The Value of Heart Rhythm Complexity in Identifying High-Risk Pulmonary Hypertension Patients

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Abstract

Pulmonary hypertension (PH) is a fatal disease even under state-of-the-art medical treatment. Non-invasive clinical tools for risk stratification are still lacking. The aim of this study was to investigate the clinical utility of heart rhythm complexity in risk stratification for PH patients. We prospectively enrolled 54 PH patients, including 20 high-risk patients (group A; defined as WHO functional class IV or class III with severely compromised hemodynamics), and 34 low-risk patients (group B). Both linear and non-linear heart rate variability (HRV) variables, including detrended fluctuation analysis (DFA) and multiscale entropy (MSE) were analyzed. In linear and non-linear HRV analysis, low frequency and high frequency ratio, DFAα1, MSE slope 5, scale 5 and area 6–20 were significantly lower in group A. Among all HRV variables, MSE scale 5 (AUC: 0.758) had the best predictive power to discriminate the two groups. In multivariable analysis, MSE scale 5 ($p = 0.010$) was the only significantly predictor of severe PH in all HRV variables. In conclusion, the patients with severe PH had worse heart rhythm complexity. MSE parameters, especially scale 5, can help to identify high-risk PH patients.

Introduction

Pulmonary hypertension (PH) is a progressive, complex, and fatal disease. It involves heterogenous etiologies and different mechanisms[1], and eventually leads to right heart failure. The mortality of PH patients is high even after contemporary treatment[2], however timely and intensive management can improve outcomes even in high-risk patients. In addition, the dynamic adjustment of PH medications based on disease status during follow-up also plays an important role in PH management[3–5]. Therefore, a useful tool for PH risk stratification is urgently needed to guide PH treatment. Several prognostic factors of PH have been verified, including sex, exercise tolerance, right heart hemodynamics, and functional performance[6–8], and they have been applied in different prediction models.

In 2015, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines first proposed a dynamic PH risk assessment tool, including a combination of imaging, biologic, hemodynamic, performance status and clinical conditions[1]. This tool has shown good survival prediction between different risk groups[9,10], however it requires right heart hemodynamic measurements, which are invasive and difficult to apply for continuous monitoring of PH severity in clinical practice. Therefore, in this study, we propose a non-invasive and convenient tool for PH risk assessment derived from heart rate variability (HRV), namely, heart rhythm complexity analysis.

Heart rhythm complexity analyzes the complexity of changes in heart rate using non-linear methods, and it has been shown to have better predictive value for the diagnosis of PH and heart failure outcomes[11–13] than traditional HRV linear analysis[14]. In our previous study, we found that heart rhythm complexity was decreased in PH patients, and that it was useful to differentiate PH patients from normal populations[13]. However, whether heart rhythm complexity is useful in the risk stratification of PH patients is unknown.

Therefore, we designed this study to investigate the clinical application of heart rhythm complexity in the risk stratification of PH patients.

Results

Patient characteristics

The clinical, echocardiographic and hemodynamic variables of the enrolled patients are listed in Table 1. There were 20 patients in the high-risk group (group A) and 34 patients in the low-risk group (group B).

Table 1
Clinical Data of the patients

	High-risk group (N = 20)	Low-risk group (N = 34)	*P* Value
Age (Years)	43.80 ± 10.70	45.76 ± 11.34	0.533
Male, n (%)	9 (45%)	12 (35%)	0.480
BMI ($kg \cdot m^{-2}$)	22.09 ± 3.85	24.21 ± 4.41	0.081
CAD, n (%)	1 (5%)	1 (3%)	1.000
DM, n (%)	2 (10%)	3 (9%)	1.000
HTN, n (%)	1 (5%)	5 (15%)	0.395
Dyslipidemia, n (%)	1 (5%)	3 (9%)	1.000
PAH (WHO group 1)	17 (55%)	18 (29%)	0.017
Hemoglobin (g/dl)	13.72 ± 3.15	13.52 ± 3.76	0.835
Creatinine (mg/dl)	1.15 ± 0.67	0.76 ± 0.26	0.024
Log NT-Pro BNP	3.34 ± 0.54	2.52 ± 0.54	< 0.001
NT-Pro BNP (ng/dl)	1510 (959 ~ 6428)	292 (116 ~ 1045)	< 0.001
LVEF (%)	68.55 ± 9.46	68.62 ± 10.07	0.977
TRPG (mmHg)	93.31 ± 31.8	64.67 ± 28.10	0.001
Pericardial effusion, n (%)	7 (35%)	1 (3%)	0.003
6MWD (m)	298.31 ± 128.00	367.42 ± 120.32	0.074
mPAP (mmHg)	58.11 ± 15.46	47.44 ± 15.27	0.021
PVR (Wood Units)	13.63 ± 6.00	8.24 ± 4.23	0.002
CO ($L \cdot min^{-1}$)	3.71 ± 1.59	4.45 ± 1.30	0.081
CI ($L \cdot min^{-1} \cdot m^2$)	2.26 ± 0.97	2.75 ± 0.86	0.069
PCWP (mmHg)	14.00 ± 4.23	12.09 ± 3.69	0.097
PAH specific medication			

Abbreviation:

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal Pro-Brain Natriuretic Peptide; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; 6MWD, 6-minute-walk-distance; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac index; PCWP, pulmonary capillary wedge pressure

	High-risk group (N = 20)	Low-risk group (N = 34)	*P* Value
Sildenafil, n(%)	8 (40%)	15 (44%)	0.768
Macitentan, n(%)	3 (15%)	1 (3%)	0.138
Riociguat, n(%)	0 (0%)	6 (18%)	0.074
Bosentan, n(%)	2 (10%)	2 (6%)	0.622
Iloprost, n(%)	4 (20%)	1 (3%)	0.057
Epoprostenol, n(%)	1 (5%)	1 (3%)	1.000
Abbreviation:			
BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; PAH, pulmonary arterial hypertension; NT-proBNP, N-terminal Pro-Brain Natriuretic Peptide; LVEF, left ventricular ejection fraction; TRPG, tricuspid regurgitation pressure gradient; 6MWD, 6-minute-walk-distance; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CO, cardiac output; CI, cardiac index; PCWP, pulmonary capillary wedge pressure			

Compared to group B, significantly more patients in group A had World Health Organization (WHO) group 1 pulmonary artery hypertension (PAH) and pericardial effusion. In addition, group A had higher levels of serum creatinine and plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), and higher tricuspid regurgitation peak gradient (TRPG) than group B. In pulmonary hemodynamic studies, pulmonary vascular resistance (PVR), and mean pulmonary artery pressure (mPAP) were significantly higher in group A. The PAH specific medication was listed in Table 1.

Predictors of interest: HRV analysis

In linear HRV analysis, group A had significantly lower the ratio of low frequency (LF) and high frequency (HF) compared to group B. Other linear parameters were comparable between the two groups (Table 2). In non-linear HRV analysis, group A had significantly lower DFAα1, lower the slope of MSE curve between scale 1–5 (slope 1–5), the entropy values of scale 5 (scale 5) and lower area under the MSE curve for scale 6–20 (area 6–20) compared to group B (Table 2). The entropies over different time scales in group A and group B are shown in Fig. 1.

Table 2
Holter parameters of the patients

	High-risk group (N = 20)	Low-risk group (N = 34)	*P* Value
Time Domain Analysis			
Mean RR (ms)	684.03 (605.77 ~ 795.63)	748.63 (678.30 ~ 805.53)	0.203
SDRR (ms)	57.14 (43.84 ~ 65.88)	64.42 (54.37 ~ 87.43)	0.162
pNN20 (%)	19.17 (9.20 ~ 26.67)	20.86 (13.94 ~ 36.88)	0.463
pNN50 (%)	3.47 (0.32 ~ 12.32)	2.21 (0.77 ~ 6.64)	0.667
Frequency Domain Analysis			
VLF (ms^{-2})	172.56 (46.43 ~ 543.01)	384.16 (169.56 ~ 604.98)	0.062
LF (ms^{-2})	64.99 (19.52 ~ 140.02)	98.00 (38.11 ~ 174.58)	0.333
HF (ms^{-2})	42.28 (12.81 ~ 227.52)	36.46 (15.94 ~ 125.03)	0.629
LF/HF ratio	1.06 (0.56 ~ 2.17)	2.14 (1.03 ~ 3.61)	0.026
Detrended fluctuation analysis			
DFAα1	0.92 (0.56 ~ 1.05)	1.04 (0.89 ~ 1.23)	0.028
DFAα2	1.12 (1.01 ~ 1.19)	1.11 (1.03 ~ 1.17)	0.900
Multiscale entropy			
Slope 1–5	-0.008 (-0.075 ~ 0.039)	0.04 (-0.03 ~ 0.07)	0.038
Scale 5	1.01 (0.73 ~ 1.14)	1.22 (1.06 ~ 1.36)	0.002
Area 1–5	3.30 (2.94 ~ 4.44)	4.18 (3.26 ~ 4.89)	0.135
Area 6–20	15.94 (12.48 ~ 18.40)	18.89 (15.16 ~ 20.91)	0.004

Comparisons of linear and non-linear HRV parameters to differentiate the high-risk PH patients (Fig. 2)

In area under the receiving operating characteristic curve (AUC) analysis, MSE scale 5 had predictive power to predict the high-risk PH patients. The AUCs of MSE scale 5 was 0.758. The AUCs of other linear and non-linear HRV parameters were 0.604 (mean RR), 0.616 (standard deviation of RR interval [SDRR]), 0.560 (percentage of absolute differences in normal RR intervals greater than 20 ms [pNN20]), 0.465 (percentage of absolute differences in normal RR intervals greater than 50 ms [pNN50]), 0.653 (VLF), 0.579 (low frequency [LF]), 0.460 (high frequency [HF]), 0.682 (LH/HF ratio), 0.681 (DFAα1), 0.510 (DFAα2), 0.671 (slope 1–5), 0.623 (area 1–5) and 0.737 (area 6–20).

Logistic regression analysis to predict the presence of high-risk PH (Table 3)

Table 3
Univariable and multivariable logistic regression model to predict the high-risk group in pulmonary hypertension

Univariable logistic regression			**Multivariable logistic regression**	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.984 (0.935 ~ 1.035)	0.525		
Sex	1.500 (0.486 ~ 4.631)	0.481		
BMI	**0.884** (0.768 ~ **1.017**)	**0.086**		
PAH group 1	**5.037 (1.242 ~ 20.43)**	**0.024**		
Creatinine	**8.301 (1.358 ~ 50.75)**	**0.022**		
NT-Pro BNP	1.001 (1.000 ~ **1.002**)	**0.019**	**1.001 (1.000 ~ 1.002)**	**0.009**
6MWD	0.995 (0.990 ~ 1.001)	0.080		
mPAP	**1.046 (1.005 ~ 1.089)**	**0.029**		
CI	**0.525 (0.258 ~ 1.067)**	**0.075**		
PVR	**1.232 (1.070 ~ 1.418)**	**0.004**		
Mean RR	0.997 (0.992 ~ 1.002)	0.198		
SDRR	0.992 (0.973 ~ 1.010)	0.373		
pNN20	0.993 (0.961 ~ 1.025)	0.647		
pNN50	1.016 (0.971 ~ 1.063)	0.503		
VLF	0.998 (0.996 ~ 1.000)	0.08**1**		
LF	0.999 (0.997 ~ 1.002)	0.543		
HF	1.000 (0.999 ~ 1.001)	0.858		
LF/HF ratio	0.622 (0.391 ~ 0.990)	0.045		
DFAα1	0.072 (0.008 ~ 0.626)	0.017		
DFAα2	0.457 (0.006 ~ 33.761)	0.721		
Slope 1–5	0.000 (0.000 ~ 0.560)	0.036		
Scale 5	0.012 (0.001 ~ 0.222)	0.003	**0.009 (< 0.001 ~ 0.324)**	**0.010**
Area 1–5	0.705 (0.418 ~ 1.189)	0.190		
Area 6–20	0.835 (0.714 ~ 0.977)	0.024		

In univariable logistic regression analysis, serum creatinine level, PAH group 1, plasma NT-pro BNP level, mPAP, PVR, LF/HF ratio, DFAα1, MSE slope 1–5, scale 5, and area 6–20 were significantly associated with the presence of high-risk PH. These parameters were further investigated in multivariable logistic regression analysis, which showed that plasma NT-pro BNP levels (odds ratio [OR]: 1.001, 95% confidence interval [CI]: 1.000 ~ 1.002, p = 0.009), and MSE scale 5 (OR: 0.009, 95% CI: <0.001 ~ 0.324, p = 0.010) were remained in the model and both NT-pro BNP level and MSE scale 5 were significantly associated with the presence of high-risk PH.

The effect of adding heart rhythm complexity to the linear HRV parameters to identify high-risk PH patients (Table 4)

Table 4
AUC, NRI, and IDI models of linear parameters before and after adding DFAα1 and MSE parameters for risk stratification in pulmonary hypertension

Parameters		AUC	R square	NRI	NRI p-value	IDI	IDI p-value
Mean RR		0.604	0.032				
	+ Scale5	0.775	0.051	0.694	0.008	0.194	0.001
	+Area 6–20	0.749	0.12	0.535	0.048	0.092	0.026
	+ DFAα1	0.701	0.126	0.494	0.071	0.095	0.028
SDRR		0.615	0.015				
	+ Scale5	0.781	0.12	0.771	0.003	0.211	0.001
	+Area 6–20	0.731	0.121	0.494	0.071	0.107	0.014
	+ DFAα1	0.681	0.123	0.535	0.048	0.108	0.017
VLF		0.653	0.061				
	+ Scale5	0.782	0.117	0.535	0.048	0.171	0.002
	+Area 6–20	0.725	0.147	0.653	0.014	0.082	0.035
	+ DFAα1	0.699	0.145	0.694	0.008	0.084	0.037
LF		0.579	0.008				
	+ Scale5	0.768	0.086	0.771	0.003	0.209	0.001
	+Area 6–20	0.731	0.118	0.494	0.071	0.112	0.012
	+ DFAα1	0.694	0.134	0.553	0.042	0.129	0.01
HF		0.54	0.001				
	+ Scale5	0.76	0.029	0.871	0.001	0.221	< 0.001
	+Area 6–20	0.734	0.116	0.553	0.042	0.118	0.01
	+ DFAα1	0.694	0.129	0.612	0.023	0.132	0.009
LF/HF ratio		0.682	0.075				
	+ Scale5	0.806	0.077	0.771	0.003	0.184	0.001
	+Area 6–20	0.76	0.156	0.394	0.154	0.068	0.039
	+ DFAα1	0.718	0.114	0.335	0.228	0.027	0.19

In both net reclassification improvement (NRI) and integrated discrimination improvement (IDI) models, the MSE scale 5 significantly improved the discrimination power of all linear HRV parameters, including mean RR, SDRR, VLF, LF, HF, and LF/HF ratio. Area 6–20 significantly improved the discrimination power of mean RR, VLF and HF in both NRI and IDI models, and SDRR, LF and LF/HF ratio in IDI model. DFAα1 significantly improved the discrimination power of SDRR, VLF, LF and HF in both the NRI and IDI models, and mean RR in the IDI model.

Discussion

The main finding of this study was that heart rhythm complexity was significantly depressed in high-risk PH patients. In addition, adding heart rhythm complexity predictors to traditional linear HRV parameters improved the power to predict high-risk PH patients. This is the first study to demonstrate an association between heart rhythm complexity and severity of PH, and the better performance of heart rhythm complexity in identifying high-risk PH patients than traditional HRV parameters.

PH is a critical disease which needs an early diagnosis and timely management. Patients classified as being at high risk according to the 2015 ESC/ERS PH guidelines have a worse prognosis compared to patients at low risk. Sitbon et al. demonstrated that poor functional status was associated with poor outcomes. In their study, PH patients in WHO functional class IV and those in class III with severely compromised hemodynamics had the worst outcomes[15]. Previous studies have demonstrated that early interventions including both pharmacological and multidisciplinary team care can improve the outcomes of PH patients, even those with severe disease and poor functional status[5]. Therefore, identifying high-risk patients is essential for the management of PH. Several survival prediction models have been proposed for PH patients, however they are complex and difficult to use[16]. Currently, the 2015 ESC/ERS PH guidelines advocate assessing the risk of PH by using a combination of several different tools, and this method is widely used in daily practice[1]. However, risk assessment requires invasive right heart catheterization, which is difficult to apply in frequent monitoring during follow-up. Therefore, there is still a strong unmet need for an easy to use tool to allow for both timely and continuous monitoring of disease status to improve the clinical care of PH patients.

HRV is a useful non-invasive tool which has been studied in many diseases including coronary artery disease, heart failure and even pulmonary hypertension[17–19]. It has been correlated with autonomic dysfunction and used as an outcome predictor. Autonomic dysfunction has also been correlated with the severity of PH[20,21]. Therefore, measuring autonomic system regulation resulting from PH using HRV could potentially be a predictor of disease severity and long-term outcomes[22–25]. Bienias et al. demonstrated that patients with arterial or chronic thromboembolic PH had significantly impaired heart rate turbulence, a linear HRV parameter[26]. Recently, Peng et al. proposed the use of heart rhythm complexity derived from two non-linear parameters of HRV, DFA and MSE, which are based on fractal and chaos therapy, respectively[27–29]. Heart rhythm complexity has been shown to have better efficacy and predictive power for various diseases than traditional HRV[14,30].

Heart rhythm complexity measures the complexity of changes in the R-R interval which contains detailed information derived from heart rate dynamics. Once a biological system has become diseased, the complexity breaks down, and non-linear HRV analysis can detect subtle changes at an early stage[31]. In a retrospective study, abnormal DFAα1 in asymptomatic heart failure patients was associated with the onset of heart failure years in advance of the first clinical event[32,33]. Tsai et al. recently demonstrated that heart rhythm complexity had a better prognostic value for cardiovascular events in patients undergoing peritoneal dialysis compared with linear HRV analysis[30]. In recent years, heart rhythm complexity has been extensively studied in many fields, including left heart failure[34], post-infarction myocardial function[35], patients undergoing dialysis[12,30,36], severity of abdominal aorta calcification[37], primary aldosteronism[38], stroke[39], and PH[40]. These studies support the importance of heart rhythm complexity in clinical practice and its potential role in disease risk stratification. In the present study, we demonstrated that heart rhythm complexity parameters, especially MSE scale 5, were significantly associated with PH disease severity and could be used in PH risk stratification. To the best of our knowledge, this is the first study to apply heart rhythm complexity to the prediction of PH disease severity.

Compared with heart rhythm complexity, linear HRV parameters, including SDRR, SDRR index, VLF, LF/HF ratio and heart rate turbulence have been widely studied to assess PH[41,42]. Recent studies have also demonstrated an association between impaired linear HRV parameter, SDRR and PH disease severity markers, including impaired WHO functional status, decreased 6MWD, impaired tricuspid annular plane systolic excursion (TAPSE), right ventricular systolic function, higher TRPG and NT-pro BNP level[43–45]. In this study, we first demonstrated a better association between heart rhythm complexity and PH disease severity compared to traditional HRV analysis. Second, the discrimination power of linear HRV for PH disease severity improved significantly after combining heart rhythm complexity parameters. The combination of linear and non-linear HRV parameters to form a new predictive model may have further improved its risk stratification ability and outcome prediction.

There are several limitations to this study. First, this is a pilot study. The number of cases was small, and further studies are needed to validate the results. Second, we only enrolled PH patients in WHO group 1 and group 4, and future studies should enroll different groups of PH patients to investigate the potential application of HRV in these patients. Third, this pilot study is a cross-sectional design and lacks clinical long-term follow-up data. A prospective cohort study with clinical end-point follow-up is needed to confirm the utility of heart rhythm complexity on clinical outcome predictions.

Conclusion

This study demonstrated that high-risk PH patients had worse heart rhythm complexity. MSE scale 5 had the best discrimination power to predict high-risk PH patients. Moreover, adding MSE scale 5, area 6–20 or DFAα1 to linear HRV parameters significantly improved the predictive power for high-risk PH patients. Heart rhythm complexity can potentially be used as an indicator of PH disease severity and to stratify the risk of PH.

Methods

Patients

We prospectively enrolled 54 Taiwanese patients with PH from a single center, including 34 with PAH (WHO group 1) and 20 with chronic thromboembolic pulmonary hypertension (CTEPH, WHO group 4) from May 2012 to April 2018. PAH and CTEPH have similar pathophysiological mechanisms as vascular arteriopathy[46], presenting as elevated pre-capillary vessel pressure and pulmonary vascular resistance[47]. Other types of PH may involve complex disease mechanisms such as lung disease or heart failure, which may result in patient heterogeneity and were excluded from this study. Therefore, we only enrolled these two PH subgroups in the present study to avoid the confounding influence of other pathophysiologies.

All patients underwent echocardiography, right heart catheterization and 24-hour ambulatory electrocardiogram Holter recording. The diagnosis of PH was confirmed by right heart catheterization, based on the ESC guidelines[1]. Holter recordings were performed 2 months before or after right heart catheterization.

The patients were divided into two groups based on PH severity[48]. There were 20 patients in the high-risk group (group A), which was defined as WHO functional class IV or class III with severely compromised hemodynamics (right atrial pressure: P_{ra} >15 mmHg or cardiac index < 2.0 $L \cdot min^{-1} \cdot m^2$)[15,49], and 34 patients in the low-risk group (group B).

This study was approved by the Institutional Review Board of National Taiwan University Hospital, and all subjects provided written informed consent.
All research was performed in accordance with relevant guidelines and regulations.

Echocardiogram

All patients underwent typical transthoracic echocardiography (iE33 x MATRIX Echocardiography System, Philips, Amsterdam, Netherlands). According to the recommendations of the American Society of Echocardiography, TRPG was measured as the peak flow velocity of tricuspid regurgitation using a simplified Bernoulli equation: TRPG = 4 x TRV^2. Left ventricular ejection fraction in M-mode was measured in the parasternal long axis view[50].

24-hour Holter recording and data processing

All patients received 24-hour ambulatory electrocardiogram Holter recording (Zymed DigiTrak Plus 24-Hour Holter Monitor Recorder and Digitrak XT Holter Recorder 24-Hour, Philips, Amsterdam, Netherlands) and maintained their original daily activity during the examination without specific limitations. A selected stable 4-hour duration of daytime RR intervals was obtained between 9 AM and 5 PM. The data were automatically processed using an algorithm and then checked by two technicians. HRV parameters were processed automatically with MATLAB software.

Linear HRV analysis

Based on the recommendations of the North American Society of Pacing Electrophysiology and the European Society of Cardiology, conventional linear HRV analysis was performed[51]. We analyzed time domain and frequency domain parameters. Time domain analysis included mean RR, SDRR, pNN_{20}, and pNN_{50}, representing autonomic nervous system modulation of heart rhythm. Frequency domain analysis, including HF (0.15–0.4 Hz), LF (0.04–0.15 Hz), and VLF (0.003–0.04 Hz) was conducted after Fourier transformation.

Non-linear HRV analysis

For non-linear HRV analysis, we analyzed MSE and DFA according to fractal and stochastic theories, respectively. Normal heartbeats have inter-beat fluctuations as long-range correlation behavior in time series. Pathophysiologically, the long-range correlation behavior disappears due to dysregulation of the competitive mechanism of sympathetic and parasympathetic systems.

DFA is used to quantify the correlation property in non-stationary inter-beat interval dynamics in time series[27]. Initially, we integrated the inter-beat interval time series, and then divided it into boxes of equal length. In each box, the trend represented the fractal correlation of the time series. On a double log graph, the slope of the line was defined as the α exponent, representing the fractal correlation property of the time series. Both short-range and long-range time scales were used, and calculated as (α1: 4–11 beats) and (α2: 11–64 beats), respectively[52].

Multiscale entropy (MSE) analysis is used to measure the complexity of finite length time series. Traditional single scale entropy estimation yields lower entropy in times series. “Coarse graining” proceeds multiple time scales and provides rich information of the complexity of the system. To estimate entropy, we calculated sample entropy (SampEn) for each coarse-grained time series, and then plotted this as a function of the scale factor. To quantify the complexity of the heartbeat dynamics in short and long time scales, we calculated scale 5, the linear-fitted slope of scale 1–5 (slope 5), area 1–5 and area 6-20[29].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation for normally distributed variables, and median (interquartile range, 25th and 75th percentiles) for non-normally distributed variables. Categorical variables were expressed as absolute and relative frequencies (percentage). Comparisons were made using the independent t-test and Mann-Whitney U test between two groups. The chi-square test or Fisher’s exact test was used to examine differences between proportions. Logistic regression analysis was used to assess associations between variables and high-risk PH. Significant determinants in univariable logistic regression analysis ($p < 0.05$) including creatinine, PAH group 1, serum creatinine level, plasma NT-pro BNP level, mPAP, PVR, LF/HF ratio, DFAα1, slope 1–5, MSE scale 5, and area 6–20 were then tested in multivariable logistic regression analysis with stepwise selection to identify independent factors that could predict high-risk PH. Category-free (continuous) NRI and IDI were used to evaluate improvements in the accuracy of the prediction after adding a single nonlinear parameter into a logistic regression model using only linear parameters[53,54]. The significance of NRI and IDI statistics was

based on approximate normal distributions. All statistical analyses were performed using R software 4.0.3 (http://www.r-project.org/) and SPSS version 25 for Windows (SPSS Inc., IL, USA). The significance level was set at 0.05 ($p < 0.05$).

Declarations

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Competing Interests: The authors declare no competing interests.

Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1 Galie, N. *et al.* 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. *Rev Esp Cardiol (Engl Ed)* **69**, 177, doi:10.1016/j.rec.2016.01.002 (2016).

2 Lilienfeld, D. E. & Rubin, L. J. Mortality from primary pulmonary hypertension in the United States, 1979-1996. *Chest* **117**, 796-800, doi:10.1378/chest.117.3.796 (2000).

3 Ghofrani, H. A. *et al.* Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann Intern Med* **136**, 515-522, doi:10.7326/0003-4819-136-7-200204020-00008 (2002).

4 Hoeper, M. M. *et al.* Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* **24**, 1007-1010, doi:10.1183/09031936.04.00051104 (2004).

5 Galie, N. *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* **37**, 67-119, doi:10.1093/eurheartj/ehv317 (2016).

6 Humbert, M. *et al.* Survival in Patients With Idiopathic, Familial, and Anorexigen-Associated Pulmonary Arterial Hypertension in the Modern Management Era. *Circulation* **122**, 156-163, doi:doi:10.1161/CIRCULATIONAHA.109.911818 (2010).

7 Wang, L. Y. *et al.* Long-Term Survival of Patients with Pulmonary Arterial Hypertension at a Single Center in Taiwan. *Acta Cardiol Sin* **33**, 498-509 (2017).

8 Benza, R. L. *et al.* An Evaluation of Long-term Survival From Time of Diagnosis in Pulmonary Arterial Hypertension From the REVEAL Registry. *CHEST* **142**, 448-456, doi:10.1378/chest.11-1460 (2012).

9 Hoeper, M. M. *et al.* Risk assessment in pulmonary arterial hypertension. *European Respiratory Journal* **51**, 1702606, doi:10.1183/13993003.02606-2017 (2018).

10 Raina, A. & Humbert, M. Risk assessment in pulmonary arterial hypertension. *European Respiratory Review* **25**, 390-398, doi:10.1183/16000617.0077-2016 (2016).

11 Ho, Y. L., Lin, C., Lin, Y. H. & Lo, M. T. The prognostic value of non-linear analysis of heart rate variability in patients with congestive heart failure–a pilot study of multiscale entropy. *PLoS One* **6**, e18699, doi:10.1371/journal.pone.0018699 (2011).

12 Ferrario, M. *et al.* Non-Linear Heart Rate Variability Indices in the Frequent Hemodialysis Network Trials of Chronic Hemodialysis Patients. *Blood Purif* **40**, 99-108, doi:10.1159/000381665 (2015).

13 Tsai, C. H. *et al.* Heart Rhythm Complexity Impairment in Patients with Pulmonary Hypertension. *Sci Rep* **9**, 10710, doi:10.1038/s41598-019-47144-1 (2019).

14 Makikallio, T. H. *et al.* Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. *Am J Cardiol* **87**, 178-182 (2001).

15 Sitbon, O. & Simonneau, G. Optimal management of severe pulmonary arterial hypertension. *Eur Respir Rev* **20**, 254-261, doi:10.1183/09059180.00007011 (2011).

16 Ling, Y. *et al.* Changing Demographics, Epidemiology, and Survival of Incident Pulmonary Arterial Hypertension. *American Journal of Respiratory and Critical Care Medicine* **186**, 790-796, doi:10.1164/rccm.201203-0383OC (2012).

17 Casolo, G., Balli, E., Taddei, T., Amuhasi, J. & Gori, C. Decreased spontaneous heart rate variability in congestive heart failure. *Am J Cardiol* **64**, 1162-1167, doi:10.1016/0002-9149(89)90871-0 (1989).

18 Goncalves, H. *et al.* Analysis of heart rate variability in a rat model of induced pulmonary hypertension. *Med Eng Phys* **32**, 746-752, doi:10.1016/j.medengphy.2010.04.018 (2010).

19 Huikuri, H. V. *et al.* Heart rate variability and progression of coronary atherosclerosis. *Arterioscler Thromb Vasc Biol* **19**, 1979-1985 (1999).

20 Ciarka, A., Doan, V., Velez-Roa, S., Naeije, R. & van de Borne, P. Prognostic significance of sympathetic nervous system activation in pulmonary arterial hypertension. *Am J Respir Crit Care Med* **181**, 1269-1275, doi:10.1164/rccm.200912-1856OC (2010).

21 Velez-Roa, S. *et al.* Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* **110**, 1308-1312, doi:10.1161/01.CIR.0000140724.90898.D3 (2004).

22 Isobe-Sasaki, Y. *et al.* Sodium balance, circadian BP rhythm, heart rate variability, and intrarenal renin-angiotensin-aldosterone and dopaminergic systems in acute phase of ARB therapy. *Physiol Rep* **5**, e13309, doi:10.14814/phy2.13309 (2017).

23 Saul, J. P. *et al.* Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol* **61**, 1292-1299, doi:10.1016/0002-9149(88)91172-1 (1988).

24 Florea, V. G. & Cohn, J. N. The autonomic nervous system and heart failure. *Circ Res* **114**, 1815-1826, doi:10.1161/CIRCRESAHA.114.302589 (2014).

25 Vaillancourt, M. *et al.* Autonomic nervous system involvement in pulmonary arterial hypertension. *Respir Res* **18**, 201, doi:10.1186/s12931-017-0679-6 (2017).

26 Bienias, P. *et al.* Severity of arterial and chronic thromboembolic pulmonary hypertension is associated with impairment of heart rate turbulence. *Ann Noninvasive Electrocardiol* **20**, 69-78, doi:10.1111/anec.12169 (2015).

27 Peng, C. K., Havlin, S., Stanley, H. E. & Goldberger, A. L. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* **5**, 82-87, doi:10.1063/1.166141 (1995).

28 Costa, M., Goldberger, A. L. & Peng, C. K. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett* **89**, 068102 (2002).

29 Costa, M., Goldberger, A. L. & Peng, C. K. Multiscale entropy analysis of biological signals. *Phys Rev E Stat Nonlin Soft Matter Phys* **71**, 021906, doi:10.1103/PhysRevE.71.021906 (2005).

30 Tsai, C. H. *et al.* Heart Rhythm Complexity Predicts Long-Term Cardiovascular Outcomes in Peritoneal Dialysis Patients: A Prospective Cohort Study. *J Am Heart Assoc* **9**, e013036, doi:10.1161/JAHA.119.013036 (2020).

31 Busa, M. A. & van Emmerik, R. E. A. Multiscale entropy: A tool for understanding the complexity of postural control. *J Sport Health Sci* **5**, 44-51, doi:10.1016/j.jshs.2016.01.018 (2016).

32 Patel, V. N. *et al.* Association of Holter-Derived Heart Rate Variability Parameters With the Development of Congestive Heart Failure in the Cardiovascular Health Study. *JACC Heart Fail* **5**, 423-431, doi:10.1016/j.jchf.2016.12.015 (2017).

33 Binkley, P. F. Promise of a New Role for Heart Rate Variability in the Clinical Management of Patients With Heart Failure. *JACC Heart Fail* **5**, 432-434, doi:10.1016/j.jchf.2017.02.008 (2017).

34 Tsuji, H. *et al.* Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. *Circulation* **94**, 2850-2855 (1996).

35 Chiu, H. C. *et al.* Serial heart rhythm complexity changes in patients with anterior wall ST segment elevation myocardial infarction. *Sci Rep* **7**, 43507, doi:10.1038/srep43507 (2017).

36 Chiang, J. Y. *et al.* Detrended Fluctuation Analysis of Heart Rate Dynamics Is an Important Prognostic Factor in Patients with End-Stage Renal Disease Receiving Peritoneal Dialysis. *PLoS One* **11**, e0147282, doi:10.1371/journal.pone.0147282 (2016).

37 Tsai, C. H. *et al.* The association between heart rhythm complexity and the severity of abdominal aorta calcification in peritoneal dialysis patients. *Sci Rep* **8**, 15627, doi:10.1038/s41598-018-33789-x (2018).

38 Lin, Y.-H. *et al.* Reversible heart rhythm complexity impairment in patients with primary aldosteronism. *Scientific Reports* **5**, 11249, doi:10.1038/srep11249 (2015).

39 Tang, S. C. *et al.* Complexity of heart rate variability predicts outcome in intensive care unit admitted patients with acute stroke. *J Neurol Neurosurg Psychiatry* **86**, 95-100, doi:10.1136/jnnp-2014-308389 (2015).

40 Folino, A. F. *et al.* Ventricular arrhythmias and autonomic profile in patients with primary pulmonary hypertension. *Lung* **181**, 321-328, doi:10.1007/s00408-003-1034-x (2003).

41 Witte, C. *et al.* Heart Rate Variability and Arrhythmic Burden in Pulmonary Hypertension. *Adv Exp Med Biol* **934**, 9-22, doi:10.1007/5584_2016_18 (2016).

42 Bienias, P. *et al.* Severity of arterial and chronic thromboembolic pulmonary hypertension is associated with impairment of heart rate turbulence. *Ann Noninvasive Electrocardiol* **20**, 69-78, doi:10.1111/anec.12169 (2015).

43 Bienias, P. *et al.* Functional class and type of pulmonary hypertension determinate severity of cardiac autonomic dysfunction assessed by heart rate variability and turbulence. *Acta Cardiol* **70**, 286-296, doi:10.2143/AC.70.3.3080633 (2015).

44 Semen, K., Solovey, L., Karapinka, M. & Yelisyeyeva, O. Heart rate variability: Possible implications for management of pulmonary arterial hypertension patients. *European Respiratory Journal* **40**, P970 (2012).

45 Andersen, M. Ø., Diederichsen, S. Z., Svendsen, J. H. & Carlsen, J. HEART RATE VARIABILITY AS ASSESSED WITH LONG-TERM CONTINUOUS CARDIAC MONITORING IN PULMONARY HYPERTENSION.

Journal of the American College of Cardiology **75**, 2088, doi:10.1016/s0735-1097(20)32715-7 (2020).

46 Humbert, M. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: pathophysiology. *Eur Respir Rev* **19**, 59-63, doi:10.1183/09059180.00007309 (2010).

47 Thenappan, T., Ormiston, M. L., Ryan, J. J. & Archer, S. L. Pulmonary arterial hypertension: pathogenesis and clinical management. *BMJ* **360**, j5492, doi:10.1136/bmj.j5492 (2018).

48 Glanville, A. R., Burke, C. M., Theodore, J. & Robin, E. D. Primary pulmonary hypertension. Length of survival in patients referred for heart-lung transplantation. *Chest* **91**, 675-681, doi:10.1378/chest.91.5.675 (1987).

49 Montani, D. *et al.* Implementing the ESC/ERS pulmonary hypertension guidelines: real-life cases from a national referral centre. *Eur Respir Rev* **18**, 272-290, doi:10.1183/09059180.00005909 (2009).

50 Mitchell, C. *et al.* Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. *Journal of the American Society of Echocardiography* **32**, 1-64, doi:10.1016/j.echo.2018.06.004 (2019).

51 Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* **93**, 1043-1065 (1996).

52 Peng, C. K. *et al.* Fractal mechanisms and heart rate dynamics: Long-range correlations and their breakdown with disease. *Journal of Electrocardiology* **28**, 59-65, doi:https://doi.org/10.1016/S0022-0736(95)80017-4 (1995).

53 Steyerberg, E. W. *et al.* Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* **21**, 128-138, doi:10.1097/EDE.0b013e3181c30fb2 (2010).

54 Kerr, K. F. *et al.* Net reclassification indices for evaluating risk prediction instruments: a critical review. *Epidemiology* **25**, 114-121, doi:10.1097/EDE.0000000000000018 (2014).

Figures

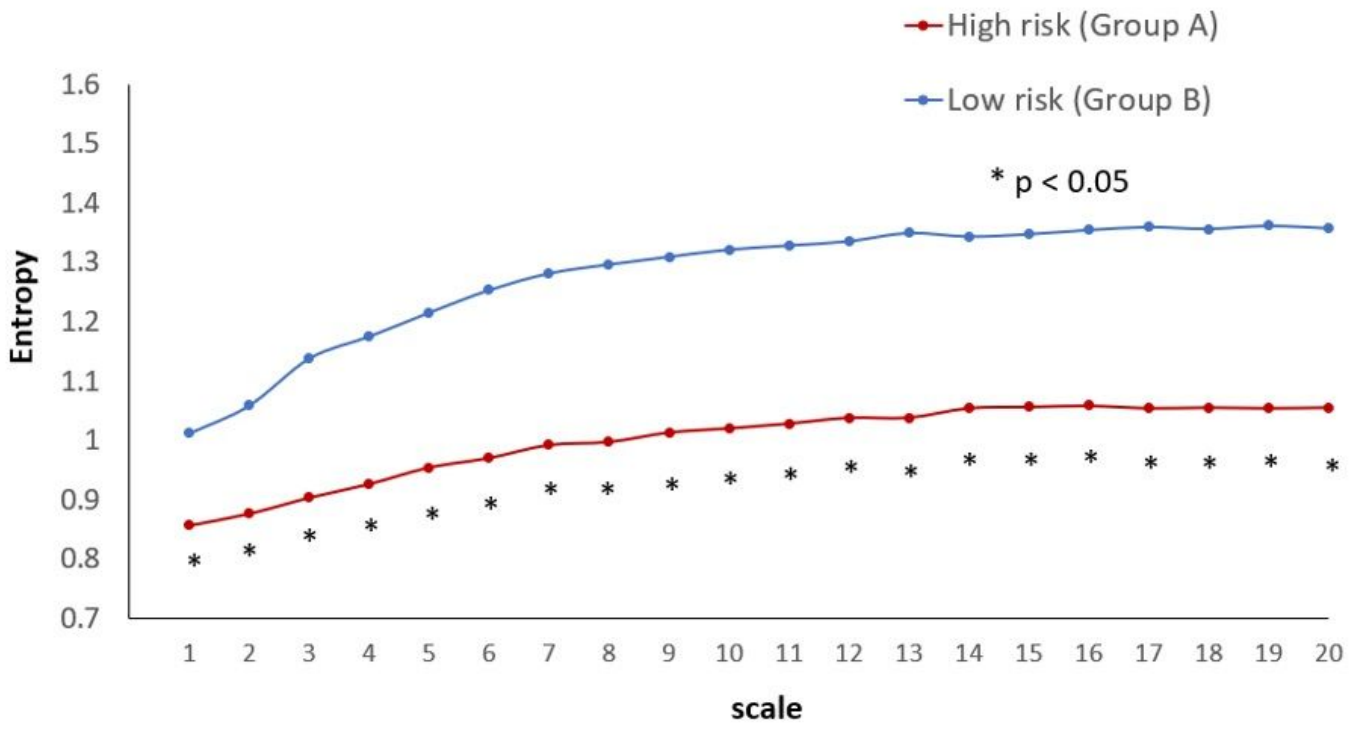

Figure 1

The entropy over different time scales in patients in high-risk group (Group A: red) and low-risk group (Group B: blue). *p<0.05.

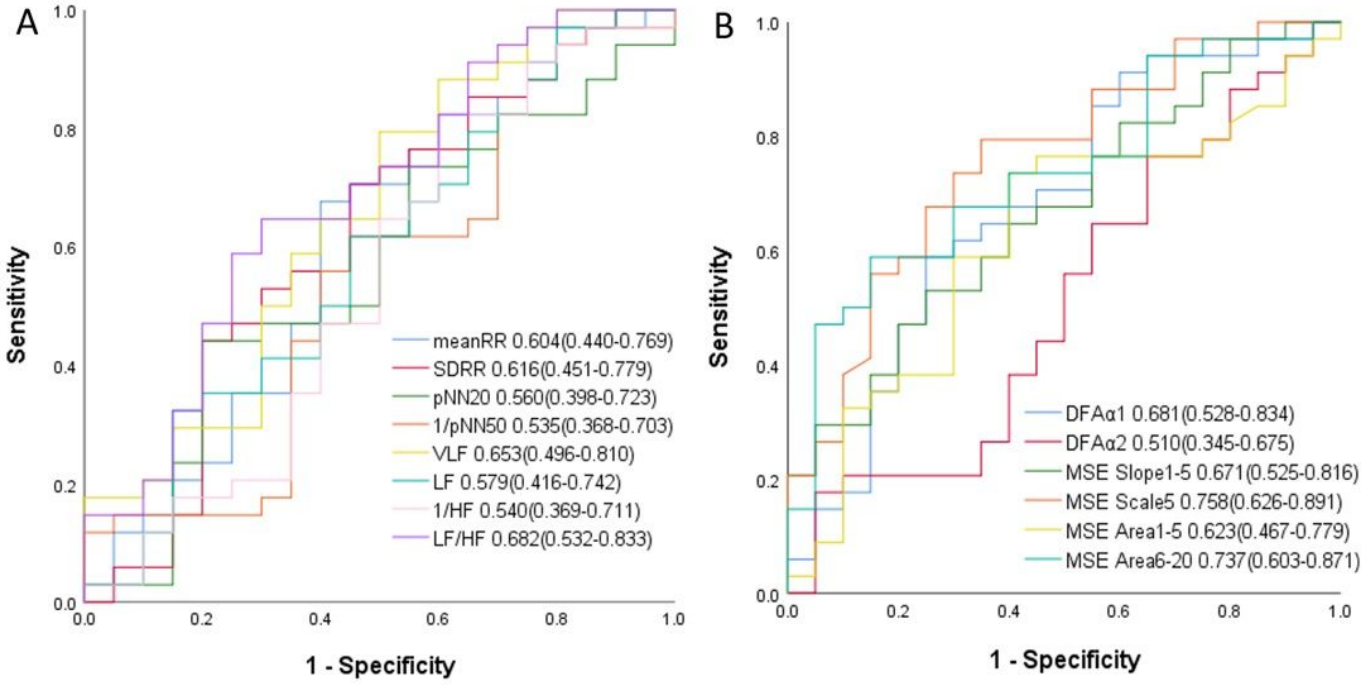

Figure 2

Analysis of the discrimination power of heart rate variability (HRV) variables for PH risk stratification using receiver operating characteristic curve analysis. Panel A: Receiver-operating characteristic (ROC) curves by using linear HRV parameters for predicting high risk PH patients; Panel B: ROC curves by using heart rhythm complexity (HRC) parameters for predicting high risk PH patients. Abbreviation: Mean RR, mean RR interval; SDRR, standard deviation of RR interval; pNN20, percentage of absolute differences in normal RR intervals greater than 20ms; pNN50, percentage of absolute differences in normal RR intervals greater than 50ms; VLF, very low frequency; LF, low frequency; HF, high frequency; DFA, detrended fluctuation analysis; area 1-5, area under the multiscale entropy (MSE) curve for scale 1-5; area 6-20, area under the MSE curve for scale 6-20; TRPG, tricuspid regurgitation pressure gradient; PVR, pulmonary vascular resistance; NT-pro BNP, N-terminal Pro-Brain Natriuretic Peptide; 6MWD, 6-minute-walk-distance;