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Decreased fractal dimension of heart rate variability is associated with early neurological deterioration and recurrent ischemic stroke after acute ischemic stroke

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ABSTRACT

Acute ischemic stroke (AIS) may experience early neurological deterioration (END) and have high risks of recurrent ischemic strokes (RIS), which are often associated with a poor outcome. Post-stroke prognosis is associated with autonomic status. Recently, studies showed that heart rate variability (HRV) is an early outcome predictor in acute stroke patients. The purpose of our study was to investigate association decreased HRV by fractal dimension (FD) with early END within 72 h of admission and 1-year RIS. In this study, we assessed autonomic function of ischemic stroke patients within 24 h from symptom onset by FD. Receiver operating characteristic (ROC) curve was utilized to determine the optimal cut point of FD for END and RIS. 516 patients (mean age 66.14 ± 10.11) with acute ischemic stroke underwent a comprehensive clinical investigation and FD test. According to the data of FD, we investigated association with END within 72 h of admission and the 1-year RIS. ROC curve analysis shown that the optimal cut point of FD for END and RIS were FD ≤ 1.05 and FD ≤ 1.15 respectively. In fully adjusted models, there was an association between FD ≤ 1.05 and END (adjusted odds ratio, 2.64; 95% confidence interval, 1.55–4.49; $P < 0.001$), there was an association between FD ≤ 1.15 and RIS (adjusted odds ratio,5.40; 95% confidence interval, 3.02–9.64; $P < .001$). These findings indicate that FD ≤ 1.05 and FD ≤ 1.15 were independently associated with increased risk of END and RIS respectively, which may have predictive value in END and RIS.

1. Introduction

Stroke is an important cause of death and major disability worldwide. Stroke is the second leading cause of death in China, with 70% of survivors disabled. Previous studies have shown that about one-third of patients with acute ischemic stroke (AIS) may suffer from early neurological deterioration (END) and recurrent ischemic stroke (RIS), which are often associated with poor clinical prognosis. Therefore, early prevention of END and RIS is essential in the treatment of acute stroke. On the other hand, stroke has been shown to cause changes in autonomic function [1–3]. The disorder of autonomic nervous system after stroke has attracted wide attention in the past decades. Studies have shown that autonomic dysfunction caused by ischemic stroke can lead to sudden death of stroke survivors and may lead to adverse clinical outcomes [4,5]. Therefore, early diagnosis of autonomic dysfunction in acute stroke may have prognostic significance [6–9].

As a parameter of autonomic dysfunction, HRV has been studied to predict stroke outcomes [10,11]. HRV is the variation over time of the period between consecutive heartbeats (R-R interval). It reflects the balance between sympathetic and parasympathetic tone and their influence on the sinus node [12]. HRV can be analyzed in the time domain and frequency domain using standard linear methods [13,14]. In recent years, however, the application of nonlinear methods in RR interval has aroused greater interest in research and clinical application.

Fractal dimension (FD) is an algorithm developed in the late 1980s to measure fractal dimension of discrete time series [15]. However, there is little literature on the application of this nonlinear method to physiological conditions in HRV. Compared with other classical methods from chaos theory, FD is more faster and simpler. FD is related to dimensional complexity and it estimates the self-similarity of a time interval in the time series [15].

We have shown that early assessment of HRV by FD can help predict

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outcomes in patients with stroke [16]. The purpose of our study was to investigate whether decreased HRV by FD is associated with END and RIS after acute ischemic stroke.

2. Methods

2.1. Study population

The consecutive patients who were admitted to the Second People's Hospital of Chengdu due to AIS within 24 h of symptom onset between May 2012 and December 2017.Stroke patients were diagnosed as AIS if the brain computed tomography (CT) (SOMATOM Perspective, Siemens Medical Solutions, Germany) scan was normal or showed acute ischemic changes according to sudden neurological deficit with a putative vascular cause. AIS was confirmed by diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI) using Siemens Magnetom Avanto 1.5 Tesla (Siemens Medical Solutions, Erlangen, Germany). The severity of stroke was assessed by National Institutes of Health Stroke Scale score(NIHSS). Eligible patients were all patients admitted to our stroke unit during the study period. This study was approved by ethics committee. Written informed consent was obtained from all study participants or their legal proxies.

2.2. Inclusion criteria

Patients were included in the study only if they fulfilled all the following criteria: 1. Admission for first-ever acute ischemic stroke within 24 h. 2.Evidence of a single acute hemispheric ischemic lesion consistent with clinical manifestations. 3.No patients received mechanical thrombectomy and thrombolytic therapy. All patients received standard therapy, which consisted of aspirin, lipid-lowering medications and so on.

2.3. Exclusion criteria

1.Brainstem stroke, cerebellar stroke, cardioembolic stroke were excluded; 2.Cardiac (include acute myocardial infarction, a history of tachyarrhythmia/bradyarrhythmia or atrial fibrillation), long-term diabetes (> 5 years after diagnosis) and those with evidence of neuropathy were also excluded; 3.Severe pulmonary disease, renal failure (estimated glomerular filtration rate < 30 ml/min.1.73m^2) and active malignancies were excluded; 4. Cerebral hemorrhage, fever(≥38 °C), hypoxia(arterial oxyhemoglobin saturation < 90%)on admission were excluded. All patients were followed up for 1 year.

2.4. Neurological assessment and definition of END and RIS

Stroke severity was assessed at admission by an experienced neurologist using NIHSS. In our study, END was defined as total NIHSS score deterioration ≥2 points within the 72 h after admission, excluding for hemorrhagic transformation of an infarct or a new infarct in another vascular territory. The experienced neurologists assessed the patients' neurological status every day.

All patients were followed up once a month for a total of 1 year. All patients were followed up by face-to-face interview, and patient's information was obtained from hospital medical records. Patients were evaluated by experienced neurologists, who were blinded to patients' baseline clinical status. 1-year RIS was defined as a new infarct in the same or another vascular territory. Etiology of stroke was classified according the modified Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.

2.5. Data collection

CT or MRI examination was conducted at the time of admission, and repeated examination was performed on 72 h after admission to confirm the location of the lesion. The presence of insular infarction was assessed by an experienced neuroradiologist blinded to clinical details.

All patients underwent ECG(FX-7542, Fukuda, Japan) and HRV monitoring between 9:00 Am and 10:00Am on the next day after admission in a relaxed supine position, in a quiet room with an ambient temperature of 22 °C, the recordings were undertaken under standardized conditions.

A series of R-R intervals were obtained from the 12-lead ECG monitor with a sampling frequency of 1000hz. The time scale was about 15 min, the beats were about 2000 beats. HRV was analyzed from 512 continuous R-R intervals. The R-R interval series were passed through a filter that eliminates interference factors, including noise, premature beats, and artifacts. First, all R-R interval series were edited automatically, and then all R-R interval were carefully edited manually. After this, all questionable portions were excluded, and only segments with > 90% pure sinus beats were included in final analysis.

The chaos feature of R-R intervals was represented by FD, which was used to quantify the complexity of the R-R dynamic variation, FD was evaluated with the following equation, $FD = \log N(\varepsilon)/\log(1/\varepsilon)$, where ε is scale and is used to measure R-R interval, N(ε) is the number of measurement of R-R interval [16–20]. A software in off-line computer (Chongqing Haikun Medical Instrument Co., Ltd) was used to calculate FD parameters for each subject.

2.6. Statistical analysis

Firstly, patients were classified into no END, END and no RIS, RIS groups. Demographic characteristics, vascular risk factors, current smoking, and so on were compared between the 2 subgroups in univariate analysis, using Pearson χ 2 test, Fisher exact 2-sided test, or Student *t*-test, distributions of continuous variables were determined by the Kolmogorov–Smirnov test, while Mann–Whitney two sample test was applied in case of non-normal distributions. Secondly, Receiver operating characteristic (ROC) curve analysis was used to evaluate sensitivity, specificity and to determine the optimal cut point of FD for END and RIS. Thirdly, We then performed logistic regressions analyses to determine the association between FD and outcome(END, RIS), adjusting for all confounders (age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use). Results were expressed as adjusted odds ratios (OR) with the corresponding 95% confidence interval (CI). The data were analyzed using SPSS software (SPASS 22.0). P values < .05 were considered as statistically significant.

3. Results

3.1. Characteristics of the study subjects

During the study period, 516 patients were identified, comprised 49.03% (253) men and 50.97% (263) women, and the mean age was 66.14 ± 10.11 years (38–96 years). In the study population, 367 patients had a history of hypertension, 154 had a history of diabetes, 274 had a history of hyperlipidemia, 149 patients smoke,153patients current alcohol drinking. Of these patients, 137 were diagnosed as insular stroke. During the 1-year follow-up period, no patients were denied follow-up, 62 out of 516(11.95%) patients had died. The cause of death was obtained through hospital records.

3.2. Univariable models for predictors of FD ≤ 1.05 and FD ≤ 1.15

According to Receiver operating characteristic (ROC) curve, the optimal cut point of FD for END and RIS were FD ≤ 1.05 and FD ≤ 1.15, respectively. Patients with FD > 1.05 were 407 (78.88%), FD ≤ 1.05 in 109 (21.12%). Patients with FD ≤ 1.05 showed

Table 1
Comparison of baseline characteristics between patients with no END and END groups.

	No END group (410)	END group (106)	OR(95%CI)	P*
Age, y(Mean SD)	65.69 ± 10.22	67.87 ± 9.52		**0.030**
NIHSS score(Mean SD)	9.49 ± 4.67	9.54 ± 4.99		0.311
FD (Mean SD)	1.39 ± 0.34	1.26 ± 0.34		< **0.001**
FD ≤ 1.05,n(%)	69(16.83)	40(37.74)	3.00(1.87–4.79)	< **0.001**
Females,n(%)	216(52.68)	47(44.34)	0.72(0.47–1.10)	0.126
Men,n(%)	194(47.32)	59(55.66)	0.72(0.47–1.10)	0.126
BMI ≥ 24 kg/m, n(%)	124(30.24)	24(22.64)	0.68(0.41–1.11)	0.123
Hypertension,n(%)	293(71.46)	74(69.81)	0.92(0.580–1.47)	0.738
Current Smoking,n(%)	115(28.05)	34(32.08)	1.21(0.76–1.92)	0.415
Current alcohol drinking,n(%)	124(30.24)	29(27.36)	0.87(0.54–1.40)	0.562
Diabetes, n(%)	122(29.76)	32(30.19)	1.02(0.64–1.63)	0.931
Hyperlipidemia,n(%)	222(54.15)	52(49.06)	0.82(0.53–1. 25)	0.349
Insular stroke,n(%)	94(22.93)	43(40.57)	2.29(1.46–3.60)	< **0.001**
Family history of stroke,n(%)	77(18.78)	24(22.64)	1.27(0.75–2.13)	0.372
Etiological classification				
Large artery atherosclerosis,n(%)	198(48.29)	53(50.00)	1.07(0.70–1.64)	0.754
Lacunar, n(%)	137(33.41)	30(28.30)	0.79(0.49–1.26)	0.316
Other known causes, n(%)	5(1.22)	2(1.89)	1.56(0.30–8.14)	0.597
Undetermined, n(%)	70(17.07)	21(19.81)	1.18(0.67–2.03)	0.550
Medications use				
Antiplatelet, n(%)	97(23.66)	29(27.36)	1.22(0.75–1.97)	0.429
Antihypertensive, n(%)	260(63.41)	61(57.55)	0.78(0.51–1.21)	0.267
Lipid-lowering medications, n(%)	175(42.69)	48(45.28)	1.11(0.72–1.71)	0.630

Bold indicates p-values less than 0.05.

* Comparison between no END and END groups. Continuous variables are expressed as mean ± standard deviation(SD). Categorical variables are expressed as frequency(percent) for *P* values, Pearson χ2 test, Fisher exact 2-sided test, and Student *t*-test were used when appropriate. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distributions.

significantly higher prevalence of insular stroke(OR,3.28; 95%CI,2.10–5,12; P < 0.001), and older age(68.50 ± 10.40 vs 65.50 ± 9.95, P = 0.003) than patients with FD > 1.05. Factors associated with FD ≤ 1.05 in univariate analyses were entered into multivariate logistic regression, which identified insular stroke associated with FD ≤ 1.05 (adjusted OR, 2.74; 95% CI, 1.64–4.59; P < 0.001).

Patients with FD > 1.15 were 385 (74.61%), FD ≤ 1.15 in 131 (25.39%). Patients with FD ≤ 1.15 showed significantly higher prevalence of insular stroke(OR,3.54; 95%CI,2.32–5,42; P < .001), and older age(68.11 ± 10.35 vs 65.46 ± 9.95,P = 0.010) than patients with FD > 1.15. Factors associated with FD ≤ 1.15 in univariate analyses were entered into multivariate logistic regression, which identified insular stroke associated with FD ≤ 1.15 (adjusted OR, 3.02; 95% CI, 1.86–4.89; P < 0.001).

3.3. Univariable models for predictors of END

106 (20.54%) patients had END. Baseline characteristics of patients in the no END and END groups were compared (Table 1). At baseline, patients with END showed significantly older age (67.87 ± 9.52 vs 65.69 ± 10.22, P = 0.030), higher prevalence of insular stroke (40.57% vs 22.93%;OR,2.29;95%CI, 1.46–3.60; P < 0.001) than patients with no END. The AUC was 0.67 (95% CI, 0.56–0.68), using a cutoff point of FD ≤ 1.05 to predict END, the odds ratio was 3.00 (95%CI, 1.87–4.79), and the sensitivity and specificity were 37.74% and 83.17% respectively. Compared with patients no END, those with END had a significantly lower FD value (1.26 ± 0.34 vs 1.39 ± 0.34, P < 0.001),and higher prevalence of FD ≤ 1.05(37.74% vs 16.83%, P < .001).

3.4. Multivariable models on the association between FD ≤ 1.05 and END

In unadjusted models, there was an association between FD ≤ 1.05 and END (OR,3.00; 95%CI1.87–4.79, P < 0.001). In the multivariable logistic regression model after adjustment for a age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use, FD ≤ 1.05 were significant predictor for END (adjusted OR, 2.64; 95%CI, 1.55–4.49; P < 0.001) (Table 3).

3.5. Univariable models for predictors of RIS

78(78/516,15.11%) patients had RIS at 1 year (Table 2), at baseline, patients with RIS showed significantly higher prevalence of insular stroke (41.03% vs 23.97%,OR,2.21;95%CI, 1.34–3.64, P = 0.002), and lower NIHSS score(8.42 ± 3.96 vs 9.69 ± 4.85;P = 0.030) than patients with no RIS. The AUC was 0.71 (95% CI, 0.65–0.77), using a cutoff point of FD ≤ 1.15 to predict RIS, the odds ratio was 4.89 (95%CI, 2.96–8.09), and the sensitivity and specificity were 55.13% and 79.91% respectively. Compared with patients no RIS, those with RIS had a significantly lower FD value (1.25 ± 0.32 vs 1.38 ± 0.34, P < 0.001),and higher prevalence of FD ≤ 1.15(55.13%vs 20.09%, P < .001).

3.6. Multivariable models on the association between FD ≤ 1.15 and RIS

In unadjusted models, there was an association between FD ≤ 1.15 and RIS group(55.13%vs 20.09%,OR,4.89;95%CI,2.96–8.09, P < 0.001).In the multivariable logistic regression model after adjustment for age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use, and FD ≤ 1.15(adjusted OR, 5.40; 95%CI, 3.02–9.64; P < 0.001) were significant predictors for 1-year RIS (Table 3).

4. Discussion

Cerebrovascular events are the second cause of death and disability in the developing countries, leaving 70% of survivors disabled [21–23]. In patients with acute ischemic stroke, the major causes of END include

Table 2
Comparison of baseline characteristics between patients with no RIS and RIS groups.

	No RIS group (438)	RIS group (78)	OR(95%CI)	P*
Age, y (Mean SD)	66.24 ± 10.16	65.55 ± 9.88		0.415
NIHSS score (Mean SD)	9.69 ± 4.85	8.42 ± 3.96		**0.030**
FD (Mean SD)	1.38 ± 0.34	1.25 ± 0.32		**0.001**
FD ≤ 1.15, n(%)	88(20.09)	43(55.13)	4.89 (2.96–8.09)	< **0.001**
Females, n(%)	224(51.14)	39(50.00)	0.96(0.59–1.55)	0.853
Men, n(%)	214(48.86)	39(50.00)	0.96(0.59–1.55)	0.853
BMI ≥ 24 kg/m, n(%)	126(28.77)	22(28.21)	0.973(0.57–1.66)	0.919
Hypertension, n(%)	308(70.32)	59(75.64)	1.31(0.75–2.29)	0.339
Current Smoking, n(%)	125(28.54)	24(30.77)	1.11 (0.66–1.88)	0.689
Current alcohol drinking, n(%)	125(28.54)	28(35.90)	1.40(0.85–2.33)	0.190
Diabetes, n(%)	132(30.14)	22(28.21)	0.91(0.53–1.55)	0.731
Hyperlipidemia, n(%)	225(51.37)	49(62.82)	1.60(0.97–2.63)	0.062
Insular stroke, n(%)	105(23.97)	32(41.03)	2.21(1.34–3.64)	**0.002**
Family history of stroke, n(%)	83(18.95)	18(23.08)	1.28(0.72–2.29)	0.397
Etiological classification				
Large artery atherosclerosis, n(%)	206(47.03)	45(57.69)	1.54(0.94–2.50)	0.083
Lacunar, n(%)	146(33.33)	21(26.92)	0.737(0.43–1.26)	0.265
Other known causes, n(%)	7(1.60)	0(0.00)	0.85(0.82–0.88)	0.261
Undetermined, n(%)	79(18.04)	12(15.38)	0.81(0.42–1.58)	0.540
Medications use				
Antiplatelet, n(%)	110(25.11)	16(20.51)	0.77(0.43–1.39)	0.383
Antihypertensive, n(%)	267(60.96)	54(69.23)	1.44(0.86–2.42)	0.165
Lipid-lowering medications, n(%)	183(41.78)	40(51.28)	1.47(0.91–2.38)	0.119

Bold indicates p-values less than 0.05.

* Comparison between no RIS and RIS groups. Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as frequency (percent) for P values, Pearson χ2 test, Fisher exact 2-sided test, and Student *t*-test were used when appropriate. Distributions of continuous variables were determined by the Kolmogorov–Smirnov test, Mann–Whitney two sample test was applied in case of non-normal distribution.

Table 3
Multivariable Models Showing Association Between FD and Prognosis.

	OR (95% CI)	P*
END(FD ≤ 1.05)	2.64 (1.55–4.49)	< **0.001**
RIS(FD ≤ 1.15)	5.40(3.02–9.64)	< **0.001**

Bold indicates p-values less than 0.05.

* Multivariable adjusted for age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use.

progressive stroke, vasogenic edema, hemorrhagic transformation of infarcts, raised intracranial pressure. On the other hand, patients with acute stroke episode are high risk of developing recurrent ischemic strokes. Many predictors of them have been proposed in previous studies, including hyperglycemia, hypertension management, no prior aspirin and lipid-lowering medications use, proximal arterial occlusion, prior transient ischemic attacks, presence of early CT changes, and so on. According to previous studies, the incidence of patients with END was ranging from 5% to 40%, and the incidence of RIS was 8%–20%, which may vary widely in previous studies, depending on the definition used(e.g time domain used to assess deterioration) [24–27]. In this study, the incidence of END was 20.54 and RIS was 15.11% in AIS. Our results were generally in line with previous publications.

Acute stroke usually causes autonomic dysfunction, which may be a potential marker of END at admission and 3-month clinical outcome [28–30]. HRV is a method for studying the control mechanism of autonomic nervous system on cardiac function. HRV has been usually analyzed with linear statistical measures (time and frequency domain methods), which measure the overall magnitude of the fluctuations of R-R intervals around its mean value. However, it may not reflect the true effects and complexities of HRV, mostly because nonlinear mechanisms might be also involved in the genesis of heart rate dynamics, which might result in inconsistent results of previous studies [31–33]. Therefore, there has been great interest in the development of tools for prognosis and diagnosis of autonomic dysfunction after stroke.

The nonlinear methods are based on chaos theory. Chaos describes natural system in the different way, because it can explain nature's randomness and no periodicity. The chaos theory could help in better understanding heart rate dynamics, because the healthy heart rate is slightly irregular and chaotic. In physiological changes, nonlinear methods might give new insights into HRV [34–36]. As a feature parameter of chaos, FD can quantify the complexity of HRV, which is one of the most common nonlinear parameters in chaos feature [15]. The algorithm from FD estimates the self-similarity of a time interval in the time series, and which is related to complexity of the time series. It is worth mentioning that the traditional linear indicators (time and frequency domain) cannot provide similar complex behavior analysis of heart rate dynamics [37].

In this study, We validated the role of FD as a new tool for predicting END and RIS. Interestingly, we found that patients with FD ≤ 1.05 and FD ≤ 1.05 showed significantly higher prevalence of insular stroke, this association was independent of established risk factors, including age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, family history of stroke, etiological classification, medications use. These results suggested insular damage might contribute to cardiac autonomic dysfunction, the underlying pathophysiological mechanism might be the downregulation of parasympathetic activity, hence the relative up-regulation of sympathetic effects on cardiac function [38,39]. Increased sympathetic nervous system might increase platelet aggregation, promote vasoconstriction, decrease fibrinolysis, and increase pulse and blood pressure, decreased parasympathetic nervous system leads to decreased arterial pressure and cardiac output, these pathophysiological changes increase the risk of thrombosis [40].

We observed that FD ≤ 1.05 was related to END, and FD ≤ 1.15 was strong associate with RIS in 1 year. The percentage of END rates in the FD ≤ 1.05 group was 36.70% (40/109),which was significantly higher than that in the FD > 1.05 group(16.22%,66/407) (P < 0.001). The percentage of RIS rates in the FD ≤ 1.15 group was 32.82%(43/131), which was significantly higher than that in the FD > 1.15 group(9.10%,35/385)(P < .001). After adjusting for fully confounders, we found a significant association of FD ≤ 1.05 and FD ≤ 1.15 with risks of END and 1-year RIS respectively after AIS. ROC curve analysis showed that FD was a useful marker for predicting END and RIS. The AUC of 0.67 in END group and 0.71 in the RIS group further indicated that FD was predictive of END and RIS with high specificity. These results suggested this association was independent of established risk factors, including age, baseline NIHSS score, sex, BMI, hypertension, current smoking, current alcohol drinking, diabetes, hyperlipidemia, insular stroke, family history of stroke, etiological classification, medications use, and FD detection could have prognostic value for END and RIS among patients with AIS.

5. Conclusions

In conclusion, our study showed a positive correlation between decreased FD and END, and 1-year RIS after an acute ischemic stroke. Our findings substantiated the importance of an early diagnosis of autonomic dysfunction in stroke survivors given the elevated risk of recurrent stroke. FD may have potential predictive value in risk stratification of ischemic stroke. Patients admitted to the stroke unit should were routinely monitored by ECG, and FD analysis only required about 15 min ECG data, our results imply that this method might be applicable in acute stroke management.

5.1. Limitation

Some limitations of this study merit consideration. Firstly, in this study, we relied on a single baseline FD and thus we could not account for variations in FD levels that occur over time, FD levels should be measured repeatedly to allow longitudinal analysis, which might provide additional information on the development and on its prognostic implications. Secondly, although we adjusted for NIHSS score, which has been show to correlate with infarction volume, we lacked data on infarction volume. Thirdly, we lack data on the possible influence of the left and right insular stroke on FD and prognosis, respectively, because left and right insular lesion have different influence on the cardiac autonomic function. Fourth, the low sensitivity of FD for prediction, which is still to be improved. In future experiments, we will avoid the aboved limitation, in order to obtain more reliable results. However, despite these limitations, our research has the advantage that its large sample size, its analysis, including models adjusting for a wide variety of confounders, and a standardized way of measuring FD among patients.

Ethics approval and consent to participate

We obtained ethical approval for this study from the Medical and Health Research Ethics Committee at Second people's Hospital of Chengdu. The current study was carried out according to Declaration of Helsinki. Written informed consent was obtained from all study participants or their legal proxies(516).

Authors' contributions

LYH was responsible for the concept and design of the study, data collection and analysis and the first draft of the paper and further manuscript. JW was responsible for concept and design of the study, the data analysis and interpretation. LLZ was responsible for the data analysis. XZ was responsible for English-editing service. WD was responsible for overseeing the concept and design of the study, the data analysis and interpretation, and HY was responsible for design software of FD in off-line compute. All authors read and approved the final manuscript for publication.

Availability of data and materials

Data used in this study may be available by request to corresponding author via email: 531324679@qq.com

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