



Association of diastolic blood pressure with history of stroke in community hypertensive patients: a cross-sectional study

Chao-Lei Chen^{1#}, Lin Liu^{1#}, Yu-Qing Huang¹, Geng Shen¹, Jia-Yi Huang¹, Yu-Ling Yu¹, Song-Tao Tang², Ji-Yan Chen¹

¹Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, China; ²Department of Cardiology, Community Health Center of Liaobu County, Dongguan 523430, China

Contributions: (I) Conception and design: JY Chen; (II) Administrative support: JY Chen, ST Tang; (III) Provision of study materials or patients: ST Tang; (IV) Collection and assembly of data: CL Chen, YQ Huang, G Shen, L Liu, JY Huang, YL Yu; (V) Data analysis and interpretation: CL Chen, L Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Ji-Yan Chen, MD, PhD. Department of Cardiology, Guangdong Provincial Key Laboratory of Coronary Heart Disease Prevention, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, No. 106, Zhongshan Second Road, Yuexiu District, 510080 Guangzhou, China. Email: chen-jian@163.com; Song-Tao Tang, BA. Department of Cardiology, Community Health Center of Liaobu County, 523430 Dongguan, China. Email: 3038384760@qq.com.

Background: Although the relationship between elevated blood pressure and risk of stroke has been well-established, most studies focused on systolic blood pressure (SBP). Association of diastolic blood pressure (DBP) with stroke, however, has not been fully addressed. Therefore, we aimed to explore the association of DBP with history of stroke in hypertensive patients.

Methods: This retrospective cross-sectional study consecutively enrolled 8,179 hypertensive residents aging more than 18 years old between January 1, 2013, and December 31, 2013. We stratified patients by baseline DBP levels in five groups, and used logistic regression to examine the association between DBP and stroke. We also performed restricted cubic spline and a two-piecewise linear regression model to elucidate the non-linearity of associations.

Results: A total of 8,130 patients were included (average age: 64.01 years, 46.7% men), and 310 of them suffered from stroke. No significant association was found from logistic regressions, but a non-linear relationship was detected between DBP and stroke in the two-piecewise linear regression analysis, with an inflection point of 80 mmHg. For patients with DBP <80 mmHg, the odds ratio and 95% CI was 0.969 (0.948 to 0.991), and 1.008 (0.991 to 1.027) for patient with DBP ≥80 mmHg.

Conclusions: We found a non-linear relationship between DBP and prior stroke among Chinese hypertensives. DBP associated with a lower probability of stroke for hypertensive patients with DBP <80 mmHg.

Keywords: Diastolic blood pressure (DBP); stroke; hypertension; community

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Introduction

Stroke is the leading cause of death and disability worldwide, and the economic cost of treatment and care is huge. With more than 2 million new cases each year

in China, stroke is associated with the highest disability-adjusted life year caused by any disease (1,2). In addition, stroke is a complex disease with many related risk factors. Among the many risk factors, hypertension is the most

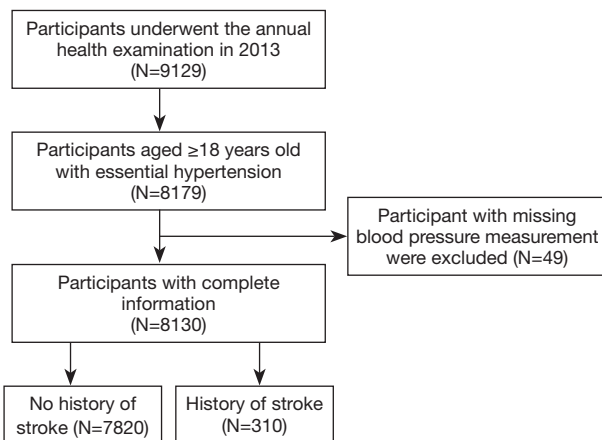


Figure 1 The flow chart of study participants.

prevalent and treatable cause for stroke and other vascular events (3,4). Previous studies have shown that blood pressure (BP) control, especially systolic blood pressure (SBP) reduction, can significantly reduce the incidence of cardiovascular events; however, stroke events were not decreased (5). Another study including 0.5 million Chinese adults concluded that SBP was continuously related to major vascular disease, especially stroke (6). However, fewer studies directly assessed how diastolic blood pressure (DBP) might predict the risk of stroke. In 1999, Voko *et al.* found that the relationship between DBP and risk of stroke was J-shaped in treated hypertensives (7). Other authors summarized that the relation between BP reduction and cardiovascular risk may follow a J-shaped curve (8,9). Vidal-Petiot *et al.* reported a J-shaped association of DBP with cardiovascular events (except for stroke) in patients with coronary artery disease (CAD) treated for hypertension (10). Recently, however, a linear relationship has been assumed to challenge the J-shaped finding but this new relationship needs more data from large and randomized controlled trials to provide definitive answers (11,12).

In summary, there is still a lot of controversy about the relationship between DBP and risk of stroke, especially the question of how much DBP should be reduced to the most appropriate. Regarding that a limited number of researches studied the correlation between DBP and stroke events in hypertensives, not to mention studies based on the Chinese population, the present cross-sectional study aimed to explore the cross-sectional relationship between DBP and prior stroke in community hypertensive patients in China.

Methods

Study design and setting

This cross-sectional study was conducted at Liaobu, China, from January 2013 to December 2013. Researchers obtained demographic characteristics, performed physical examination, laboratory tests, as well as obtaining information on past medical history and medical prescriptions. Stroke cases were self-reported by patients. When participants attended the annual health examination, history of stroke was also recorded by trained interviewer.

Study participants

We included patients with at least 18 years old with diagnosed essential hypertension. We excluded patients that had missing data on blood pressure measurement and blood tests (*Figure 1*). A total of 8,130 participants were enrolled for data analysis. This study complied with the principles outlined in the Declaration of Helsinki. Institutional medical ethical committee from Guangdong Provincial People's Hospital, China has approved this study. All participants have provided informed consent in written form.

Data collection and variables

Well-trained staff conducted a structured questionnaire to acquire information on demographic characteristics and social-economic factors (including age, sex, smoking, and drinking), medical history [diabetes mellitus (DM), CAD, and stroke], and use of antihypertensive drugs. Anthropometry and biomarkers including body mass index (BMI), SBP, DBP, heart rate, fasting blood glucose (FBG), estimated glomerular filtration rate (eGFR), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG) were assessed by laboratory analyses. Patients with SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg, and/or use of antihypertensive medicine within 2 weeks were classified as hypertensive patients, with reference to 2010 Chinese guidelines for the management of hypertension (13). Diabetic patients were classified by diagnosis made by registered medical practitioner, the use of antidiabetic drugs within 2 weeks, and/or with FBG ≥ 7.0 mmol/L. Stroke cases were adjudicated by

a neurologist in a hospital based on the self-reported history of stroke and cranial computed tomography or magnetic resonance imaging.

Statistical analysis

First, we categorized patients into five groups by their DBP levels by 10 mmHg increment, then tested the normality of data using Kolmogorov-Smirnov test. Baseline characteristics were presented as mean \pm standard error for normally distributed continuous variables and numbers (percentages) for categorical variables, as appropriate. We detected subgroup differences by one-way ANOVA, Kruskal-Wallis H test and Chi-square test according to the normality of data distribution. Second, we performed logistic regression model to evaluate the associations of DBP with stroke. Restricted cubic spline was then performed to evaluate whether the non-linear relationship existed. For any non-linearity in association being detected, two-piecewise linear regression model was used to calculate the threshold values of DBP in predicting stroke. All analyses were performed with the statistical software package R 3.5.1 (<https://cran.r-project.org/mirrors.html>), statistical significance was detected by P values less than 0.05.

Results

Baseline characteristics of study participants

Table 1 showed the baseline characteristics of 8,130 participants. The average age was 64.01 ± 12.40 years, 46.7% were men, and approximately 26.3% of them were smokers. There were 310 cases of stroke events. No statistically significant difference was found in smoking status and prevalence of stroke among different DBP groups. Age, sex, BMI, SBP, DBP, drink status, heart rate, eGFR, TC, TG, LDL-C, HDL-C, FBG, use of antihypertensive drugs, CAD and DM prevalence differed significantly by DBP values.

Relationship between DBP and stroke

Results from logistic regression are summarized in Table 2, but not significant associations were found. We then presented results from minimally and fully adjusted models in Table 3. In the non-adjusted model, DBP showed did not associate with stroke (OR: 0.991, 95% CI, 0.980, 1.003).

Fully adjusted models also demonstrated no significant associations. For sensitivity analysis, we treated DBP as a categorical variable, and did not find significant trend (P for trend was 0.605).

The analysis of the non-linear relationship

In Figure 2, we found that non-linear relationship between DBP and stroke in fully adjusted model. According to the two-piecewise linear regression model, the inflection point of DBP was 80 mmHg. A negative relationship between DBP and stroke was only significant for patients with DBP <80 mmHg (OR: 0.969, 95% CI, 0.948, 0.991) (Table 4).

Discussion

We studied the cross-sectional relationship between DBP and prior stroke among 8,130 hypertensive patients in China. A total of 310 stroke events occurred during the whole year. Neither the univariable logistic regression analysis nor the multivariate adjustment models found a statistically significant relationship between DBP and stroke. However, a non-linear relationship between DBP and stroke was observed using restricted cubic spline. The two-piecewise linear regression model showed a cut-off point of 80 and a negative relationship between DBP and stroke was discovered on the left side of the inflection point.

It has been widely debated whether a J-curve phenomenon reflecting an adverse relationship between excessive BP reduction and cardiovascular risk exists in prognosis prediction, especially for stroke. The SPRINT (Systolic Blood Pressure Intervention Trial) concluded that achieving SBP <120 mmHg resulted in fewer major cardiovascular events and all-cause death compared with <140 mmHg, but the number of strokes was not reduced (HR, 0.89; 95% CI, 0.63–1.25; P=0.50) (5). SPRINT results showed benefits and safety of BP reduction and have profoundly affected the newest US guidelines on management of hypertension in adults, adopting lower BP criteria for the definition of hypertension from the previous 140/90 to 130/80 mmHg (14). Although the latest 2018 ESC/ESH Guidelines for the management of arterial hypertension still maintained 140/90 mmHg as diagnostic criteria, it was recommended that all patients with hypertension should be reduced DBP down to below 80 mmHg, independent of the level of risk and comorbidity (15). It also emphasized that high normal BP (130–139/85–89 mmHg) should consider drug treatment

Table 1 Baseline characteristics of participants

Characteristics	DBP groups					P value
	<60 (n=33)	≥60, <70 (n=684)	≥70, <80 (n=2,435)	≥80, <90 (n=3,406)	≥90 (n=1,572)	
Age (years)	74.667±9.433	68.098±13.638	64.451±13.837	62.628±13.110	56.260±13.183	<0.001
Sex (n, %)						<0.001
Male	13 (39.394)	284 (41.520)	1,086 (44.600)	1,550 (45.508)	864 (54.962)	
Female	20 (60.606)	400 (58.480)	1,349 (55.400)	1,856 (54.492)	708 (45.038)	
BMI (kg/m ²)	21.698±4.468	22.914±3.739	24.378±3.901	25.187±3.957	25.892±3.779	<0.001
SBP (mmHg)	111.212±19.765	116.180±17.353	123.455±12.508	131.947±11.956	145.569±14.763	<0.001
DBP (mmHg)	54.515±3.906	63.776±3.314	73.450±3.269	82.346±2.964	95.356±6.262	<0.001
Smoking (n, %)						0.184
No	24 (72.727)	494 (72.222)	1,798 (73.840)	2,550 (74.868)	1,128 (71.756)	
Yes	9 (27.273)	190 (27.778)	637 (26.160)	856 (25.132)	444 (28.244)	
Drinking (n, %)						<0.001
No	33 (100.000)	624 (91.228)	2,162 (88.789)	2,983 (87.581)	1,253 (79.707)	
Yes	0 (0.000)	60 (8.772)	273 (11.211)	423 (12.419)	319 (20.293)	
Heart rate (beats/min)	69.758±10.753	69.465±11.069	70.823±11.143	71.623±11.365	72.917±11.537	<0.001
eGFR (mL/min/1.73 m ²)	87.423±34.875	100.232±37.357	105.399±47.092	105.765±54.989	108.704±44.690	0.001
TC (mg/dL)	189.527±40.185	197.546±49.106	197.286±45.175	201.900±45.837	206.491±44.494	<0.001
TG (mg/dL)	127.150±83.963	135.309±128.284	148.941±114.138	167.605±150.898	191.068±185.192	<0.001
LDL-C (mg/dL)	90.351±27.397	97.805±29.354	96.871±27.908	98.492±28.578	100.173±28.794	0.004
HDL-C (mg/dL)	53.891±14.793	50.602±16.658	49.166±14.989	48.247±13.164	48.187±17.799	<0.001
FBG (mmol/L)	4.771±1.250	5.131±1.715	5.250±1.831	5.125±1.524	5.062±1.466	0.003
Antihypertensive drugs (n, %)						<0.001
No	22 (66.667)	438 (64.035)	1,253 (51.458)	1,387 (40.722)	540 (34.351)	
Yes	11 (33.333)	246 (35.965)	1,182 (48.542)	2,019 (59.278)	1,032 (65.649)	
CAD (n, %)						0.002
No	30 (90.909)	653 (95.468)	2,353 (96.632)	3,296 (96.770)	1,543 (98.155)	
Yes	3 (9.091)	31 (4.532)	82 (3.368)	110 (3.230)	29 (1.845)	
DM (n, %)						<0.001
No	29 (87.879)	539 (78.801)	1,885 (77.413)	2,780 (81.621)	1,323 (84.160)	
Yes	4 (12.121)	145 (21.199)	550 (22.587)	626 (18.379)	249 (15.840)	
Stroke (n, %)	3 (9.091)	32 (4.678)	99 (4.066)	116 (3.406)	60 (3.817)	0.209

SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; CAD, coronary artery disease; DM, diabetes mellitus.

Table 2 Univariable logistic regression model for stroke

Covariates	OR	95% CI	P value
Age	1.033	1.024, 1.042	<0.001
Sex			
Male	1.0		
Female	0.742	0.591, 0.932	0.010
Smoking			
No	1.0		
Yes	1.481	1.165, 1.883	0.001
Drinking			
No	1.0		
Yes	1.029	0.738, 1.434	0.866
DM			
No	1.0		
Yes	1.132	0.858, 1.495	0.381
CAD			
No	1.0		
Yes	2.895	1.884, 4.447	<0.001
Antihypertensive			
Yes	1.0		
No	2.774	2.123, 3.624	<0.001
SBP	1.006	0.999, 1.013	0.080
DBP	0.991	0.980, 1.003	0.138
BMI	0.996	0.967, 1.025	0.770
Heart rate	0.996	0.986, 1.007	0.489
eGFR	0.996	0.993, 0.999	0.004
TC	0.993	0.990, 0.996	<0.001
TG	1.000	1.000, 1.001	0.431
LDL-C	0.992	0.987, 0.996	<0.001
FBG	1.000	0.931, 1.074	0.999

OR, odds ratios; CI, confidence interval; DM, diabetes; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose.

when cardiovascular risk is very high (15). Besides, the Rotterdam observational study showed that higher rates of stroke happened in elderly hypertensive participants who were treated to DBP <60 mmHg compared with DBP 65–74 mmHg (7). These findings supported the idea of the J-curve phenomenon.

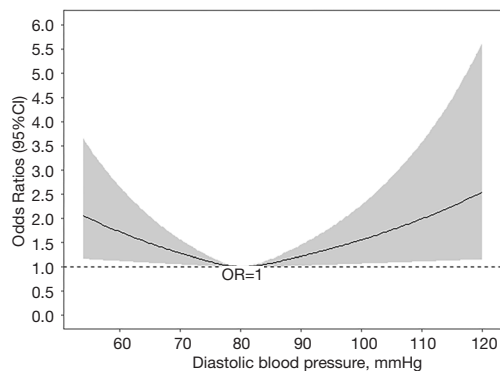
However, the HOT (Hypertension Optimal Treatment) trial (16) found that advantages from tight BP control were not so obvious. No direct effect on stroke risk of DBP reduction to ≤ 90 , ≤ 85 , ≤ 80 or 70 mmHg in the overall patients or the subgroup participants with DM was discovered. Similarly, Vidal-Petiot *et al.* (10) also revealed that among patients with stable CAD, DBP <60 mmHg or at 60–69 mmHg had no significant effect on stroke risk comparing to DBP at 70–79 mmHg. Nevertheless, in the ACCORD (Action to Control Cardiovascular Risk in Type 2 Diabetes) trial, there were fewer stroke events in the intensive BP control group, but benefits for other endpoints were not seen. Among these patients with DM, DBP 64.4 mmHg of intensive therapy resulted in a significant reduction in all strokes (HR, 0.59; 95% CI, 0.39–0.89; $P=0.01$) and non-fatal strokes (HR, 0.63; 95% CI, 0.41–0.96; $P=0.03$) compared with 70.5 mmHg of standard therapy (17). In accordance with the ACCORD study, the SHEP (Systolic Hypertension in the Elderly Program) trial displayed that patients with a DBP of less than 70 mmHg in the active BP control group had fewer strokes, and in patients older than 60 years, intensive treatment of DBP down to 68 mmHg had a lower risk of stroke than the placebo group with DBP 72 mmHg (relative risk was 0.64; 95% CI, 0.50–0.82; $P=0.0003$) (18). Another study named Hypertension in the Very Elderly Trial (19), suggesting the cause-and-effect relationship between low DBP and adverse cerebrovascular outcomes, indicated that DBP <80 mmHg was associated with a significant decrease in fatal stroke events. This result was contrary to our present study given that we found stroke risk is higher when DBP <80 mmHg. This disagreement could be attributed to the difference of specific study population and clinical variables that were considered, collected and adjusted.

In addition, several studies have questioned the ability of DBP to be used independently for risk prediction. A nationwide population-based study from Korea found

Table 3 Relationship between diastolic blood pressure and stroke in different models

Exposure	Non-adjusted model (OR, 95% CI, P value)	Adjust I model (OR, 95% CI, P value)	Adjust II model (OR, 95% CI, P value)
DBP (per 10 mmHg change)	0.991 (0.980, 1.003) 0.138	0.993 (0.978,1.009) 0.388	0.998 (0.982,1.014) 0.800
DBP groups			
<60	1.0	1.0	1.0
≥60, <70	0.491 (0.142, 1.694) 0.260	0.516(0.148,1.804) 0.300	0.510(0.139,1.870) 0.310
≥70, <80	0.424 (0.127, 1.412) 0.162	0.468 (0.138,1.586) 0.223	0.404 (0.114,1.437) 0.162
≥80, <90	0.353 (0.106, 1.172) 0.089	0.399 (0.117,1.360) 0.142	0.370 (0.104,1.322) 0.126
≥90	0.397 (0.118, 1.337) 0.136	0.491 (0.137,1.759) 0.274	0.489 (0.131,1.826) 0.287
P for trend	0.130	0.426	0.605

OR, odds ratios; CI, confidence interval; DBP, diastolic blood pressure. Adjust I model: adjust for age, sex, systolic blood pressure and body mass index. Adjust II model: adjust for age, sex, body mass index, systolic blood pressure, smoking, drinking, estimated glomerular filtration rate, heart rate, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, diabetes mellitus, and antihypertensive drugs.

**Figure 2** The non-linear relationship between diastolic blood pressure and stroke. OR, odds ratios; CI, confidence interval.

that both SBP and DBP increased cardiovascular risk in a J-shaped manner which could extend down to 90/40 mmHg, but the association of DBP independent of SBP was variable. These authors raised that the difference between DBP <80 mmHg and 80–89 mmHg for estimate cardiovascular risk disappeared after adjustment (20). Sobieraj *et al.* (21) used the SPRINT data to investigate how low DBP influenced stroke risk and concluded that after adjusting age, smoke status, clinical cardiovascular events, and high SBP, DBP <70 mmHg was not related to stroke risk. What the authors trying to explain was that DBP is unlikely to predict outcomes independent of individual characteristics. Stensrud *et al.* detected that DBP <60 mmHg was related to poor outcome risk including

Table 4 The results of two-piecewise linear regression model

Inflection point of DBP (per 10 mmHg change)	OR	95% CI	P value
<80	0.969	0.948, 0.991	0.005
≥80	1.008	0.991, 1.027	0.353

Adjust for age, sex, body mass index, systolic blood pressure, smoking, drinking, estimated glomerular filtration rate, heart rate, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting blood glucose, diabetes mellitus, and antihypertensive drugs. OR, odds ratios; CI, confidence interval; DBP, diastolic blood pressure.

stroke (HR, 1.9; 95% CI, 1.46–2.47) and after adjustment, HR improved (HR, 1.04; 95% CI, 0.98–1.10). In further analysis in subjects aged >75 years, no adverse connection was observed (22). Same conclusion has been conducted by two other studies that question the clinical significance of DBP independent of SBP (23,24). Meanwhile, Williams (25) also proposed controversies about DBP being applied to define hypertension and initiate treatment. These studies seem to support the inability of DBP to be used for prediction while emphasizing the importance of other clinical variables. In our study, we analyzed the non-linear relationship between DBP and stroke and DBP <80 mmHg was significantly associated with increased risk of stroke, but the model in multivariate logistic regression did not find a statistically significant relationship between them. One explanation is that adjusting the clinical variables weakens

the direct impact of DBP on stroke. Besides, the differences in the study population and individual characteristics of the subjects may also be the cause of these diversities. Perhaps, DBP maybe not as important as SBP in diagnosis and management of hypertension or predicting prognosis currently, but DBP must be essential and it needs more large, randomized and controlled trials to prove itself. Considering that the results of relationship between DBP and stroke differ in different study groups, future studies should be committed to providing different guidance and advice to different groups of people.

There are some limitations needs to be noted in our study. First and most importantly, we only can reveal that DBP was non-linearly relevant to stroke, but it was difficult to distinguish causal relationship between them considering that this study was a retrospective cross-sectional study. Well-designed prospective cohort study is needed to clarify it. Second, regarding stroke is a multivariate related disease, although we consider many confounding factors which are related to the occurrence of stroke in our analysis, we were unable to adjust physical activity due to raw data limitations since the lack of exercise is closely associated with higher stroke risk (26). Third, because this study is a retrospective investigation, the history of stroke mainly comes from patient self-reporting, there may be deviations in reporting; in addition, there may be ambiguous memory, and some patients may have recurrent stroke. Fourth, the population of this study came from a single center of the Chinese population, so the conclusions of the study cannot be extrapolated to other populations and ethnic groups.

Conclusions

In conclusion, our study found a non-linear relationship between DBP and prior stroke in patients with essential hypertension. DBP was negatively correlated with stroke when less than 80 mmHg, suggesting there might be no benefit for lower DBP control. These data might provide evidence on stroke prevention and blood pressure control in the future.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jxym.2020.02.04>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our experimental study was approved by the institutional medical ethical committee the Guangdong General Hospital, Guangzhou, China (No. GDREC2012143H). All participants have provided informed consent in written form.

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