ORIGINAL RESEARCH

Heart Rhythm Complexity Predicts Long-Term Cardiovascular Outcomes in Peritoneal Dialysis Patients: A Prospective Cohort Study

Cheng-Hsuan Tsai, MD; Jenq-Wen Huang, MD, PhD; Chen Lin, PhD; Hsi-Pin Ma, PhD; Men-Tzung Lo, PhD; Li-Yu Daisy Liu, PhD; Lian-Yu Lin, MD, PhD; Chih-Ting Lin, PhD; Chi-Sheng Hung, MD, PhD; Chung-Kang Peng, PhD; Yen-Hung Lin, MD, PhD

***Background*—**Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease. Heart rhythm complexity analysis has been shown to be useful in predicting outcomes in various diseases; however, data on patients with end-stage renal disease are limited. In this study, we analyzed the association between heart rhythm complexity and long-term cardiovascular outcomes in patients with end-stage renal disease receiving peritoneal dialysis.

***Methods and Results*—**We prospectively enrolled 133 patients receiving peritoneal dialysis and analyzed linear heart rate variability and heart rhythm complexity variables including detrended fluctuation analysis (DFA) and multiscale entropy. The primary outcome was cardiovascular mortality, and the secondary outcome was the occurrence of major adverse cardiovascular events. After a median of 6.37 years of follow-up, 21 patients (22%) died from cardiovascular causes. These patients had a significantly lower low-frequency band of heart rate variability, low/high-frequency band ratio, total power band of heart rate variability, heart rate turbulence slope, deceleration capacity, short-term DFA (DFAα1); and multiscale entropy slopes 1 to 5, scale 5, area 1 to 5, and area 6 to 20 compared with the patients who did not die from cardiovascular causes. Time-dependent receiver operating characteristic curve analysis showed that DFAα1 had the greatest discriminatory power for cardiovascular mortality (area under the curve: 0.763) and major adverse cardiovascular events (area under the curve: 0.730). The best cutoff value for DFAα1 was 0.98 to predict both cardiovascular mortality and major adverse cardiovascular events. Multivariate Cox regression analysis showed that DFAα1 (hazard ratio: 0.076; 95% CI, 0.016–0.366; P=0.001) and area 1 to 5 (hazard ratio: 0.645; 95% CI, 0.447–0.930; P=0.019) were significantly associated with cardiovascular mortality.

***Conclusions*—**Heart rhythm complexity appears to be a promising noninvasive tool to predict long-term cardiovascular outcomes in patients receiving peritoneal dialysis. **(*J Am Heart Assoc*. 2020;9:e013036. DOI: 10.1161/JAHA.119.013036.)**

Key Words: cardiovascular mortality • heart rhythm complexity • peritoneal dialysis

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in patients with end-stage renal disease (ESRD).[1,2] ESRD patients have mortality rates up to 30-fold higher than the general population, and CVD accounts for ≈38% of all deaths.[3] In the US Renal Data System database, 62% of cardiac deaths were attributable to arrhythmic mechanisms including sudden cardiac death (SCD).[4] Identifying the ESRD patients at high risk of CVD and providing better risk stratification are crucial issues.

Analysis of variations in heart rate, known as heart rate variability (HRV), is a noninvasive tool that uses 24-hour ECG to assess dysregulation of the autonomic nervous system.[5] Conventional linear HRV measures have been associated with the outcomes of CVD patients.[6] Heart rhythm

From the Department of Internal Medicine, National Taiwan University Hospital JinShan Branch, New Taipei, Taiwan (C.-H.T.); Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan (J.-W.H., L.-Y.L., C.-S.H., Y.-H.L.); Department of Biomedical Sciences and Engineering, National Central University, Taoyuan City, Taiwan (C.L., M.-T.L.); Department of Electrical Engineering, National Tsing Hua University, Hsinchu, Taiwan (H.-P.M.); Biometry Division, Department of Agronomy (L.-Y.D.L.) and Graduate Institute of Biomedical Electronics and Bioinformatics (C.-T.L.), National Taiwan University, Taipei, Taiwan; Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA (C.-K.P.).

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Correspondence to: Yen-Hung Lin, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. E-mail: austinr34@gmail.com and Chi-Sheng Hung, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. E-mail: petrehcs@gmail.com

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Clinical Perspective

What Is New?

- In this study, we provide compressive linear and nonlinear heart rate variability outcome analysis in patients receiving peritoneal dialysis.
- Worse nonlinear heart rate variability analysis including multiscale entropy and detrended fluctuation analysis is strongly associated with worse long-term cardiovascular outcomes.

What Are the Clinical Implications?

- Cardiovascular disease is the major cause of morbidity and mortality in peritoneal dialysis patients.
- Nonlinear heart rate variability analysis can help clinicians identify high-risk patients and provide timely management.

complexity variables can be obtained from nonlinear signal analysis methods such as detrended fluctuation analysis (DFA) and multiscale entropy (MSE).[7] These new analysis methods are based on the assumption that a healthy organism has an interactive and commutative system that is able to maintain operation in a rapidly changing environment.[8,9] These new methods have been reported to have better prognostic power in patients with CVD than traditional linear analysis.[10–12] To the best of our knowledge, few studies have investigated heart rhythm complexity in ESRD patients, especially long-term follow-up results. In this study, we aimed to investigate the predictive ability of heart rhythm complexity regarding cardiovascular outcomes in patients with ESRD undergoing peritoneal dialysis (PD) after long-term follow-up.

Material and Methods

Anonymized patient-level data will be made available by the corresponding author upon reasonable request.

Patients

In this prospective cohort study, we enrolled 133 ESRD patients undergoing PD. The inclusion criteria were (1) ESRD patients aged ≥20 years; (2) ESRD patients who had received maintenance PD at National Taiwan University Hospital for >3 months; (3) patients without chronic atrial fibrillation, clinical signs of acute infection, or receipt of a kidney transplant. The medical history of each participant, including demographics and medications, was carefully recorded, and biochemical data were measured at the initial evaluation. These patients were also reported in our previous studies of dyslipidemia, left ventricular diastolic dysfunction, and heart rhythm complexity.[13–16]

This study was approved by the institutional review board of National Taiwan University Hospital, and written informed consent was obtained from all patients who participated in this study.

Outcomes

The patients were prospectively followed from February 2009 at our PD clinic. The primary outcome measure was cardiovascular mortality, and the secondary outcome measure was major adverse cardiovascular events (MACE). Cardiovascular mortality was defined as mortality due to acute coronary syndrome, SCD, life-threatening arrhythmia, progressive heart failure, and ischemic or hemorrhagic stroke. SCD was defined as cardiac arrest occurring suddenly and within 1 hour of witnessed symptom onset.[3] Patients with documented ventricular tachycardia or ventricular fibrillation were categorized as having life-threatening arrhythmia. MACE was defined as cardiovascular mortality, nonlethal ischemic or hemorrhagic stroke, or nonlethal acute coronary syndrome. Patients who received kidney transplants were censored in cardiovascular mortality and MACE analyses.

ECG Holter and Data Analysis

All participants received 24-hour ECG Holter examinations (ZymedDigiTrak Plus 24-Hour Holter Monitor Recorder and Digitrak XT Holter Recorder 24 Hour; Philips). A stable 4-hour segment of daytime R-R intervals was selected for HRV analysis based on the following criteria: (1) between 9 AM and 6 PM and (2) without sudden increases in heart rate of >40 beats/min within 1 minute. The selected ECGs were automatically annotated using an algorithm and carefully examined and corrected by 2 experienced technicians who were blinded to the patients' clinical information to avoid intentional selection bias.

Predictors of Interest

The predictors of interest included linear and nonlinear HRV variables. The linear HRV variables included time-domain HRV, frequency-domain HRV, heart rate turbulence (HRT), and heart rate deceleration capacity (DC). The nonlinear HRV variables included DFA and MSE.

First, time-domain HRV variables were calculated as statistics of R-R intervals, and frequency-domain HRV variables were analyzed using spectrum analysis as R-R interval variance within specific frequency bands. The time-domain variables, mean R-R interval, standard deviation of normal R-R intervals (SDRR), percentage of absolute differences in normal

R-R intervals >50 and >20 ms were calculated to represent the total variance and vagal modulation of heart rate. The frequency domain variables including high-frequency (HF) band (0.15–0.4 Hz), low-frequency (LF) band (0.04–0.15 Hz) and very LF (VLF) band (0.003–0.04 Hz), and the sum of the energy in HF, LF, and VLF bands (total power, 0.0–0.4 Hz) were calculated by averaging the absolute power (ms^2) after Fourier transformation.

Second, HRT was represented by 2 numeric descriptors: turbulence onset (TO), reflecting the initial acceleration of heart rate after a premature beat, and turbulence slope (TS), describing subsequent deceleration.[17,18] HRT was calculated using a computer algorithm to detect changes in R-R intervals surrounding ventricular or atrial premature beats. The heart rate DCs were calculated in 5 steps, including definition of anchors, definition of segments, phase rectification, signal averaging, and quantification of DCs using the following formula: DC (AC)=[X(0)+X(1)−X(−1)–X(−2)]/4.[19,20]

Third, DFA is a type of nonlinear HRV analysis that can be used to evaluate the self-affinity and fractal behavior beneath seemingly nonstationary R-R dynamics, and the scaling exponents are calculated using DFA.[21] The slope (α exponent) of the log-log plot of fluctuations against time scales indicates the fractal correlation properties of the time series. The crossover phenomenon of α exponents of R-R dynamics over short (α1; 4–11 beats) and long (α2; 11–64 beats) time scales has been observed in both patients with disease and healthy subjects.[21] Both short- and long-term α exponents were calculated in our study to better understand the fractal property of the physiologic system.

Fourth, MSE analysis is another type of nonlinear HRV analysis that can be used to estimate the physiologic signals in time scales and evaluate the degree of predictable sequential changes over different time scales.[22] Time series of different time scales were calculated via a coarse-graining process (ie, averaging consecutive beats to form a new time series). The estimated entropy over different time scales represents the complexity of the physiologic signals.[23] In this study, 4 different MSE variables were analyzed: the entropy value of scale 5 (scale 5), the linear-fitted slope of scales 1 to 5 (slopes 1–5), the summation of entropy values of scales 1 to 5 (area 1–5) and 6 to 20 (area 6–20) to quantify the complexity of the R-R dynamics exhibited in short and long time scales.

Covariates

The covariates in this study included baseline demographic data including age, sex, body mass index, prevalence of diabetes mellitus, hypertension, medication use at enrollment, and duration of PD. The results of biochemistry analysis and echocardiography including fasting glucose level, hemoglobin A_{1c}, serum creatinine, PD Kt/V (urea clearance, normalized for total body water), triglycerides, total cholesterol, LDL (low-density lipoprotein), HDL (high-density lipoprotein), serum electrolytes, CRP (C-reactive protein), and left ventricular ejection fraction were also analyzed as covariates in this study.

Statistical Analysis

Data were expressed as mean±SD and median (25th–75th percentiles) for normally and nonnormally distributed data (determined using the Kolmogorov–Smirnov test), respectively. Comparisons of data between the patients who died from cardiovascular causes (cardiovascular mortality group) and those who did not experience the event (group without cardiovascular mortality) were made using the independent *t* test and Mann–Whitney U test, as appropriate. Differences in proportions between groups were assessed using the χ^2 test. Comparisons of data among the cardiovascular mortality group, patients who died from noncardiovascular causes, and survivors were analyzed using the Kruskal–Wallis test, and the Mann–Whitney U test was used for post hoc analysis with Bonferroni correction for type I errors.

The predicted probability of an event for each patient (ie, cardiovascular mortality) at the last follow-up was obtained using a Cox proportional hazards model. The discriminatory ability of each marker was assessed using the time-dependent area under the receiver operating characteristic (ROC) curve (AUC). Differences between 2 AUCs (from the time-dependent ROC analysis) were compared using the DeLong test.[24]

We further determined the optimal cutoff point of the marker with the highest AUC among all markers for cardiovascular mortality and MACE. Kaplan–Meier survival curves according to the cutoff were plotted, and the log-rank test was used for comparisons. Finally, Cox regression analysis was used to explore associations between variables and cardiovascular mortality and MACE. Significant determinants in univariate Cox regression analysis ($P<0.05$) were then tested in multivariate Cox regression analysis with stepwise subset selection to identify the associated factors of cardiovascular mortality and MACE. The patients who died from noncardiovascular causes and those who received a kidney transplant were censored in the model. Category-free (continuous) net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to examine improvements in the accuracy of prediction after adding nonlinear HRV variables (ie, DFAα1 or area 1–5) into the model with only a linear HRV variable (ie, SDRR).

The predicted probability of an event in the Cox model was obtained using the "phreg" procedure in SAS v9.4 (SAS Institute). The AUCs, DeLong test, IDI, and NRI were

calculated using the "add_predictive" SAS macro (SAS v9.4). The optimal cutoff point of a marker in the survival analysis was determined using R v3.6.1 (R Development Core Team) and the "survminer" package (v0.4.6, updated September 3, 2019). Other analyses were done using SPSS v25 for Windows (IBM Corp). The significance level of the statistical analysis was set at 0.05.

Results

Patients

A total of 133 PD patients (61 men) were enrolled in this study. After a median 6.37 years (interquartile range: 2.95–9.17 years) of follow-up, 21 patients (cumulative incidence: 22%) died from cardiovascular causes (cardiovascular mortality group), including 8 from SCD, 8 from life-threatening arrhythmias (ventricular tachycardia/ventricular fibrillation), 4 from acute decompensated heart failure, and 1 from an intracranial hemorrhagic stroke. There were 24 non–cardiovascular-related deaths (non–cardiovascular-mortality group; cumulative incidence: 26%), including 22 from sepsis and 2 from advanced lung cancer. The cumulative incidence of MACE was 26% during follow-up, including 21 patients who died from cardiovascular causes, 4 from nonlethal acute myocardial infarctions, and 1 from nonlethal ischemic stroke.

There were no significant differences in baseline characteristics between the groups with and without cardiovascular mortality except for age (Table 1). Participants with cardiovascular mortality were significantly older than those without cardiovascular mortality. In addition, the cardiovascular-mortality group had borderline lower left ventricular ejection fraction compared with the group without cardiovascular mortality (P=0.05).

Table 1. Clinical Characteristics by Cardiovascular Mortality

	Cardiovascular Mortality (n=21)	No Cardiovascular Mortality (n=112)	*P* Value
Age, y	59±8.3	53±13	0.006
BMI	24±3.9	23±2.4	0.384
Male	8 (38)	53 (47)	0.436
DM	6 (29)	22 (20)	0.357
HTN	18 (86)	95 (85)	0.916
ACEI or ARB	10 (48)	55 (49)	0.900
β-Blocker	10 (48)	67 (60)	0.299
CCB	17 (81)	72 (64)	0.136
Statin	5 (24)	41 (37)	0.258
Glucose AC, mg/dL	115±33	106±34	0.278
HbA_{1c}, %	6.1±0.81	5.7±0.91	0.062
Creatinine, mg/dL	11±2.4	11±2.7	0.155
PD, Kt/V	1.9±0.30	1.9±0.37	0.512
PD duration, mo	48±32	42±43	0.528
TGs, mg/dL	170±88	201±182	0.447
T-Chol, mg/dL	184±38	197±47	0.208
LDL, mg/dL	93±44	90±38	0.745
HDL, mg/dL	37±11	41±12	0.184
Na, mmol/L	136±5.3	136±4.2	0.916
K, mmol/L	3.8±0.71	3.9±0.68	0.687
Ca, mmol/L	9.5±1.1	9.6±0.92	0.673
P, mmol/L	5.3±1.1	5.4±1.2	0.599
CRP, mg/dL	1.0±1.1	1.1±2.2	0.875
LVEF, %	60±17	68±10	0.050

Data are presented as mean±SD or number (percentage). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CRP, C-reactive protein; DM, diabetes mellitus; HbA_{1c}, hemglobin A_{1c}; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; PD, peritoneal dialysis; T-Chol, total cholesterol; TGs, triglycerides. Glucose AC, fasting blood glucose; Kt/V, urea clearance, normalized for total body water.

Linear HRV and Heart Rhythm Complexity Variables in the Groups With and Without Cardiovascular Mortality

The heart rhythm complexity variables including DFAα1, MSE slopes 1 to 5, scale 5, area 1 to 5, and area 6 to 20 were significantly lower in the cardiovascular-mortality group compared with the group without cardiovascular mortality (Table 2). Among the linear HRV variables, LF, LH/HF ratio, total power, TS of HRT, and DC were significantly lower in the cardiovascular-mortality group. In the group without cardiovascular mortality (including patients who died from noncardiovascular causes and survivors), subgroup analysis showed that all linear HRV and heart rhythm complexity variables were comparable between the patients who died from noncardiovascular causes and the survivors (Table S1).

Discrimination of HRV Variables for Cardiovascular Mortality and MACE

The results showed that DFAα1 had the greatest discriminatory power to differentiate the groups with and without cardiovascular mortality in the time-dependent ROC curve analysis (Figure 1). The significant heart rhythm complexity predictors of cardiovascular mortality included DFAα1 (AUC: 0.763; 95% CI, 0.681–0.845), slope 5 (AUC; 0.695; 95% CI, 0.595–0.795), scale 5 (AUC: 0.705; 95% CI, 0.604–0.805), area 1 to 5 (AUC: 0.674; 95% CI, 0.564–0.783), and area 6 to 20 (AUC: 0.682; 95% CI, 0.574–0.791). The significant linear HRV predictors of cardiovascular mortality included VLF (AUC:

Table 2. Holter Variables by Cardiovascular Mortality

	Cardiovascular Mortality (n=21)	No Cardiovascular Mortality (n=112)	*P* Value
Time domain analysis			
Mean R-R interval, ms	775.05 (691.95–873.86)	763.58 (686.45–866.23)	0.730
SDRR, ms	37.53 (29.76–46.42)	40.84 (27.05–57.56)	0.521
pNN20, %	5.03 (2.11–16.64)	5.47 (1.50–16.89)	0.836
pNN50, %	0.81 (0.21–2.59)	0.33 (0.05–1.91)	0.332
Frequency domain analysis			
VLF, ms^2	315.90 (158.39–799.24)	618.81 (256.84–1206.39)	0.060
LF, ms^2	46.54 (26.07–140.48)	117.52 (43.48–255.24)	0.023
HF, ms^2	35.97 (18.93–90.63)	43.65 (15.50–98.45)	0.758
LF/HF ratio	1.11 (0.86–1.85)	2.21 (1.32–3.82)	0.001
TP, ms^2	366.35 (206.17–994.72)	792.28 (346.98–1642.62)	0.040
TO of HRT	0.29 (−0.34 to 1.27)	−0.35 (−1.47 to 0.81)	0.146
TS of HRT	4.30 (3.37–5.87)	6.36 (3.72–9.31)	0.035
DC, ms	3.07 (2.08–3.87)	3.86 (2.58–5.41)	0.044
Heart rhythm complexity analysis			
DFAα1	0.94 (0.81–1.11)	1.21 (1.01–1.37)	<0.001
DFAα2	1.27 (1.13–1.35)	1.23 (1.16–1.29)	0.294
Slopes 1–5	0.0039 (−0.020 to 0.044)	0.053 (0.0033–0.087)	0.002
Scale 5	0.83 (0.72–0.97)	1.015 (0.82–1.19)	0.001
Area 1–5	3.96 (3.05–4.56)	4.55 (3.76–5.39)	0.009
Area 6–20	15.47 (13.48–17.91)	18.21 (15.66–20.97)	0.006

Data are presented as median (25th–75th percentiles). DC indicates deceleration capacity; DFA, detrended fluctuation analysis; HF, high frequency; HRT, heart rate turbulence; LF, low frequency; pNN20, percentage of the absolute change in consecutive normal R-R interval >20 ms; pNN50, percentage of the absolute change in consecutive normal R-R interval >50 ms; SDRR, standard deviation of normal R-R intervals; TO, turbulence onset; TP, total power; TS, turbulence slope; VLF, very low frequency.

0.632; 95% CI, 0.505–0.760), LF (AUC: 0.662; 95% CI, 0.533–0.791), LF/HF ratio (AUC: 0.725; 95% CI, 0.613–0.838), total power (AUC: 0.645; 95% CI, 0.517–0.772), TO of HRT (AUC: 0.645; 95% CI, 0.534–0.757), TS of HRT (AUC: 0.654; 95% CI, 0.540–0.768), and DC (AUC: 0.649; 95% CI, 0.516–0.782). The AUC values of all HRV variables to predict cardiovascular mortality are listed in Table S2.

DFAα1 had the greatest discriminatory power to differentiate the patients who did and did not have MACE in the time-dependent ROC curve analysis compared with other HRV variables. The significant heart rhythm complexity predictors of MACE included DFAα1 (AUC: 0.730; 95% CI, 0.633–0.826), slope 5 (AUC: 0.688; 95% CI, 0.590–0.786), scale 5 (AUC: 0.676; 95% CI, 0.572–0.779), and area 6 to 20 (AUC: 0.662; 95% CI, 0.556–0.769). The significant linear HRV predictors of MACE included VLF (AUC: 0.640; 95% CI, 0.539–0.742), LF (AUC: 0.669; 95% CI, 0.564–0.773), LF/HF ratio (AUC: 0.702; 95% CI, 0.593–0.810), total power (AUC: 0.654; 95% CI, 0.553–0.755), TS of HRT (AUC: 0.668; 95% CI, 0.572–0.764), and DC (AUC: 0.653; 95% CI, 0.538–0.768). The AUC values of all HRV variables to predict MACE are listed in Table S2.

Optimal Cutoff Value for DFAα1 to Predict Cardiovascular Outcomes

We then determined the optimal cutoff value for DFAα1 to predict cardiovascular mortality and MACE. The best cutoff value for DFAα1 was 0.98 to predict both cardiovascular mortality and MACE, and the patients with DFAα1 ≤0.98 had higher risks of cardiovascular mortality and MACE (Figure 2A and 2B).

Factors Associated With Cardiovascular Mortality and MACE Using a Cox Model

In univariate Cox regression analysis, age, hemoglobin A_{1c}, left ventricular ejection fraction, VLF, LF/HF ratio, total power, TS of HRT, DFAα1, MSE slopes 1 to 5, scale 5, area 1 to 5, and area 6 to 20 were significantly associated with

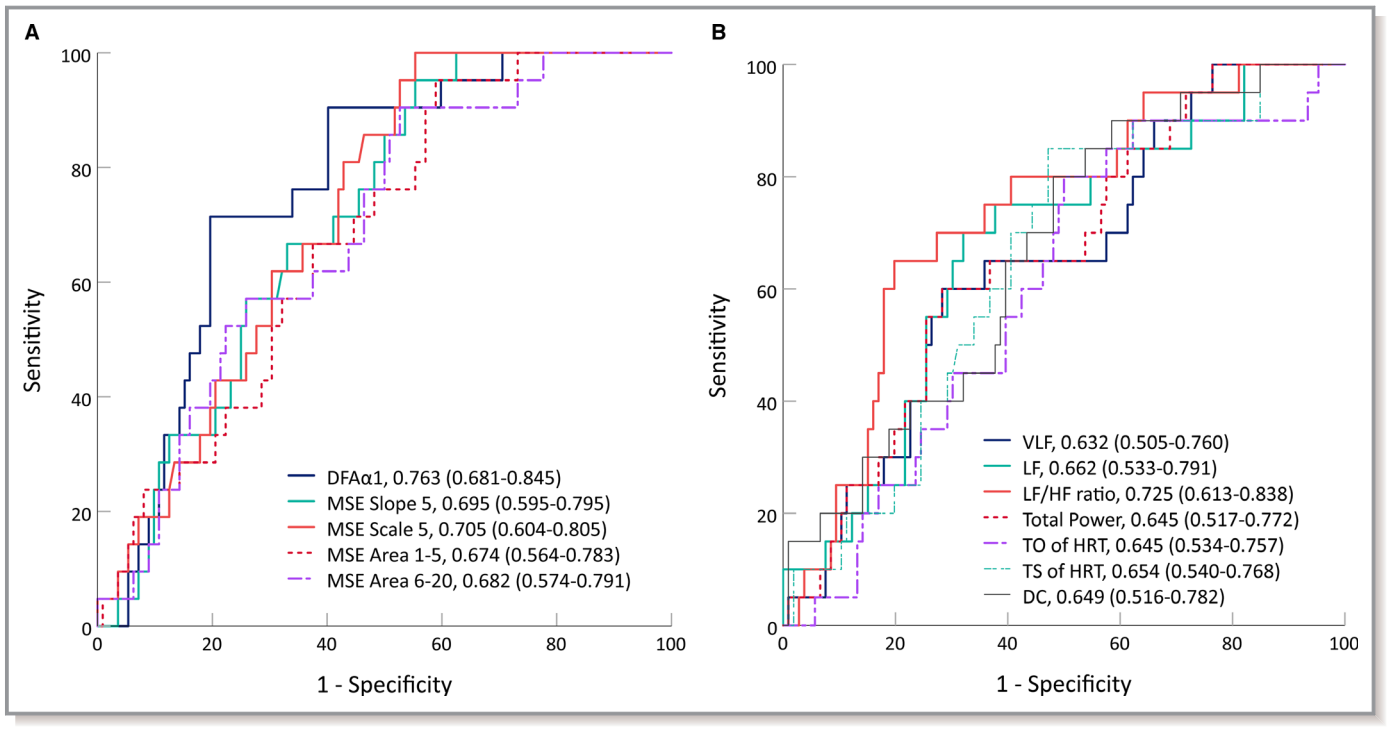

Figure 1. Analysis of the discrimination power of heart rate variability (HRV) variables of cardiovascular mortality using receiver operating characteristic curve analysis. **A**, Areas under the curve of significant cardiovascular mortality predictors of heart rhythm complexity including detrended fluctuation analysis α1 (DFAα1), slope 5, scale 5, area 1 to 5, and area 6 to 20. **B**, Areas under the curves of significant cardiovascular mortality predictors of linear HRV including very low frequency (VLF), low frequency (LF), low/high-frequency (LF/HF) ratio, total power, turbulence slope (TS) and turbulence onset (TO) of heart rate turbulence (HRT), and deceleration capacity (DC). MSE indicates multiscale entropy.

cardiovascular mortality. In multivariate Cox regression analysis, only DFAα1 (hazard ratio [HR]: 0.076; 95% CI, 0.016–0.366; *P*=0.001) and area 1 to 5 (HR: 0.645; 95% CI, 0.447–0.930; *P*=0.019) remained in the model (Table 3).

Age, left ventricular ejection fraction, VLF, LF, LF/HF ratio, total power, TS of HRT, DFAα1, DFAα2, slopes 1 to 5, scale 5, area 1 to 5, and area 6 to 20 were associated with MACE in univariate Cox regression analysis. In multivariate Cox regression analysis, age (HR: 1.058; 95% CI, 1.007–1.111; *P*=0.026), DFAα1 (HR: 0.063; 95% CI, 0.012–0.338; *P*=0.001), and DFAα2 (HR: 497.548; 95% CI, 12.991–19056; *P*=0.001) remained in the model (Table 4).

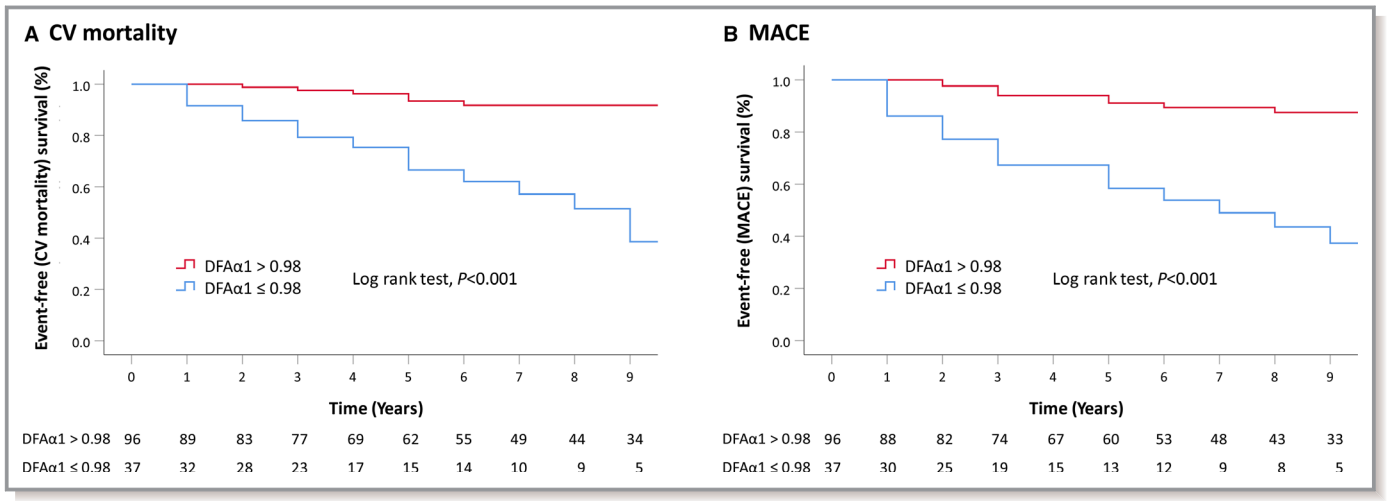

Figure 2. Event-free survival curves for cardiovascular (CV) mortality (**A**) and major adverse cardiac events (MACE) (**B**) in the patients according to detrended fluctuation analysis α1 (DFAα1) ≤0.98 or >0.98.

Table 3. Univariate and Multivariate Cox Regression Analyses to Predict Cardiovascular Mortality

	Univariate Regression		Multivariate Regression	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.058 (1.013–1.105)	0.011	. . .	. . .
Sex	1.209 (0.500–2.290)	0.673	. . .	. . .
DM	1.844 (0.713–4.768)	0.207	. . .	. . .
HTN	2.282 (0.304–17.112)	0.422	. . .	. . .
PD, Kt/V	1.346 (0.479–3.782)	0.573	. . .	. . .
PD duration, mo	−0.003 (0.988–1.007)	0.605	. . .	. . .
Creatinine, mg/dL	0.885 (0.741–1.058)	0.180	. . .	. . .
TGs, mg/dL	0.999 (0.996–1.002)	0.485	. . .	. . .
T-Chol, mg/dL	0.993 (0.983–1.003)	0.163	. . .	. . .
LDL, mg/dL	1.002 (0.992–1.013)	0.678	. . .	. . .
HDL, mg/dL	0.966 (0.924–1.009)	0.120	. . .	. . .
Glucose AC, mg/dL	1.007 (0.997–1.017)	0.196	. . .	. . .
HbA_{1c}, %	1.479 (1.008–2.170)	0.046	. . .	. . .
CRP, mg/dL	1.032 (0.847–1.259)	0.753	. . .	. . .
LVEF, %	0.965 (0.939–0.992)	0.010	. . .	. . .
Mean R-R interval, ms	1.001 (0.997–1.004)	0.749	. . .	. . .
SDRR, ms	0.992 (0.971–1.014)	0.475	. . .	. . .
pNN20, %	0.998 (0.966–1.030)	0.881	. . .	. . .
pNN50, %	1.000 (0.936–1.069)	0.994	. . .	. . .
VLF, ms^2	0.999 (0.998–1.000)	0.040	. . .	. . .
LF, ms^2	0.995 (0.991–1.000)	0.058	. . .	. . .
HF, ms^2	0.999 (0.995–1.003)	0.692	. . .	. . .
LF/HF ratio	0.537 (0.339–0.851)	0.008	. . .	. . .
TP, ms^2	0.999 (0.998–1.000)	0.044	. . .	. . .
TO of HRT	25 574 (0.145–4.5×10^9)	0.100	. . .	. . .
TS of HRT	0.826 (0.704–0.969)	0.019	. . .	. . .
DC, ms	0.788 (0.601–1.034)	0.085	. . .	. . .
DFAα1	0.071 (0.017–0.290)	<0.001	0.076 (0.016–0.366)	0.001
DFAα2	25.232 (0.439–1449)	0.118	. . .	. . .
Slopes 1–5	0.001 (<0.001–0.238)	0.015	. . .	. . .
Scale 5	0.061 (0.011–0.320)	0.001	. . .	. . .
Area 1–5	0.598 (0.414–0.864)	0.006	0.645 (0.447–0.930)	0.019
Area 6–20	0.858 (0.774–0.951)	0.003	. . .	. . .

CRP indicates C-reactive protein; DC, deceleration capacity; DFA, detrended fluctuation analysis; DM, diabetes mellitus; HbA_{1c}, hemglobin A_{1c}; HDL, high-density lipoprotein; HF, high frequency; HR, hazard ratio; HRT, heart rate turbulence; HTN, hypertension; LDL, low-density lipoprotein; LF, low frequency; LVEF, left ventricular ejection fraction; PD, peritoneal dialysis; pNN20, percentage of the absolute change in consecutive normal R-R interval >20 ms; pNN50, percentage of the absolute change in consecutive normal R-R interval >50 ms; SDRR, standard deviation of normal R-R intervals; T-Chol, total cholesterol; TGs, triglycerides; TO, turbulence onset; TP, total power; TS, turbulence slope; VLF, very low frequency. Glucose AC, fasting blood glucose; Kt/V, urea clearance, normalized for total body water.

Factors Associated With Noncardiovascular Mortality and MACE Using a Cox Model

In univariate Cox regression analysis, age, hypertension, duration of PD, and DFAα2 were significantly associated with noncardiovascular mortality. In multivariate Cox regression analysis, only age (HR: 1.085; 95% CI, 1.036–1.137; *P*=0.001) and duration of PD (HR: 1.009; 95% CI, 1.003–1.016; *P*=0.006) and none of the HRV variables remained in the model (Table S3).

Adding Heart Rhythm Complexity Variables to Linear HRV Variables or Another Heart Rhythm Complexity Variable to Discriminate Cardiovascular Mortality

DFAα1 significantly improved the discriminatory power of SDRR, VLF, LF, and HF in the IDI model and SDRR, LF, and HF in the NRI model (Table 5). In addition, area 1 to 5 significantly improved the discriminatory power of SDRR, VLF, LF, HF, and LF/HF ratio in the IDI model and SDRR, VLF, LF, and HF in the NRI model. Furthermore, the combination of DFAα1 and area 1 to 5 significantly improved the AUC to 0.787 (P=0.0144) from the original AUC of area 1 to 5, and the improvement was significant in both the NRI and IDI models.

Discussion

This study had 3 major findings. First, cardiovascular mortality in the PD patients was highly associated with worse heart rhythm complexity. Second, of all linear HRV variables and the heart rhythm complexity variables, DFAα1 had the greatest single discriminatory power to predict cardiovascular mortality and MACE. Third, heart rhythm complexity variables DFAα1 and MSE area 1 to 5 significantly improved the discriminatory power of the linear HRV variables for cardiovascular mortality.

The increasing prevalence of chronic kidney disease is a major burden for healthcare systems, and a significant portion of these patients will progress to ESRD and require renal replacement therapy.[25] In these patients, CVD is the leading cause of morbidity and mortality.[26,27] Consequently, predicting the cardiovascular outcomes in this high-risk population is of paramount importance in clinical practice. The pathophysiology of CVD in ESRD patients includes accelerated atherosclerosis, congestive heart failure, poor control of hypertension, left ventricular hypertrophy, autonomic dysfunction, pulmonary hypertension, and SCD.[4,25,28–31] HRV analysis is a powerful tool for evaluating these diseases, and worse HRV has been reported to be associated with the risk of atherosclerosis-related vascular complications,[14,32,33] SCD,[34] poor outcomes of congestive heart failure,[6,10] and pulmonary hypertension.[35,36] In ESRD patients, traditional linear HRV variables have also been shown to predict the outcomes.[37] Brotman et al reported that autonomic dysfunction as measured by traditional linear HRV analysis might be an important risk factor for ESRD- and chronic kidney disease–related hospitalizations.[38] However, traditional linear HRV variables, and especially time-domain variables, have limited predictive power for clinical outcomes.[39] In contrast to the abundant data on linear HRV variables, few studies have investigated heart rhythm complexity in ESRD patients. Ferrario et al reported that heart rhythm complexity and MSE variables were associated with physical condition and left ventricular systolic function.[40] However, to the best of our knowledge, only 1 outcome study has used heart rhythm complexity variables in ESRD patients. Suzuki et al showed that DFAα1, but not linear HRV variables, was an independent risk factor associated with clinical outcomes in hemodialysis patients.[37] However, they did not perform MSE analysis, which has been shown to have remarkable power to predict outcomes in various diseases.[10,16,41] In contrast to the study by Suzuki et al, we enrolled patients receiving PD in the present study. In hemodialysis patients, large variations in hemodynamic and fluid status are caused by the hemodialysis process and schedule. These variations will influence linear HRV and heart rhythm complexity and possibly confound their results in ESRD patients. In contrast, PD patients have more stable fluid and hemodynamic status than hemodialysis patients.[42] Consequently, HRV and heart complexity variables obtained from PD patients have less variation and fewer confounders than those from patients receiving hemodialysis. Consequently, we chose PD patients to investigate changes in heart rhythm complexity in this study. In our previous studies, we found that PD patients had worse heart rhythm complexity compared with patients with normal renal function.[15] In addition, heart rhythm complexity has been associated with the severity of abdominal aorta calcification, which is a documented risk factor for cardiovascular events.[14] We also previously showed the strength of DFAα1 in the prediction of short-term outcomes (follow-up time: 2.8 years).[43] In the current study, we evaluated more linear HRV and heart rhythm complexity variables with a long follow-up period (up to 9 years; median follow-up time: 6.37 years) and showed the ability of heart rhythm complexity variables to predict long-term cardiovascular outcomes in PD patients.

Heart rhythm complexity measures the complexity rather than only changes in the variability of heart rate interval. MSE and DFA are based on different theories to measure the complexity underlying heart rate dynamics. MSE analysis, based on chaos theory, has been shown to be capable of extending the traditional entropy algorithm to quantify information richness over multiple time scales in physiologic systems.[22] DFA, another heart rhythm complexity analysis method, based on fractal theory, can be used to determine the statistical self-affinity of a biological signal.[21] The breakdown of DFA has been shown to cause more random dynamics during coactivation of sympathetic and vagal systems.[44] Measurements of heart rhythm complexity have been associated with the prognosis of heart failure,[10] outcomes of acute stroke,[41] primary aldosteronism,[45] critical illnesses requiring extracorporeal life support,[16] and post–myocardial infarction heart function.[46] In the patients with congestive heart failure included in the DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide) trial, DFAα1, rather than traditional linear HRV

Table 4. Univariate and Multivariate Cox Regression Analyses to Predict MACE

	Univariate Regression		Multivariate Regression	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.044 (1.007–1.083)	0.019	1.058 (1.007–1.111)	0.026
Sex	1.025 (0.470–2.234)	0.950	. . .	. . .
DM	1.997 (0.865–4.606)	0.105	. . .	. . .
HTN	3.056 (0.413–22.638)	0.274	. . .	. . .
PD, Kt/V	1.202 (0.456–3.170)	0.710	. . .	. . .
PD duration, mo	1.002 (0.993–1.010)	0.679	. . .	. . .
Creatinine, mg/dL	0.917 (0.786–1.071)	0.273	. . .	. . .
TGs, mg/dL	0.998 (0.995–1.002)	0.341	. . .	. . .
T-Chol, mg/dL	0.994 (0.985–1.003)	0.162	. . .	. . .
LDL, mg/dL	1.004 (0.994–1.014)	0.411	. . .	. . .
HDL, mg/dL	0.977 (0.941–1.014)	0.222	. . .	. . .
Glucose AC, mg/dL	1.007 (0.998–1.015)	0.124	. . .	. . .
HbA_{1c}, %	1.369 (0.964–1.945)	0.080	. . .	. . .
CRP, mg/dL	1.013 (0.837–1.225)	0.896	. . .	. . .
LVEF, %	0.966 (0.943–0.990)	0.005	. . .	. . .
Mean R-R interval, ms	1.001 (0.998–1.004)	0.373	. . .	. . .
SDRR, ms	0.989 (0.969–1.008)	0.262	. . .	. . .
pNN20, %	0.992 (0.963–1.022)	0.598	. . .	. . .
pNN50, %	0.986 (0.920–1.058)	0.702	. . .	. . .
VLF, ms^2	0.999 (0.998–1.000)	0.027	. . .	. . .
LF, ms^2	0.995 (0.991–1.000)	0.030	. . .	. . .
HF, ms^2	0.998 (0.994–1.003)	0.450	. . .	. . .
LF/HF ratio	0.742 (0.506–0.983)	0.038	. . .	. . .
TP, ms^2	0.999 (0.999–1.000)	0.024	. . .	. . .
TO of HRT	6008 (0.080–4.5×10^8)	0.129	. . .	. . .
TS of HRT	0.829 (0.719–0.955)	0.009	. . .	. . .
DC, ms	0.793 (0.621–1.011)	0.062	. . .	. . .
DFAα1	0.120 (0.034–0.428)	0.001	0.063 (0.012–0.338)	0.001
DFAα2	45.451 (1.194–1730.765)	0.040	497.548 (12.991–19056.259)	0.001
Slopes 1–5	0.001 (<0.001–0.183)	0.009	. . .	. . .
Scale 5	0.096 (0.022–0.427)	0.002	. . .	. . .
Area 1–5	0.668 (0.483–0.925)	0.015	. . .	. . .
Area 6–20	0.881 (0.804–0.966)	0.007	. . .	. . .

CRP indicates C-reactive protein; DC, deceleration capacity; DFA, detrended fluctuation analysis; DM, diabetes mellitus; HbA_{1c}, hemglobin A_{1c}; HDL, high-density lipoprotein; HF, high frequency; HR, hazard ratio; HRT, heart rate turbulence; HTN, hypertension; LDL, low-density lipoprotein; LF, low frequency; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; PD, peritoneal dialysis; pNN20, percentage of the absolute change in consecutive normal R-R interval >20 ms; pNN50, percentage of the absolute change in consecutive normal R-R interval >50 ms; SDRR, standard deviation of normal R-R intervals; T-Chol, total cholesterol; TGs, triglycerides; TO, turbulence onset; TP, total power; TS, turbulence slope; VLF, very low frequency.

variables, was shown to be an independent predictor of mortality after adjusting for clinical variables.[11] In the present study, our data supported that worse heart rhythm complexity, as indicated by both DFA and MSE variables, was significantly associated with cardiovascular mortality and MACE. Among these variables, DFAα1 had the best predictive power for cardiovascular mortality and MACE compared with the other linear HRV and heart rhythm complexity variables.

SCD and life-threatening arrhythmias accounted for 76% of all cases of cardiovascular mortality in this study. Previous

Table 5. AUCs of Cardiovascular Mortality Prediction Before and After Adding DFAα1 and MSE Area 1 to 5 to Linear and Nonlinear Variables in NRI and IDI Models

Variables	AUC (95% CI)	*P* Value, DeLong test	cNRI (95% CI)	*P* Value, cNRI	IDI (95% CI)	*P* Value, IDI
Area 1–5	0.674 (0.564–0.783)	…	…	…	…	…
Plus DFAα1	0.787 (0.709–0.864)	0.0144	0.75 (0.326–1.174)	0.0016	0.103 (0.043–0.163)	0.0008
SDRR	0.519 (0.408–0.631)	…	…	…	…	…
Plus DFAα1	0.757 (0.672–0.841)	0.003	0.821 (0.399–1.244)	<0.001	0.097 (0.041–0.154)	0.0007
Plus Area 1–5	0.792 (0.715–0.869)	0.0004	0.952 (0.551–1.353)	<0.001	0.176 (0.075–0.277)	0.0006
VLF	0.632 (0.505–0.760)	…	…	…	…	…
Plus DFAα1	0.758 (0.675–0.840)	0.0029	0.416 (−0.037 to 0.870)	0.0797	0.057 (0.017–0.097)	0.0056
Plus Area 1–5	0.787 (0.709–0.864)	0.0008	0.75 (0.326–1.174)	0.0007	0.124 (0.042–0.206)	0.0029
LF	0.662 (0.533–0.791)	…	…	…	…	…
Plus DFAα1	0.755 (0.672–0.839)	0.0099	0.553 (0.125–0.981)	0.0199	0.058 (0.017–0.100)	0.0057
Plus Area 1–5	0.788 (0.712–0.865)	0.0053	0.720 (0.313–1.127)	0.0025	0.118 (0.032–0.203)	0.0068
HF	0.544 (0.399–0.689)	…	…	…	…	…
Plus DFAα1	0.764 (0.684–0.845)	0.0002	0.785 (0.362–1.209)	0.001	0.101 (0.045–0.158)	0.0004
Plus Area 1–5	0.790 (0.713–0.868)	0.0001	0.839 (0.417–1.26)	0.0004	0.175 (0.071–0.280)	0.001
LF/HF ratio	0.725 (0.613–0.838)	…	…	…	…	…
Plus DFAα1	0.739 (0.635–0.843)	0.2597	−0.012 (−0.477 to 0.453)	0.9601	0.003 (−0.014 to 0.021)	0.7149
Plus Area 1–5	0.775 (0.682–0.867)	0.0824	0.232 (−0.229 to 0.693)	0.329	0.074 (0.005–0.142)	0.0345

AUC indicates area under the curve; cNRI, category-free (continuous) net reclassification improvement; DFA, detrended fluctuation analysis; DFAα1, short-term DFA; HF, high frequency; IDI, integrated discrimination improvement; LF, low frequency; MSE, multiscale entropy; NRI, net reclassification improvement; SDRR, standard deviation of normal R-R intervals; VLF, very low frequency.

studies have shown that worse traditional HRV can predict SCD and life-threatening arrhythmias.[47,48] The current study provides solid evidence that both linear HRV including HRT and heart rhythm complexity analysis can be used to predict cardiovascular outcomes in PD patients. The linear HRV variables including VLF, LF/HF ratio, total power and TS of HRT were significantly associated with cardiovascular mortality after univariate Cox regression analysis in this study. The heart rhythm complexity analysis had better correlation with cardiovascular mortality and MACE compared with linear HRV variables, which implies that heart rhythm complexity variables provide more useful information. Furthermore, combining linear HRV and heart rhythm complexity variables further significantly improved the discriminatory power to predict cardiovascular mortality, and this combination provided more accurate information to build the ROC curve model to predict cardiovascular mortality in the PD patients. Overall, we demonstrated the superiority of heart rhythm complexity, and especially DFAα1, compared with linear HRV analysis in predicting cardiovascular mortality and MACE in PD patients.

This study has several limitations. First, this was a cohort study conducted at a single center with a small number of patients, and consequently only a few significant associations between the outcomes and predictors were observed. Therefore, the results of this study may have been underpowered, and further studies with larger sample sizes are needed to confirm our findings. Second, we enrolled PD patients in this study, and further studies are needed to confirm whether the results can be applied to hemodialysis patients. Patients receiving hemodialysis have high variation in daily hemodynamic status due to the hemodialysis process, making cardiac rhythm analysis and interpretation of the results more complex.

In conclusion, heart rhythm complexity analysis could predict long-term cardiovascular mortality and MACE in the PD patients in this study. DFAα1 had the greatest discriminatory power to predict cardiovascular outcomes. In addition, DFAα1 and MSE area 1 to 5 significantly improved the discriminatory power of the linear HRV variables for cardiovascular outcomes, suggesting the advantage of combining linear HRV and heart rhythm complexity variables in outcome evaluations.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1: Holter variables in the CV-mortality, non-CV-mortality and survival groups

	CV mortality (N=21)	Non-CV mortality (N=24)	Survival (N=88)	P Value
Time Domain Analysis				
Mean RR, ms	775.05(691.95~873.86)	737.04 (666.43~833.07)	775.28 (693.96~870.03)	0.690
SDRR, ms	37.53 (29.76~46.62)	36.96 (21.89~45.94)	42.93 (28.92~58.40)	0.227
pNN50, %	0.81 (0.21~2.59)	0.25 (0.04~1.58)	0.36 (0.07~2.17)	0.524
pNN20, %	5.03 (2.11~16.64)	3.17 (1.21~13.56)	6.02 (1.91~19.03)	0.377
Frequency Domain Analysis				
VLF, ms^2	315.90 (158.39~799.24)	441.70 (132.54~971.36)	667.63 (326.79~1291.94)	0.029
LF, ms^2	46.54 (26.07~140.48)	115.53 (26.78~178.73)	117.52 (43.48~271.73)	0.048
HF, ms^2	35.97 (18.93~90.63)	39.58 (10.48~64.91)	45.32 (17.44~105.24)	0.529
LF/HF ratio	1.11 (0.86~1.85)	2.42 (0.94~4.97)	2.21 (1.40~3.73)	0.003¶
TP, ms^2	366.35 (206.17~994.72)	613.19 (184.49~1191.64)	801.91 (376.83~1805.07)	0.035
TO of HRT	0.29 (-0.34~1.27)	0.34 (-1.18~1.42)	-0.44 (-1.50~0.66)	0.198
TS of HRT	4.30 (3.37~5.87)	4.80 (3.48~9.01)	6.98 (3.93~9.33)	0.041
DC, ms	3.07 (2.08~3.87)	3.55 (1.89~4.46)	3.94 (2.74~5.80)	0.046
Detrended fluctuation analysis				
DFAα1	0.94 (0.81~1.11)	1.22 (0.90~1.39)	1.21 (1.04~1.37)	<0.001¶

DFAα2	1.27 (1.13~1.35)	1.20 (1.08~1.27)	1.24 (1.18~1.29)	0.271
Multiscale entropy				
Slope1-5	0.0039 (-0.020~0.44)	0.054 (-0.0007~0.089)	0.053 (0.0052~0.086)	0.008¥
Scale5	0.84 (0.72~0.97)	1.025 (0.81~1.20)	1.01 (0.83~1.18)	0.005¶
Area1-5	3.96 (3.05~4.56)	4.41 (3.37~5.31)	4.60 (3.85~5.42)	0.025¶
Area6-20	15.47 (13.48~17.91)	17.85 (15.60~20.72)	18.21 (15.66~21.13)	0.020¶

Post hoc analysis with Bonferroni correction

1. ¶: CV-mortality group only significantly lower than the survival group, P<0.05/3
2. ¥: CV-mortality group significantly lower than both the non-CV-mortality and survival groups, P<0.05/3

Data are presented as median (25th~75th percentile). SDNN=standard deviation of normal RR intervals; pNN20=percentage of the absolute change in consecutive normal RR interval > 20 ms; pNN50=percentage of the absolute change in consecutive normal RR interval > 50 ms; VLF=very low frequency; LF=low frequency; HF=high frequency; TP=total power; HRT=heart rate turbulence; TO=turbulence onset; TS=turbulence slope; DC=deceleration capacity and DFA=detrended fluctuation analysis

Table S2: Analysis of the discriminatory power of HRV variables for CV mortality and MACEs with receiver operating characteristic curves

	CV mortality	MACEs
	AUC (95% CI)	AUC (95% CI)
Linear HRV variables		
Mean RR	0.534 (0.398 to 0.670)	0.536 (0.425 to 0.647)
SDRR	0.519 (0.408 to 0.631)	0.560 (0.461 to 0.659)
pNN20	0.487 (0.347 to 0.628)	0.512 (0.388 to 0.637)
pNN50	0.577 (0.437 to 0.717)	0.443 (0.322 to 0.565)
VLF	0.632 (0.505 to 0.760)	0.640 (0.539 to 0.742)
LF	0.662 (0.533 to 0.791)	0.669 (0.564 to 0.773)
HF	0.544 (0.399 to 0.689)	0.563 (0.441 to 0.685)
LF/HF ratio	0.725 (0.613 to 0.838)	0.702 (0.593 to 0.810)
TP, ms^2	0.645 (0.517 to 0.772)	0.654 (0.553 to 0.755)
TO of HRT	0.645 (0.534 to 0.757)	0.624 (0.531 to 0.718)
TS of HRT	0.654 (0.540 to 0.768)	0.668 (0.572 to 0.764)
DC, ms	0.649 (0.516 to 0.782)	0.653 (0.538 to 0.768)
Heart rhythm complexity variables		
DFAα1	0.763 (0.681 to 0.845)	0.730 (0.633 to 0.826)

DFAα2	0.583 (0.440 to 0.725)	0.614 (0.501 to 0.728)
Slope 1-5	0.695 (0.595 to 0.795)	0.688 (0.590 to 0.786)
Scale 5	0.705 (0.604 to 0.805)	0.676 (0.572 to 0.779)
Area 1-5	0.674 (0.564 to 0.783)	0.639 (0.532 to 0.746)
Area 6-20	0.682 (0.574 to 0.791)	0.662 (0.556 to 0.769)

SDRR=standard deviation of normal RR intervals; pNN20=percentage of the absolute change in consecutive normal RR interval > 20 ms; pNN50=percentage of the absolute change in consecutive normal RR interval > 50 ms; VLF=very low frequency; LF=low frequency; HF=high frequency; TP=total power; HRT=heart rate turbulence; TO=turbulence onset; TS=turbulence slope; DC=deceleration capacity and DFA=detrended fluctuation analysis

Table S3: Univariate and multivariate Cox regression analyses to predict non-CV mortality

	Univariate regression		Multivariate regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years	1.077 (1.031~1.125)	0.001	1.085 (1.036~1.137)	0.001
Sex	0.452 (0.198~1.033)	0.060		
DM	1.312 (0.488~3.526)	0.590		
HTN	0.381 (0.151~0.961)	0.041		
PD KT/V	0.931 (0.318~2.722)	0.896		
PD duration, month	1.008 (1.002~1.015)	0.015	1.009 (1.003~1.016)	0.006
Creatinine, mg/dL	0.927 (0.788~1.090)	0.360		
TGs, mg/dL	1.000 (0.998~1.002)	0.824		
T-Chol, mg/dL	1.001 (0.993~1.009)	0.801		
LDL, mg/dL	1.005 (0.995~1.014)	0.313		
HDL, mg/dL	1.003 (0.971~1.037)	0.838		
Glucose AC, mg/dL	0.995 (0.981~1.011)	0.556		
HbA1c, %	0.913 (0.558~1.494)	0.717		
CRP, mg/dL	1.041 (0.879~1.231)	0.644		
LVEF, %	1.023 (0.980~1.068)	0.306		

Mean RR, ms	0.998 (0.995~1.001)	0.291
SDRR, ms	0.990 (0.969~1.010)	0.319
pNN20, %	0.985 (0.951~1.021)	0.423
pNN50, %	1.021 (0.974~1.070)	0.391
VLF, ms^2	0.999 (0.999~1.000)	0.141
LF, ms^2	0.999 (0.997~1.002)	0.595
HF, ms^2	1.001 (0.999~1.003)	0.254
LF/HF ratio	1.053 (0.936~1.185)	0.391
TP, ms^2	1.000 (0.999~1.000)	0.279
TO of HRT	48.31 (<0.001~$2.4*10^8$)	0.622
TS of HRT	0.910 (0.809~1.024)	0.117
DC, ms	0.998 (0.820~1.215)	0.982
DFAα1	0.546 (0.132~2.264)	0.404
DFAα2	0.058 (0.005~0.699)	0.025
Slope 1-5	7.731 (0.008~7499)	0.560
Scale 5	1.033 (0.238~4.476)	0.965
Area 1-5	0.976 (0.716~1.330)	0.875
Area 6-20	0.981 (0.882~1.091)	0.729

DM=diabetes mellitus; HTN=hypertension; PD=peritoneal dialysis;

TGs=triglycerides; T-Chol=total cholesterol; LDL=low-density lipoprotein; HDL=high-density lipoprotein; CRP=C-reactive protein; LVEF=left ventricular ejection fraction; SDRR=standard deviation of normal RR intervals; pNN20=percentage of the absolute change in consecutive normal RR interval > 20 ms; pNN50=percentage of the absolute change in consecutive normal RR interval > 50 ms; VLF=very low frequency; LF=low frequency; HF=high frequency; TP=total power; HRT=heart rate turbulence; TO=turbulence onset; TS=turbulence slope; DC=deceleration capacity and DFA=detrended fluctuation analysis