JC, Tsai JC, Lin MY, et al. Echocardiographic parameters are independently associated with increased cardiovascular events in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2012 Mar;27(3):1064–70.
- 21 Peterson GE, de Backer T, Contreras G, Wang X, Kendrick C, Greene T, et al.; African American Study of Kidney Disease Investigators. Relationship of left ventricular hypertrophy and diastolic function with cardiovascular and renal outcomes in African Americans with hypertensive chronic kidney disease. *Hypertension*. 2013 Sep;62(3):518–25.
- 22 Paoletti E, De Nicola L, Gabbai FB, Chiodini P, Ravera M, Pieracci L, et al. Associations of Left Ventricular Hypertrophy and Geometry with Adverse Outcomes in Patients with CKD and Hypertension. *Clin J Am Soc Nephrol*. 2016 Feb;11(2):271–9.
- 23 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al.; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005 Dec;18(12):1440–63.

- 24 Goldwasser P, Michel MA, Collier J, Mittman N, Fein PA, Gusik SA, et al. Prealbumin and lipoprotein(a) in hemodialysis: relationships with patient and vascular access survival. [Am J Kidney Dis](#). 1993 Jul;22(1):215–25.
- 25 Avram MM, Goldwasser P, Erroa M, Fein PA. Predictors of survival in continuous ambulatory peritoneal dialysis patients: the importance of prealbumin and other nutritional and metabolic markers. [Am J Kidney Dis](#). 1994 Jan;23(1):91–8.
- 26 Sreedhara R, Avram MM, Blanco M, Batish R, Avram MM, Mittman N. Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. [Am J Kidney Dis](#). 1996 Dec;28(6):937–42.
- 27 Collins N. The difference between albumin and prealbumin. [Adv Skin Wound Care](#). 2001 Sep-Oct;14(5):235–6.
- 28 Beck FK, Rosenthal TC. Prealbumin: a marker for nutritional evaluation. [Am Fam Physician](#). 2002 Apr;65(8):1575–8.
- 29 Ingenbleek Y, Young VR. Significance of transthyretin in protein metabolism. [Clin Chem Lab Med](#). 2002 Dec;40(12):1281–91.
- 30 Lin MY, Liu WY, Tolan AM, Aboulia A, Petrie BA, Stabile BE. Preoperative serum albumin but not prealbumin is an excellent predictor of postoperative complications and mortality in patients with gastrointestinal cancer. [Am Surg](#). 2011 Oct;77(10):1286–9.
- 31 Fujii T, Sutoh T, Morita H, Katoh T, Yajima R, Tsutsumi S, et al. Serum albumin is superior to prealbumin for predicting short-term recurrence in patients with operable colorectal cancer. [Nutr Cancer](#). 2012;64(8):1169–73.
- 32 Zhang SQ, Peng B, Stary CM, Jian ZH, Xiong XX, Chen QX. Serum prealbumin as an effective prognostic indicator for determining clinical status and prognosis in patients with hemorrhagic stroke. [Neural Regen Res](#). 2017 Jul;12(7):1097–102.
- 33 Parfrey PS, Foley RN, Harnett JD, Kent GM, Murray DC, Barre PE. Outcome and risk factors for left ventricular disorders in chronic uraemia. [Nephrol Dial Transplant](#). 1996 Jul;11(7):1277–85.
- 34 Zoccali C, Benedetto FA, Mallamaci F, Tripepi G, Giaccone G, Stancanelli B, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. [Kidney Int](#). 2004 Apr;65(4):1492–8.