Research Article

Association of Ambulatory Blood Pressure with All-Cause Mortality and Cardiovascular Outcomes in Peritoneal Dialysis Patients

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Keywords

Peritoneal dialysis · Ambulatory blood pressure monitoring · Mortality · Pulse pressure · Calcification

Abstract

Background: Ambulatory blood pressure monitoring is the gold standard for the diagnosis of hypertension, but its effects on all-cause mortality and cardiovascular outcomes in peritoneal dialysis (PD) patients remain uncertain. We aimed to investigate the association between ambulatory blood pressure and clinical outcomes in PD patients. **Methods:** A prospective, observational cohort study was conducted in PD patients enrolled from March 2001 to July 2018 and followed until October 2019. Blood pressure was evaluated using 24-h ambulatory blood pressure monitoring. The endpoints included all-cause mortality, cardiovascular mortality, and cardiovascular events. Multivariable Cox regression was used to identify the associations between ambulatory blood pressure and endpoints. Subsequently, multivariable logistic regression was conducted to identify factors associated with elevated pulse pressure (PP). **Results:** A total of 260 PD patients (154 men, 59.2%) were recruited. The median follow-up duration was 40.7 months. Our studies revealed that PP was an independent predictor of all-cause mortality (hazard ratio [HR], 1.018; 95% CI, 1.001–1.034; $p = 0.032$), cardiovascular mortality (HR, 1.039; 95% CI, 1.017–1.061; $p < 0.001$), and cardiovascular events (HR, 1.028; 95% CI, 1.011–1.046; $p = 0.001$). Systolic blood pressure was an independent predictor of cardiovascular mortality (HR, 1.023;

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95% CI, 1.007–1.040; $p = 0.005$) and cardiovascular events (HR, 1.018; 95% CI, 1.006–1.030; $p = 0.003$). Vascular calcification was significantly associated with elevated PP (OR, 3.069; 95% CI, 1.632–5.772; $p = 0.001$). **Conclusion:** 24-h ambulatory PP was the most significant predictor of all blood pressure indicators for clinical outcomes in PD patients.

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Introduction

Cardiovascular death is the leading cause of mortality in patients on peritoneal dialysis (PD) [1]. Hypertension is a general and controllable cardiovascular risk factor and is highly prevalent in PD patients [2, 3]. Compared to the general population, blood pressure control is more challenging in PD patients due to complex pathophysiology such as fluid overload [4]. Therefore, clarifying the relationship between blood pressure and prognosis in PD patients is particularly important for blood pressure management.

In previous studies, associations between blood pressure and outcomes in the dialysis population remain uncertain, probably because of short duration of follow-up or small sample size [5, 6]. It has been demonstrated that ambulatory blood pressure monitoring is the gold standard for the diagnosis of hypertension [7, 8]. In the general population, higher 24-h blood pressure value was significantly associated with greater risks of death and cardiovascular outcomes [9]. In the hemodialysis population, several studies reported a U-shaped relationship between systolic blood pressure (SBP) or pulse pressure (PP) and mortality [10, 11]. Yet, little prospective evidence on the utility of ambulatory blood pressure monitoring for risk prediction exists in PD patients. Thus, the present study aimed to examine the associations between 24-h blood pressure and all-cause mortality, cardiovascular mortality, and cardiovascular events of PD patients and to explain the underlying cause of the association.

Materials and Methods

Population and Study Design

Adult PD patients from Huashan Hospital, Fudan University in China were recruited in this prospective, observational, longitudinal cohort study. Patients were enrolled from March 2001 to July 2018 and followed until death, changes in treatment modality, renal transplantation, or October 2019. Patients were excluded if they had an ongoing infection or were clinically unstable, with a life expectancy of fewer than 6 months. All of the patients received regular PD for >3 months and provided written informed consent. The study protocol was approved by the Ethics Committee of Huashan Hospital affiliated to Fudan University.

Outcome Measurements

All-cause mortality was the primary endpoint of the study. The secondary endpoints included cardiovascular mortality and cardiovascular events. Cardiovascular events included coronary artery events (e.g., new ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, unstable angina, and stable angina), heart failure, cerebrovascular diseases (ischemic and hemorrhagic strokes), and peripheral artery disease (e.g., arterial embolization and diabetic foot). Cardiovascular mortality was defined as death caused by cardiovascular events. Patients who received renal transplantation, switched to hemodialysis (HD), transferred, or died were censored for survival analysis.

Blood Pressure Measurements

Blood pressure was assessed for 24 h using SCHILLER BR-102 plus (Schiller AG, Baar, Switzerland), which is validated according to standard protocols [12, 13]. Daytime (07:00–23:00) blood pressure was measured every 10–20 min and nighttime (23:00–07:00) blood pressure was measured every 30–60 min. Ambulatory recordings had to contain over 80% of valid readings for further analysis. Recorded parameters include 24-h average SBP, diastolic blood pressure (DBP), and PP (PP = SBP – DBP).

Clinical and Laboratory Data

Clinical characteristics including age, sex, BMI, history of diabetes, medication status, and smoking status were obtained at the time of enrollment. PD adequacy parameters including total Kt/V, residual Kt/V, total clearance of creatinine, and residual clearance of creatinine were evaluated using Baxter PD Adequest 2.0 software (Baxter Healthcare Corporation, Deerfield, IL, USA) at baseline. Vascular calcification was evaluated by coronary artery calcification using multi-slice spiral CT. When the coronary calcification score was >0, the presence of calcification was considered.

Laboratory data including hemoglobin, serum albumin, calcium, phosphorus, potassium, intact parathyroid hormone, glycated hemoglobin (HbA1c), serum insulin, cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein (LDL), N-terminal pro-brain natriuretic peptide (NT-proBNP), and high-sensitivity C-reactive protein were determined using standard laboratory methods. Homeostasis model of assessment-insulin resistance (HOMA-IR) was used to evaluate insulin resistance using the validated equation: fasting serum insulin (mU/L) × fasting serum glucose (mmol/L)/22.5.

Statistical Analysis

SPSS (version 26.0) and R (version 3.6.2) were used to perform the statistical analysis. Continuous variables were presented as mean ± standard deviation or as median (interquartile range) according to the normality test results, with categorical variables as percentages. Comparisons between the groups were carried out using a *t* test or Mann-Whitney U test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Univariable Cox regression was used to identify the potential risk factors for endpoints (all-cause mortality, cardiovascular mortality, and cardiovascular events) in PD patients, and multivariable Cox regression was used to identify independent predictors. Variables previously demonstrated to be significant in univariable Cox analysis or thought to be clinically important were included in the multivariable Cox regression model. The hazard ratios (HRs) for the endpoints were expressed per 1 mm Hg increase in blood pressure. For the generation of the Kaplan-Meier (KM) survival curves, participants were stratified into 2 groups based on the median PP level. Nonlinear associations between blood pressure and outcomes were determined using restricted cubic spline methods. Furthermore, multivariable logistic regression was conducted to verify the risk factors associated with elevated PP. All of the statistical tests were 2-sided, and values were considered statistically significant at the *p* value <0.05.

Results

Characteristics of Study Participants

Our study population included 260 patients (154 men, 59.2%) with a median age of 63.61 (46.64, 73.2) years. The patients were divided into 2 groups according to the median PP level (ranging from 25 to 100): low (PP ≤49 mm Hg, *n* = 132) and high (PP >49 mm Hg, *n* = 128). Baseline characteristics of all patients and those with low PP and high PP are shown in Table 1.

Table 1. Baseline characteristics of the study participants

	Total (n = 260)	24-h pulse blood pressure		p value
		≤49 mm Hg (n = 132)	>49 mm Hg (n = 128)	
<i>Clinical characteristics</i>				
Age, years	63.61 (46.64, 73.2)	53.85 (40.83, 68.38)	70.16 (59.74, 78.61)	<0.001
BMI, kg/m ²	22.99±3.59	22.60±3.76	23.39±3.38	0.078
Male, n (%)	154 (59.2)	81 (61.4)	73 (57.0)	0.477
History of diabetes, n (%)	69 (26.5)	12 (9.1)	57 (44.5)	<0.001
History of smoking, n (%)	46 (17.7)	24 (18.2)	22 (17.2)	0.834
Use of statins, n (%)	99 (38.1)	41 (31.1)	58 (45.3)	0.018
Use of anticoagulation drug, n (%)	55 (21.2)	22 (16.7)	33 (25.8)	0.072
Use of calcitriol, n (%)	120 (46.2)	60 (46.9)	60 (45.5)	0.818
Use of calcium acetate, n (%)	97 (37.3)	47 (35.6)	50 (39.1)	0.565
Use of antihypertensive drug, n (%)	245 (94.2)	120 (90.9)	125 (97.7)	0.020
Residual renal Kt/V	0.57 (0.18, 0.96)	0.62 (0.19, 1.02)	0.51 (0.18, 0.91)	0.286
Total Kt/V	1.93 (1.69, 2.29)	1.95 (1.72, 2.30)	1.92 (1.67, 2.28)	0.747
Residual renal Ccr, L/week	29.86 (12.67, 49.02)	34.78 (14.79, 50.21)	26.27 (11.39, 47.57)	0.245
Total Ccr, L/week	67.64 (53.34, 85.47)	69.34 (55.46, 86.72)	61.94 (51.37, 81.77)	0.096
Calcification, n (%)	134 (51.5)	41 (31.1)	93 (72.7)	<0.001
PD duration, months	7.73 (3.0, 33.07)	9.28 (3, 26.43)	7.67 (3, 37.52)	0.700
All-cause mortality, n (%)	64 (24.6)	17 (12.9)	47 (36.7)	<0.001
Cardiovascular mortality, n (%)	33 (12.7)	6 (4.5)	27 (21.1)	<0.001
Cardiovascular events, n (%)	57 (21.9)	13 (9.8)	44 (34.4)	<0.001
<i>Laboratory data</i>				
Hemoglobin, g/L	109.12±19.22	111.50±17.74	106.66±20.41	0.042
Serum albumin, g/L	36 (33, 40)	37.5 (34, 41)	34.5 (32, 38)	<0.001
Calcium, mmol/L	2.22±0.21	2.23±0.21	2.20±0.20	0.213
Phosphorus, mmol/L	1.44 (1.21, 1.71)	1.50 (1.24, 1.79)	1.41 (1.14, 1.67)	0.040
Potassium, mmol/L	4.2 (3.8, 4.6)	4.2 (3.7, 4.6)	4.2 (3.8, 4.6)	0.890
iPTH, pg/mL	292.3 (159.3, 428.6)	293.3 (162.5, 449.3)	279 (156.3, 390)	0.190
HbA1c, %	5.5 (5.2, 6.1)	5.3 (5.1, 5.7)	5.8 (5.3, 6.7)	<0.001
Serum insulin, mU/L	10.0 (6.8, 15.78)	9.4 (6.6, 14.23)	10.7 (7.7, 17.15)	0.017
HOMA-IR	2.44 (1.53, 4.04)	2.13 (1.42, 3.36)	2.99 (1.78, 5.80)	<0.001
Cholesterol, mmol/L	4.31 (3.58, 5.1)	4.25 (3.41, 4.9)	4.56 (3.9, 5.2)	0.017
Triglyceride, mmol/L	1.69 (1.14, 2.36)	1.67 (1.27, 2.30)	1.70 (1.04, 2.43)	0.808
HDL, mmol/L	0.95 (0.78, 1.20)	0.94 (0.76, 1.16)	0.97 (0.78, 1.23)	0.245
LDL, mmol/L	2.26 (1.74, 2.79)	2.16 (1.66, 2.62)	2.34 (1.83, 2.95)	0.030
NT-proBNP (per 1,000 pg/mL)	1.45 (0.60, 3.78)	0.96 (0.41, 2.09)	2.22 (0.88, 5.69)	<0.001
hsCRP, mg/L	1.03 (0.36, 3.22)	1.00 (0.26, 3.00)	1.08 (0.43, 3.29)	0.272

Values denote the mean ± SD or median (interquartile range) unless specified otherwise. Kt/V, urea clearance; Ccr, creatinine clearance; PD, peritoneal dialysis; iPTH, intact parathyroid hormone; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N-terminal pro brain natriuretic peptide; hsCRP, high-sensitivity C-reactive protein.

Compared to the low PP group, patients with a higher PP were older and more likely to have vascular calcification and to have a history of diabetes. They had higher HbA1c, serum insulin, HOMA-IR, cholesterol, LDL, and NT-proBNP but lower albumin and phosphorus. Meanwhile, more people in high PP group were on statins and antihypertensive drugs.

The median follow-up duration was 40.7 (26.1, 67.8) months. During the follow-up period, 57 patients experienced cardiovascular events and 64 patients died, with 33 deaths attributable to cardiovascular diseases. More all-cause mortality, cardiovascular mortality, and cardiovascular events occurred in the high PP group.

Table 2. Adjusted proportional hazard ratios for mortality and cardiovascular events for SBP, DBP, and PP per mm Hg increase

Predictor	All-cause mortality		Cardiovascular mortality		Cardiovascular events	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
<i>24-h SBP</i>						
Model 1	1.012 (1.000–1.024)	0.044	1.029 (1.013–1.045)	<0.001	1.021 (1.009–1.033)	<0.001
Model 2	1.014 (1.002–1.026)	0.019	1.030 (1.014–1.047)	<0.001	1.021 (1.009–1.033)	0.001
Model 3	1.014 (1.002–1.026)	0.019	1.030 (1.014–1.047)	<0.001	1.021 (1.009–1.033)	0.001
Model 4	1.014 (1.002–1.026)	0.020	1.030 (1.014–1.047)	<0.001	1.021 (1.009–1.033)	0.001
Model 5	–	0.105	1.023 (1.007–1.040)	0.005	1.018 (1.006–1.030)	0.003
<i>24-h DBP</i>						
Model 1	–	0.745	–	0.085	–	0.076
Model 2	–	0.443	–	0.089	–	0.079
Model 3	–	0.443	–	0.089	–	0.079
Model 4	–	0.490	–	0.089	–	0.079
Model 5	–	0.727	–	0.900	–	0.164
<i>24-h PP</i>						
Model 1	1.020 (1.005–1.036)	0.010	1.047 (1.027–1.067)	<0.001	1.032 (1.015–1.050)	<0.001
Model 2	1.022 (1.006–1.039)	0.006	1.043 (1.023–1.064)	<0.001	1.032 (1.014–1.049)	<0.001
Model 3	1.022 (1.006–1.039)	0.006	1.043 (1.023–1.064)	<0.001	1.032 (1.014–1.049)	<0.001
Model 4	1.023 (1.007–1.040)	0.006	1.043 (1.023–1.064)	<0.001	1.032 (1.014–1.049)	<0.001
Model 5	1.018 (1.001–1.034)	0.032	1.039 (1.017–1.061)	<0.001	1.028 (1.011–1.046)	0.001

The multivariable Cox regression analysis and sequentially adjusted models for the covariates were used to calculate the HRs for the endpoints. Model 1, adjusted for age and sex. Model 2, adjusted for age, sex, BMI, and duration of PD. Model 3, adjusted for age, sex, BMI, duration of PD, HbA1c, and HOMA-IR. Model 4, adjusted for age, sex, BMI, duration of PD, HbA1c, HOMA-IR, and albumin. Model 5, adjusted for age, sex, BMI, duration of PD, HbA1c, HOMA-IR, albumin, and NT-proBNP. SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HR, hazard ratio; PD, peritoneal dialysis; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model of assessment-insulin resistance; NT-proBNP, N-terminal pro brain natriuretic peptide.

Association of Ambulatory Blood Pressure with Mortality and Cardiovascular Events

Univariable linear Cox regression showed that both SBP and PP were risk factors for all endpoints of study participants, while DBP was not a risk factor for any endpoints (see online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510298). Multivariable Cox regression revealed that SBP was still an independent predictor of cardiovascular mortality and cardiovascular events but not for all-cause mortality after adjustments for age, sex, BMI, duration of PD, HbA1c, HOMA-IR, albumin, and NT-proBNP. Furthermore, DBP was still not a risk factor for any endpoints, while PP was still an independent predictor of all 3 endpoints after adjustments (Table 2).

The KM survival curves for all endpoints revealed a significant difference between the PP groups (Fig. 1A–C). Furthermore, univariable nonlinear Cox regression with restricted cubic spline showed the HRs for PP related to the median value (Fig. 2A–C). Similarly, we conducted the KM curves and restricted cubic spline for SBP (shown in online suppl. Fig. 1, 2A–C), which showed that the pattern for cardiovascular mortality and cardiovascular events is more obvious than that for all-cause mortality. As for DBP, there are no correlations between DBP and cardiovascular mortality and outcomes both in the KM curves and restricted cubic spline (shown in online suppl. Fig. 3, 4A–C). The above analysis confirmed the effects of PP and SBP on mortality and cardiovascular events.

Fig. 1. Kaplan-Meier analysis of PP (mm Hg) with all-cause mortality ($p < 0.0001$) (A), cardiovascular mortality ($p < 0.0001$) (B), and cardiovascular events ($p < 0.0001$) (C). The PD patients with higher PP levels were associated with higher all-cause mortality, cardiovascular mortality, and cardiovascular events. PP, pulse pressure; PD, peritoneal dialysis.

Fig. 2. Nonlinear Cox regression analysis using penalized smoothing splines for association of PP with all-cause mortality (A), cardiovascular mortality (B), and cardiovascular events (C). The hazard ratio is represented by the solid line and the 95% CI by the shaded area. The PD patients with higher PP levels were associated with higher all-cause mortality, cardiovascular mortality, and cardiovascular events. PP, pulse pressure; PD, peritoneal dialysis.

Table 3. ORs for the likelihood of high pulse pressure in PD patients based on logistic regression analyses

Variable	Univariable		Multivariable	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.059 (1.040–1.078)	<0.001	1.040 (1.019–1.061)	<0.001
Sex	1.197 (0.729–1.963)	0.477	–	–
Calcification	5.898 (3.452–10.077)	<0.001	3.069 (1.632–5.772)	0.001
NT-proBNP (per 1,000 pg/mL)	1.082 (1.033–1.132)	0.001	1.074 (1.026–1.124)	0.002
HbA1c (%)	2.042 (1.495–2.789)	<0.001	–	–
HOMA-IR	1.127 (1.039–1.224)	0.004	–	–
Serum albumin (g/dL)	0.906 (0.858–0.956)	<0.001	–	–
LDL (mmol/L)	1.410 (1.027–1.936)	0.034	–	–
Hemoglobin (g/dL)	0.987 (0.974–1.000)	0.044	–	–

OR, odds ratio; PD, peritoneal dialysis; NT-proBNP, N-terminal pro brain natriuretic peptide; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model of assessment-insulin resistance; LDL, low-density lipoprotein.

Risk Factors of Elevated PP

According to the results in Table 1, age, sex, calcification, NT-proBNP, HbA1c, HOMA-IR, albumin, LDL, and hemoglobin were added to the model for multivariable logistic analysis. As listed in Table 3, we found that age, NT-proBNP, and the presence of calcification were independent factors associated with elevated PP.

Discussion and Conclusion

In the present study, the associations of ambulatory blood pressure recordings with mortality and cardiovascular events in patients on PD were evaluated. During the follow-up period, we identified that PP was an independent predictor of all-cause mortality, cardiovascular mortality, and cardiovascular events, and SBP was an independent predictor of cardiovascular mortality and cardiovascular events. Meanwhile, we investigated the risk factors associated with elevated PP, and it revealed that age, NT-proBNP, and the presence of calcification were significantly associated with elevated PP. These findings revealed that 24-h PP was a superior tool for the prediction of mortality and cardiovascular diseases compared with other blood pressure parameters in PD patients. To our knowledge, this is the largest prospective study conducted so far in the PD population, which revealed the associations of ambulatory blood pressure recordings with mortality and cardiovascular events in a long follow-up period.

Goldfarb-Rumyantzev et al. [14] found that low SBP and PP were associated with increased mortality in PD patients. We speculated that the reason for the discrepancy between our results and their findings was short follow-up times in their study (mean follow-up of 23 months). Some studies suggested that longer follow-up leads to a better understanding of the long-term effects of blood pressure on survival in dialysis patients, as hypertension was a significant risk factor for late mortality, which supports the findings in our current study [5, 6, 15].

In our study, the association of SBP with all-cause mortality lost statistical significance after adjustment for NT-proBNP. NT-proBNP is not only a biomarker of left ventricular hypertrophy and ventricular dysfunction, but also able to mirror changes in fluid status [16, 17]. Fluid overload has long been known common among dialysis patients, which can also predict mortality independent of blood pressure [18, 19]. Therefore, the strict volume control is vital for PD patients. Besides, the role of SBP in cardiovascular risks cannot be ignored in PD patients.

PP is generally considered a superior tool for the prediction of mortality and cardiovascular diseases compared with other blood pressure parameters in both general and dialysis populations [20, 21]. Our study has reached similar conclusions, and possible explanation has been suggested: vascular calcification may have played an important role in the associations of PP with clinical outcomes in PD patients. Increased arterial stiffness is believed to be closely linked to elevated PP [22], and substantial evidence suggests the importance of vascular calcification in arterial stiffening [23–25]. In our previous study, coronary calcification was common in PD patients and coronary artery calcification score was an independent predictor of all-cause mortality, cardiovascular mortality, and cardiovascular events [26–28]. Hence, we believed that the tight association between vascular calcification and PP may potentially explain the associations of PP with all 3 study endpoints.

Several studies reported a U-shaped relationship between SBP or PP and mortality in patients on HD, while numerous cohort studies in the general population found a positive correlation between increased blood pressure and clinical outcomes [8–11]. Explanations for the U-shaped association in HD patients include that low blood pressure may be a marker for

severe comorbidities including heart failure, atrial fibrillation, chronic inflammation, and malnutrition, which may have a major impact on outcomes [29]. In the current study, the U-shaped association between SBP or PP and mortality was not found, probably for the following reasons: patients in our study were in relatively good nutritional condition and the average albumin level of our study subjects is 36.2 g/L, which is significantly higher than that of other dialysis population. For example, a study by Balafa et al. [30] reported that the average albumin level of their PD patients was 33.9 g/L. Second, in contrast to hemodialysis patients, we have a lower prevalence of cardiac comorbidities including heart failure and atrial fibrillation. In the study about ambulatory blood pressure in HD patients conducted by Mayer et al. [11], the prevalence of heart failure and atrial fibrillation are 18 and 20%, respectively. However, in our study, only 12 (4.6%) participants had heart failure and 2 (0.7%) had atrial fibrillation. Therefore, no hypotension occurred in our study subjects, leading to our results more similar to those of the general population.

Strengths of this study include the sample size, follow-up time, and inclusion of detection of calcification. However, certain limitations remained. First, our study was a single-center study and multicenter research is required to be conducted to confirm our conclusions. Second, the number of death and events was relatively small, which may affect the statistical power. Third, we did not analyze the effects of underlying cardiac diseases such as heart failure and atrial fibrillation on blood pressure due to too few events occurring during the period.

In conclusion, 24-h ambulatory PP was the most significant predictor of all blood pressure indicators for clinical outcomes in PD patients. Thus, we suggest that the goal of antihypertensive therapy in PD patients should be not only to decrease SBP but also to reduce PP. Furthermore, this study highlights the need to investigate measures that would lessen arterial stiffness and optimize volume control to improve clinical outcomes in PD patients.

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Statement of Ethics

The study protocol was approved by the Ethics Committee of Huashan Hospital affiliated to Fudan University. All patients gave informed consent prior to the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.D. collected, analyzed, and interpreted data, and drafted the manuscript. Y.C. interpreted the data and drafted the manuscript. D.S. and X.G. collected the data. C.H. and Q.X. coordinated and revised the manuscript. T.Z. conceived and designed the study, helped draft the manuscript, had full access to all the study data, and take responsibility for the integrity of the data and the accuracy of the analysis. All authors provided critical feedback and approved the final manuscript.

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