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Subclinical Left Ventricular Myocardial Impairment and the Threshold Effect of Intact Parathyroid Hormone in Maintenance Hemodialysis Patients with Secondary Hyperparathyroidism: A Two-Dimensional Speckle-Tracking Echocardiographic Study

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Abstract

Background: To investigate the value of two-dimensional speckle-tracking echocardiography (2D-STE)-derived global longitudinal strain (GLS), 17-segment strain and peak strain dispersion (PSD) for detecting left ventricular myocardial impairment in maintenance hemodialysis (MHD) patients with secondary hyperparathyroidism (SHPT), and to define the cutoff of intact parathyroid hormone (iPTH) that signals myocardial impairment.

Methods: A total of 88 consecutive maintenance hemodialysis patients fulfilling the diagnostic criteria of SHPT (December 2023 – December 2025) were retrospectively enrolled and divided by iPTH into a low-PTH group (n = 36) and a high-PTH group (n = 52); 43 healthy volunteers served as controls. All underwent 2D-STE. Myocardial impairment was defined as an absolute GLS < 16%. Logistic regression and ROC analysis assessed the predictive performance and optimal cutoff of iPTH. Patients were followed up until July 2026, and Cox regression was used exploratorily for cardiovascular events.

Results: GLS decreased stepwise across the three groups (17.6%, 16.5% and 12.2%; P < 0.001). Although EF was normal in all 88 dialysis patients, GLS was already < 16% in 71.6%. Segmental strain showed a basal-predominant, relatively apically preserved pattern (high- vs. low-PTH: basal 11.32% vs. 15.39%, apical 14.51% vs. 18.78%, both

P < 0.001), and PSD was higher in the high- than in the low-PTH group (75.60 vs. 55.00 ms, P < 0.001). iPTH was an independent determinant of GLS (β = −0.0044, P < 0.001); each 100 pg/mL increase conferred a 3.8-fold higher odds of myocardial impairment (adjusted OR 4.531, 95% CI 1.978 – 10.380, P < 0.001), with an optimal cutoff of 190.8 pg/mL (AUC 0.859, sensitivity 82.5%, specificity 92.0%). In exploratory Cox regression (median follow-up 22.0 months), only age remained an independent predictor.

Conclusions: Patients with MHD complicated by SHPT have subclinical myocardial impairment preceding the decline in EF, characterized by reduced global GLS, a basal-predominant segmental pattern with relative apical preservation, and impaired mechanical synchrony. The iPTH – impairment association is threshold-like, and approximately 190.8 pg/mL may serve as a warning cutoff. Combining GLS with 17-segment strain and PSD may allow earlier detection of myocardial impairment.

Keywords: secondary hyperparathyroidism; maintenance hemodialysis; two-dimensional speckle-tracking echocardiography; global longitudinal strain; segmental strain; peak strain dispersion; parathyroid hormone

Background

Secondary hyperparathyroidism (SHPT) is highly prevalent in the maintenance hemodialysis (MHD) population and is closely associated with target-organ damage such as left ventricular hypertrophy [1]. Chronically elevated serum iPTH acts on the heart both indirectly, through disturbances of calcium and phosphate metabolism, and directly, via uremic toxin accumulation and dysregulation of the FGF23/Klotho axis [2-7], manifesting as left ventricular hypertrophy, interstitial myocardial fibrosis, and valvular and vascular calcification with accompanying diastolic dysfunction, ultimately increasing the risks of arrhythmia, heart failure and cardiovascular death.

Conventional echocardiography is widely available and highly reproducible and remains the first-line modality for assessing cardiac structure and function; however, its measurements are affected by loading conditions and operator dependence, and its

ability to detect early, mild myocardial dysfunction is limited. Two-dimensional speckle-tracking echocardiography (2D-STE), which tracks the frame-by-frame displacement of myocardial acoustic speckles, can depict global and regional myocardial deformation while ejection fraction (EF) is still normal, and has been shown to be more sensitive than EF in dialysis populations [8-10]; it has also been applied to arrhythmic risk assessment and prognostic stratification [11,12], and its apical-sparing pattern is used to identify infiltrative cardiomyopathy [13]. In patients with MHD complicated by SHPT, however, the gradient of strain across PTH levels, the segmental distribution pattern, and whether PTH is an independent determinant of GLS remain insufficiently reported.

Methods

Study participants

This retrospective cohort study was based on structured electronic medical records. Eighty-eight patients receiving regular hemodialysis and diagnosed with SHPT at our hospital between December 2023 and December 2025 were enrolled as the case group, and 43 healthy volunteers examined during the same period were enrolled as the control group. The study was approved by the Ethics Committee of Nanjing Medical University Affiliated BenQ Hospital (approval No. 2026-KL006) and conducted in accordance with the Declaration of Helsinki; all participants provided informed consent. Referring to the KDIGO and Chinese guidelines [14,15], a PTH level of three times the upper limit of normal (195 pg/mL; a value within the guideline-recommended 2–9× ULN target range) was used as the cutoff, and patients were divided into a high-PTH group (n = 52, > 195 pg/mL) and a low-PTH group (n = 36, 65–195 pg/mL). Inclusion criteria: (i) renal insufficiency with regular hemodialysis (2–3 sessions per week, dialysis vintage ≥ 3 months); (ii) parathyroid hormone ≥ 65 pg/mL (normal range 15–65 pg/mL); (iii) adequate echocardiographic acoustic windows. Exclusion criteria: (i) severe congenital heart disease, valvular heart disease, cardiomyopathy, coronary artery disease, or

arrhythmia; (ii) primary hyperparathyroidism; (iii) severe thoracic deformity or poor acoustic windows.

Study methods

Medical history, baseline demographic information and laboratory results were collected. Echocardiography was performed with a GE Vivid E95 ultrasound system equipped with an M5Sc phased-array probe (1.5 – 4.5 MHz) and the EchoPAC 204 speckle-tracking analysis software.

Participants rested for 10 min before the examination. After chest ECG electrodes were attached to determine the phase of the cardiac cycle, they were placed in the left lateral decubitus position and, when necessary, instructed to hold their breath. Images were acquired at a frame rate > 50 frames/s. Parasternal left ventricular long-axis views and apical two-, three- and four-chamber views were routinely acquired, with each cine loop containing at least five cardiac cycles. M-mode echocardiography was used to measure EDV, ESV, SV, EF and FS; from the apical four-chamber view, the E and A wave velocities of the mitral inflow were obtained, and tissue Doppler imaging was used to measure the lateral mitral annular e′ velocity and to calculate E/e′ .

All images were analyzed offline in EchoPAC 204. The three-, four- and two-chamber views were selected, and the AFI module was entered; the software automatically traced the endocardial border starting from three endocardial landmarks, with manual correction when the tracing deviated markedly. Segmental division followed the American Heart Association 17-segment model, and regional and global longitudinal peak strain (GLS) were read from the time-strain curves and bull's-eye plots. In addition, 30 cases were randomly selected and measured independently by two physicians; intraclass correlation coefficients (ICCs) were used to evaluate intra- and inter-observer agreement, and Bland-Altman analysis was used to display the distribution of differences.

Observational indices

Data were collected in four categories: (1) demographic and clinical data — age, sex, body mass index (BMI), systolic blood pressure and diastolic blood pressure; (2) two-dimensional and Doppler echocardiographic parameters — left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), left ventricular ejection fraction (EF), mitral E and A wave velocities, E/A, mitral annular e′ and E/e′; (3) strain parameters — GLS, 17-segment strain and peak strain dispersion (PSD); and (4) laboratory and dialysis data — PTH, serum calcium, serum phosphate, albumin and dialysis vintage. The strain threshold defining myocardial impairment was an absolute GLS < 16%.

Statistical analysis

Statistical analysis was performed with SPSS 26.0. Normally distributed continuous variables were expressed as mean ± standard deviation, and between-group differences were assessed by one-way analysis of variance (ANOVA) followed by LSD post hoc comparisons; skewed variables were expressed as median (interquartile range) and compared using the Kruskal-Wallis H test, with pairwise comparisons by the Mann-Whitney U test and Bonferroni correction; categorical variables were expressed as frequencies and percentages and compared using the χ^2 test. Pearson or Spearman coefficients were used for correlation analysis depending on the data distribution. Univariate linear regression was first performed with GLS as the dependent variable, and variables with $P < 0.10$ entered a backward multivariable model (removal threshold $P > 0.10$); sex was included as a covariate to adjust for the significant imbalance in sex distribution among the three groups ($\chi^2 = 16.28$, $P < 0.001$). After myocardial impairment was defined as an absolute GLS < 16%, binary logistic regression was performed (ORs and 95% CIs reported) and ROC curves were plotted; the 95% CI of the AUC was derived from 2000 bootstrap resamples, and the optimal cutoff was taken at the maximum Youden index. ANCOVA (with sex and systolic blood pressure as covariates) was used to compare the adjusted GLS means

among the three groups, and a Cox proportional-hazards model was constructed with cardiovascular events as the endpoint. A two-sided $\alpha = 0.05$ was used as the level of significance.

Results

Comparison of general clinical characteristics

Age, body weight and BMI did not differ significantly among the three groups ($P > 0.05$), whereas sex distribution did; sex was therefore included in the multivariable regression to control for confounding. Systolic and diastolic blood pressure were higher in both dialysis groups than in controls ($P < 0.001$), but the median systolic pressure differed by only about 3 mmHg between the low- and high-PTH groups ($P > 0.05$), suggesting that the elevated blood pressure was mainly attributable to the dialysis state rather than to the PTH level. On echocardiography, the dialysis groups had higher A wave velocity and E/e′ than controls (both $P < 0.01$), mildly increased EDV and ESV (ESV: $F = 3.88$, $P = 0.023$), slightly lower EF ($F = 6.23$, $P = 0.003$) and significantly reduced E/A and e′ (both $P < 0.001$), indicating marked diastolic dysfunction. Albumin, serum calcium, serum phosphate and dialysis vintage did not differ significantly between the two dialysis groups (all $P > 0.05$), with a median dialysis vintage of 48–66 months; PTH differed significantly between the two groups ($P < 0.001$). The results are shown in Table 1.

Table 1 Comparison of general clinical characteristics among the three groups

Variable	High-PTH group (n = 52)	Low-PTH group (n = 36)	Control group (n = 43)	Statistic	*P*
Age (years)	52.77±12.87	54.31±13.76	48.23±13.19	F=2.35	0.100
Sex (male/female)	28/24	24/12	10/33	χ^2=16.95	<0.001
BMI	23.3 (20.6–25.4)	21.8 (20.1–24.0)	22.9 (20.4–24.6)	H=2.05	0.359
Systolic BP (mmHg)	148.0 (133.0–158.2)	144.5 (134.2–150.8)	120.0 (117.5–128.5)	H=43.71	<0.001
Diastolic BP (mmHg)	85.40±10.90	83.83±10.43	77.21±6.98	F=8.44	<0.001

EDV (mL)	98.0 (79.5 – 111.5)	103.5 (79.5 – 128.2)	91.0 (84.0 – 100.0)	H=2.56	0.278
ESV (mL)	35.5±11.1	37.7±15.0	30.7±8.6	F=3.88	0.023
SV (mL)	62.0 (52.5 – 70.0)	65.5 (50.8 – 78.2)	60.0 (56.5 – 66.0)	H=1.35	0.510
EF (%)	62.98±5.32*	64.31±6.41*	66.88±4.51	F=6.23	0.003
E (cm/s)	68.00 (55.25, 90.00)	79.00 (69.50, 97.50)#	78.00 (70.00, 92.00)	H=7.03	0.030
A (cm/s)	94.48±21.58*	95.50±23.79*	67.58±15.45	F=25.77	<0.001
E/A	0.73 (0.59, 0.97)*	0.85 (0.71, 1.19)*	1.27 (0.86, 1.60)	H=30.53	<0.001
e′ (cm/s)	5.90±1.80*	6.64±2.19*	9.65±3.17	H=36.00	<0.001
E/e′	12.27 (10.16, 16.00)*	13.15 (9.61, 17.97)*	8.33 (6.90, 9.44)	H=35.02	<0.001
Dialysis vintage (months)	48.0 (24.0 – 72.0)	66.0 (45.0 – 87.0)	-	U=1105.5	0.150
Serum calcium (mmol/L)	2.3 (2.2 – 2.5)	2.2 (2.2 – 2.4)	-	U=750.5	0.116
Serum phosphate (mmol/L)	1.9±0.6	1.9±0.7	-	t=−0.46	0.648
PTH (pg/mL)	354.8 (258.3 – 441.3)	134.5 (101.1 – 167.0)	-	U=0.0	<0.001
Albumin (g/L)	39.0±4.5	39.3±4.9	—	t=0.26	0.799

Comparison of global longitudinal strain (GLS) among the three groups

GLS decreased in a stepwise manner across the three groups: 12.2 (11.2 – 13.6)% in the high-PTH group, 16.5 (15.4 – 17.2)% in the low-PTH group and 17.6 (16.4 – 19.8)% in controls, with significant pairwise differences ($P < 0.05$). Using GLS < 16% to define myocardial impairment, the detection rates were 8/43 (18.6%) in controls, 13/36 (36.1%) in the low-PTH group and 50/52 (96.2%) in the high-PTH group ($P < 0.05$). EF was ≥ 50% in all 88 dialysis patients, yet GLS was already < 16% in 63 of them (71.6%), suggesting that GLS detects myocardial impairment earlier than EF. After adjustment for sex and systolic blood pressure by ANCOVA, the adjusted GLS means still showed a stepwise gradient of 18.03 ± 0.43%, 16.54 ± 0.40% and 12.39 ± 0.34% ($F = 59.28$, $P < 0.001$), indicating that the between-group differences were not confounded by sex or blood pressure. The results are shown in Table 2.

Table 2 Global longitudinal strain parameters among the three groups

Variable	High-PTH group (n = 52)	Low-PTH group (n = 36)	Control group (n = 43)	F	P
GLS (%), median (IQR)	12.2 (11.2 – 13.6)	16.5 (15.4 – 17.2)	17.6 (16.4 – 19.8)	H=74.39	<0.001
Controls vs. low-PTH	—	—	—	U=1024.5	0.014
Controls vs. high-PTH	—	—	—	U=2132.5	<0.001
High-PTH vs. low-PTH	—	—	—	U=1718.5	<0.001
Abnormal GLS < 16%, n (%)	50 (96.2)	13 (36.1)	8 (18.6)	χ^2=63.56	<0.001
ANCOVA-adjusted	12.39±0.34	16.54±0.40	18.03±0.43	F=59.28	<0.001

Determinants of GLS

Univariate linear regression showed that PTH (β = −0.0046, r = −0.425, P < 0.001) and albumin (β = 0.1420, r = 0.217, P = 0.042) were associated with GLS, whereas EF, sex, E/e′, serum calcium, serum phosphate, dialysis vintage and systolic blood pressure were not (all P > 0.05). In the backward multivariable regression (n = 88, R^2 = 0.313, adjusted R^2 = 0.271), PTH, EF, albumin, serum calcium and sex were retained; PTH (β = −0.0044, 95% CI −0.0063 to −0.0024, P < 0.001), albumin (β = 0.1840, P = 0.004) and serum calcium (β = −3.1057, P = 0.015) were independent determinants of GLS. The results are shown in Table 3.

Table 3 Univariable and multivariable linear regression analyses of GLS

Predictor	Univariable β	r	P	Multivariable β	95% CI	P
PTH (pg/mL)	−0.0046	−0.425	<0.001	−0.0044	[−0.0063, −0.0024]	<0.001
EF (%)	0.0902	0.172	0.110	0.0847	[−0.0120, 0.1815]	0.085
E/e′	−0.0051	−0.009	0.931	Excluded	Excluded	Excluded
Albumin (g/L)	0.1420	0.217	0.042	0.1840	[0.0592, 0.3088]	0.004
Calcium (mmol/L)	−1.5014	−0.117	0.280	−3.1057	[−5.5928, −0.6187]	0.015
Phosphate (mmol/L)	0.3037	0.066	0.540	Excluded	Excluded	Excluded
Dialysis vintage (months)	0.0064	0.150	0.162	Excluded	Excluded	Excluded
Systolic BP (mmHg)	−0.0096	−0.059	0.582	Excluded	Excluded	Excluded
Sex (male = 1)	0.8577	0.139	0.195	1.1114	[−0.0320, 2.2548]	0.057

Predictive value of PTH for myocardial impairment and ROC analysis

With GLS < 16% as the endpoint of myocardial impairment, logistic regression showed that each 1 pg/mL increase in PTH raised the odds of myocardial impairment by 1.6% (OR = 1.016, 95% CI 1.008 – 1.024, P < 0.001), and each 100 pg/mL increase raised the odds approximately 3.8-fold (OR = 4.832, 95% CI 2.201 – 10.608, P < 0.001). Multivariable logistic regression (adjusted for albumin, serum calcium, age, sex and systolic blood pressure) yielded a virtually unchanged adjusted OR of 4.531 (95% CI 1.978 – 10.380, P < 0.001), with VIFs of 1.00 – 1.21 indicating no collinearity. The ROC curve showed an AUC of 0.859 (95% CI 0.772 – 0.932) for PTH in predicting myocardial impairment, with an optimal cutoff of 190.8 pg/mL corresponding to a sensitivity of 82.5% and a specificity of 92.0% (Fig. 1, Table 4).

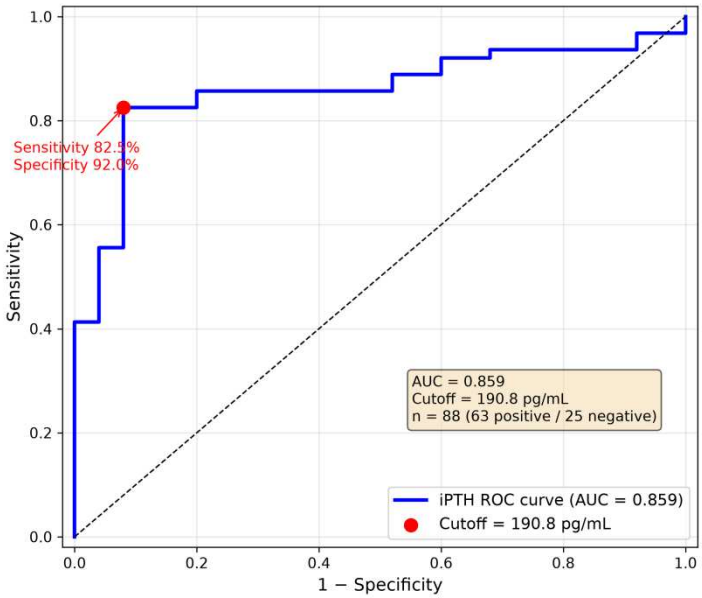


Fig. 1 ROC curve of iPTH for predicting myocardial impairment (GLS < 16%)

Table 4 Logistic regression and ROC analysis for predicting myocardial impairment (GLS < 16%)

Parameter	Estimate / value	95% CI	P
PTH, +1 pg/mL	1.016	[1.008, 1.024]	<0.001
PTH, +100 pg/mL	4.832	[2.201, 10.608]	<0.001
AUC	0.859	[0.772, 0.932]	—
Optimal cutoff (pg/mL)	190.8	—	—
Sensitivity (%)	82.5	—	—
Specificity (%)	92.0	—	—
Events / total	63 / 88	—	—

Note: *The multivariable model was adjusted for albumin, serum calcium, age, sex and systolic blood pressure; the variance inflation factors of the included variables were 1.00 – 1.21 (no collinearity), and no covariate other than iPTH reached statistical significance.

Left ventricular segmental strain and the relative apical preservation pattern

The 17 segments were stratified into basal (6 segments), mid (6 segments) and apical (4 + 1 segments) layers for comparison. Strain increased from the base to the apex in all three groups: basal segments were 17.60 ± 2.56%, 15.39 ± 2.60% and 11.32 ± 2.42% in controls, the low-PTH group and the high-PTH group, respectively (the same order hereinafter; H = 75.40, P < 0.001, pairwise P < 0.001); mid segments were 18.46 ± 2.93%, 17.36 ± 2.33% and 13.32 ± 2.63% (H = 62.36, P < 0.001; controls vs. low-PTH P = 0.140); apical segments were 18.55 ± 4.19%, 18.78 ± 4.13% and 14.51 ± 3.38% (H = 29.32, P < 0.001; controls vs. low-PTH P = 1.000). These findings indicate that SHPT-related myocardial impairment starts in the basal segments and extends toward the mid and apical segments as PTH rises. The results are shown in Table 5 and Fig. 2.

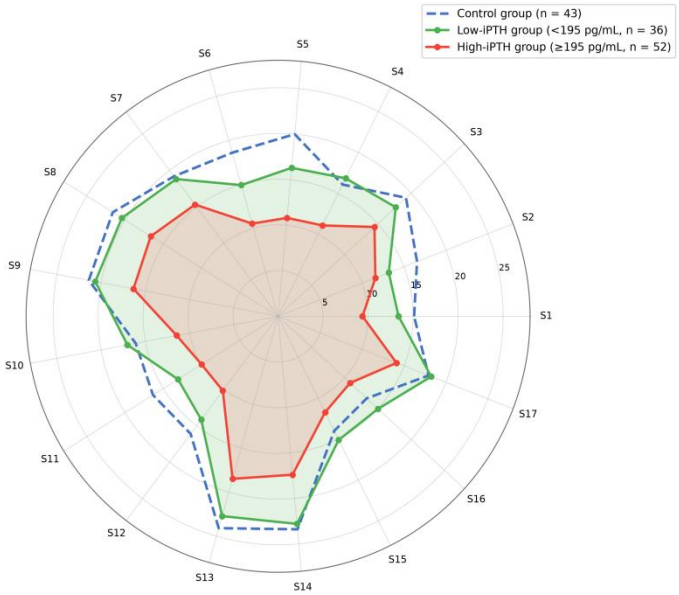


Fig. 2 Polar plots of regional longitudinal strain across the 17 left ventricular segments in the control, low-iPTH and high-iPTH groups (absolute strain values, %)

The apical preservation ratio (the ratio of apical to basal absolute longitudinal strain; a ratio > 1 indicates milder apical than basal involvement) was used to quantify this spatial pattern: the median ratio was 1.029 (0.867 – 1.270) in controls, 1.228 (0.955 –

1.512) in the low-PTH group and 1.321 (0.976 – 1.657) in the high-PTH group (H = 9.82, P = 0.007 across the three groups), with a significant difference between controls and the high-PTH group (P = 0.009), indicating that the higher the PTH level, the more pronounced the pattern of basal predominance with relative apical preservation (Table 5, Fig. 3).

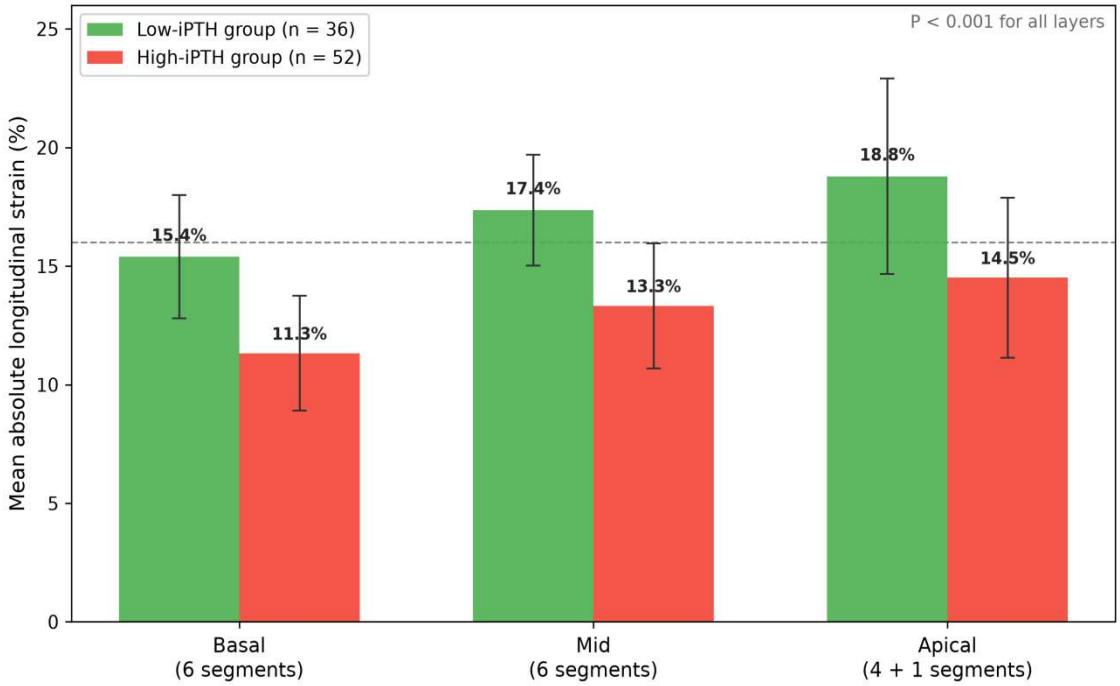


Fig. 3 Comparison of regional longitudinal strain of the basal, mid and apical segments between the low- and high-PTH groups

Table 5 Left ventricular segmental strain and the apical preservation pattern

Variable	High-PTH group (n = 52)	Low-PTH group (n = 36)	Control group (n = 43)	Statistic	*P*
Basal longitudinal strain (%)	11.32±2.42	15.39±2.60	17.60±2.56	H=75.40	<0.001
Mid longitudinal strain (%)	13.32±2.63	17.36±2.33	18.46±2.93	H=62.36	<0.001
Apical longitudinal strain (%)	14.51±3.38	18.78±4.13	18.55±4.19	H=29.32	<0.001
Apical preservation ratio*	1.321 (0.976–1.657)	1.228 (0.955–1.512)	1.029 (0.867–1.270)	H=9.82	0.007

Note: *Apical preservation ratio = mean absolute longitudinal strain of the apical segments (the four apical segments plus the apical cap) divided by that of the basal segments (6 segments); a ratio > 1 indicates milder apical than basal involvement (relative apical preservation). The statistic is the Kruskal-Wallis test across the three groups; pairwise comparisons are reported in the text.

Comparison of peak strain dispersion (PSD) among groups

PSD differed significantly among the three groups (H = 28.31, P < 0.001): it was similar between controls and the low-PTH group (U = 657.5, P = 0.254) but markedly higher in the high-PTH group than in both other groups (both P < 0.001). Using PSD ⩾ 65 ms to define left ventricular systolic dyssynchrony, the detection rate was 73.1% (38/52) in the high-PTH group versus 41.7% (15/36) in the low-PTH group (χ^2 = 7.50, P = 0.006). PSD was positively correlated with PTH (Spearman rho = 0.441, P < 0.001).

Table 6 Comparison of peak strain dispersion (PSD) among groups

Variable	High-PTH group (n = 52)	Low-PTH group (n = 36)	Control group (n = 43)	Statistic	*P*
PSD (ms)	75.60 [64.70–108.30]	55.00 [49.60–70.50]	52.50 [45.10–65.85]	H=28.31	<0.001
Low-PTH vs. controls	—	U=657.5	—	P=0.254	
High-PTH vs. controls	U=457.0	—	—	P<0.001	
High-PTH vs. low-PTH	U=487.5	—	—	P<0.001	

Note: Of the 43 controls, 7 had a PSD > 80 ms (maximum 208.6 ms), which raised the group mean PSD (61.4 ms) above the typical reference value for healthy adults; these cases were retained in the analysis and are addressed in the Discussion.

Cox proportional-hazards regression for cardiovascular events

All 88 patients completed follow-up. Four patients had established cardiovascular disease diagnosed before the echocardiographic examination, and their follow-up time could not be calculated in the conventional manner; they were therefore excluded from the survival analysis. Ultimately, 84 patients entered the Cox model, with a median follow-up of 22.0 months; during follow-up, 53 patients (63.1%) experienced cardiovascular events and 4 (4.8%) died.

In univariable Cox models, each 10 ms increase in PSD was associated with an approximately 14% higher risk of cardiovascular events (HR = 1.139, 95% CI 1.05 – 1.24, P = 0.002); age (HR = 1.519 per 10 years, P < 0.001) and systolic blood pressure (HR = 1.214 per 10 mmHg, P = 0.006) were also significant predictors, whereas GLS, EF, PTH group, sex and albumin did not reach statistical significance.

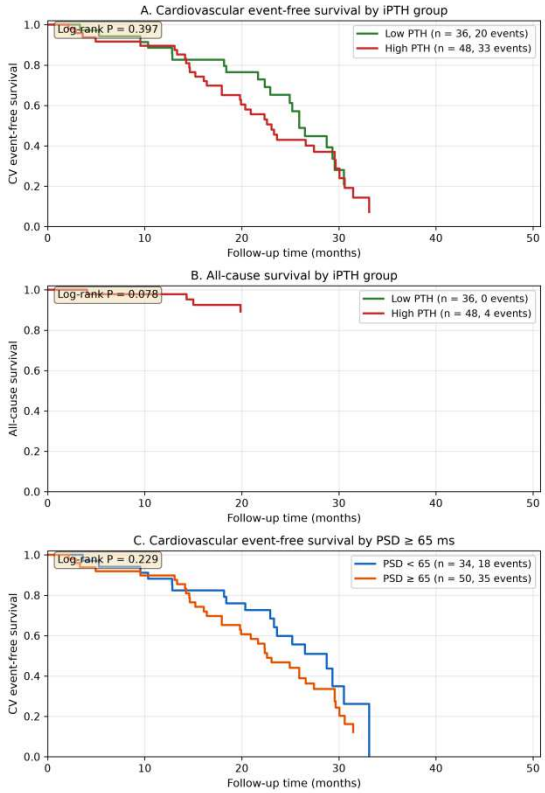


Fig. 4 Kaplan-Meier curves for the Cox cohort (n = 84): A, cardiovascular event-free survival stratified by PTH group; B, all-cause survival; C, cardiovascular event-free survival stratified by PSD ⩾ 65 ms

In the multivariable Cox model (including PSD, GLS, EF, age, systolic blood pressure and PTH group; six variables in total), only age retained independent predictive value (HR = 1.464, 95% CI 1.14 – 1.88, P = 0.003), while the effect of PSD attenuated to borderline significance (HR = 1.088, P = 0.094) and the remaining variables were no longer significant. The all-cause death endpoint, with only 4 events and no deaths in the low-PTH group (complete separation), could not be modeled reliably and is reported descriptively only: in univariable analysis, each 10 ms increase in PSD was associated with a 29% higher risk of all-cause death (HR = 1.290, 95% CI 1.02 – 1.64, P = 0.036). Details are shown in Table 7.

Table 7 Cox proportional-hazards regression for risk factors of cardiovascular events

Variable	Univariable HR (95% CI)	P	Multivariable HR (95% CI)*	P
PSD (per 10 ms)	1.139 (1.05 – 1.24)	0.002	1.088 (0.99 – 1.20)	0.094

GLS (per 1%)	0.958 (0.88 – 1.05)	0.345	1.094 (0.92 – 1.30)	0.309
EF (per 1%)	0.974 (0.94 – 1.01)	0.166	0.971 (0.92 – 1.02)	0.240
Age (per 10 years)	1.519 (1.20 – 1.93)	<0.001	1.464 (1.14 – 1.88)	0.003
Systolic BP (per 10 mmHg)	1.214 (1.06 – 1.40)	0.006	1.127 (0.97 – 1.31)	0.114
High-PTH vs. low-PTH	1.273 (0.73 – 2.23)	0.399	1.470 (0.63 – 3.43)	0.372
Female vs. male	0.809 (0.46 – 1.42)	0.460	—	—
Albumin (per 1 g/L)	0.960 (0.91 – 1.02)	0.159	—	—
PSD ≥ 65 vs. < 65 ms	1.416 (0.80 – 2.51)	0.232	—	—

Note: *The multivariable model included PSD, GLS, EF, age, systolic blood pressure and PTH group (six variables in total); n = 84, with 53 cardiovascular events. Multivariable Cox analysis was not performed for all-cause death because of the small number of events (4) and the absence of deaths in the low-PTH group (complete separation); in univariable analysis the HR of PSD was 1.290 per 10 ms (95% CI 1.02 – 1.64, P = 0.036), and the Fisher exact test for deaths between the two groups gave P = 0.138.

Reproducibility of strain parameters

Thirty participants were randomly selected, and GLS was measured independently by two senior physicians using EchoPAC 204. Bland-Altman analysis showed that nearly all points fell within the 95% limits of agreement, indicating good reproducibility of the GLS measurements (Fig. 5).

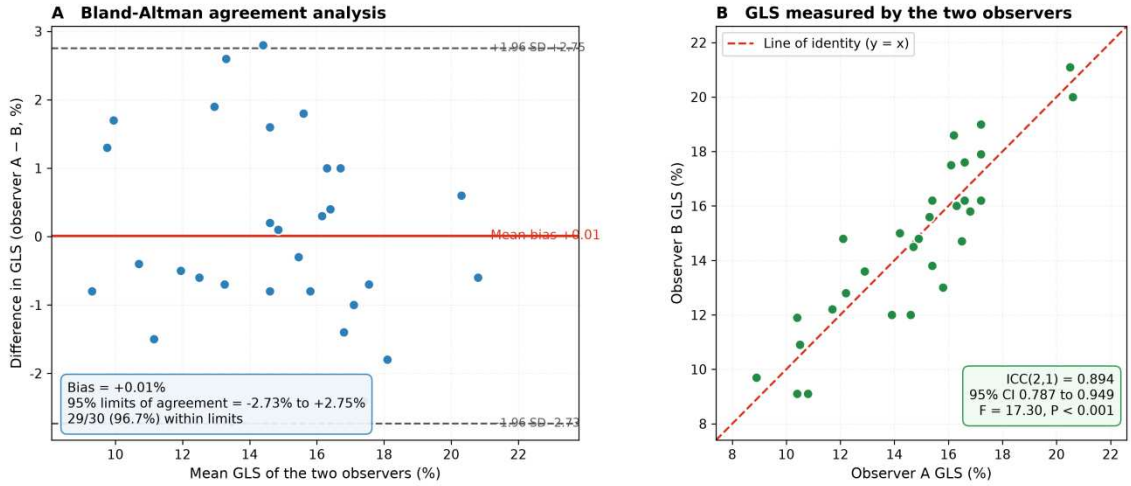


Fig. 5 Inter-observer reproducibility of GLS: A, Bland-Altman plot; B, scatter plot of the measurements of the two observers with ICC

Discussion

Early detection value of GLS: a normal EF does not exclude myocardial impairment

EF is commonly used in clinical practice to assess left ventricular systolic function, yet in this study 63 of the 88 dialysis patients (71.6%) already had GLS < 16% despite an EF ≥ 50%, corroborating the clinical dilemma that a normal EF does not imply an unaffected myocardium — 2D-STE can capture subclinical cardiac dysfunction while EF is still preserved. In patients with SHPT, PTH-driven sodium and water retention, anemia, calcium-phosphate disturbances and uremic toxin accumulation all injure the heart [2,3], consistent with previous studies in ESRD and dialysis populations showing that GLS reflects uremic myocardial impairment earlier and more sensitively than EF [8,9,16,17]. The GLS gradient remained robust after ANCOVA adjustment for sex and systolic blood pressure ($F = 59.28$, $P < 0.001$), indicating that the between-group differences were not attributable to confounding.

Correlation and regression analyses of GLS

Correlation analysis showed a moderate negative correlation between PTH and GLS ($r = -0.425$, $P < 0.001$) and a weak positive correlation for albumin ($r = 0.217$, $P = 0.042$), with no significant correlations for the other variables. The merely moderate correlation between PTH and GLS reflects the multifactorial nature of SHPT-related myocardial impairment: beyond the toxicity of PTH, calcium-phosphate load, nutritional and microinflammatory status, and volume and pressure overload all contribute. Notably, the association between iPTH and GLS was not linear: the Pearson r was −0.425 whereas the Spearman ρ was −0.671, and after adding a quadratic iPTH term the quadratic component was significant ($P < 0.001$; R^2 increased from 0.181 to 0.371). Stratification by quartiles showed that the decline in GLS was concentrated in the lower quartiles (a 2.64% drop from Q1 to Q2, $P = 0.006$) and then plateaued, forming a steep-then-flat saturating shape. This pattern suggests a threshold-like relationship: iPTH has limited power to explain the severity of impairment as a continuous variable but good discriminative power for judging whether the impairment threshold has been crossed, which is why logistic regression

and ROC analysis were added beyond the linear framework.

In this study, variables were screened at $P < 0.10$, and iPTH, albumin and serum calcium remained independent in the final model. Variables that were significant univariably but not multivariably (EF, E/e′) suggest collinearity or a downstream position in the causal chain, whereas a variable that became significant only after adjustment (serum calcium) suggests a suppression effect: the univariable correlation of serum calcium was only -0.117 ($P = 0.280$), but after adjustment for albumin it emerged as an independent negative determinant ($\beta = -3.1057$, $P = 0.015$), because approximately 40%–50% of serum calcium is bound to albumin, causing the two opposing effects to cancel each other. Univariate analysis should therefore be regarded as a screening step only; the existence, direction and magnitude of independent effects should be judged by the multivariable model.

Binary logistic regression with GLS < 16% defining myocardial impairment complemented the linear models by addressing whether the clinical impairment threshold is crossed and by accommodating threshold effects. Each 100 pg/mL increase in iPTH yielded an OR of 4.832 (95% CI 2.201–10.608), and the multivariable-adjusted OR was 4.531 (95% CI 1.978–10.380, $P < 0.001$), consistent with the unadjusted estimate, with VIFs of 1.00–1.21 excluding collinearity. Taken together with the finding that the PTH group was not an independent predictor of events in the Cox framework, iPTH appears better suited as a continuous marker of the severity of impairment.

Seventeen-segment strain reveals a characteristic phenotype of SHPT-related myocardial impairment

GLS is the mean of the strains of the 17 segments and, although it summarizes global contractile function, it conceals inter-segmental differences [18]. In the low-PTH stage, basal strain was already significantly lower than in controls ($P < 0.001$) while mid and apical strains were not; in the high-PTH stage, all three layers were significantly lower than in controls (all $P < 0.05$), forming a gradient pattern of

basal predominance with relative apical preservation (apical sparing). The implications are threefold: (i) the basal segments are the earliest and most severely affected region and may serve as a clue for early screening; (ii) apical sparing was first described in infiltrative cardiomyopathies such as cardiac amyloidosis [13] and can also occur in ESRD, where it is associated with dialysis dependence and elevated left ventricular filling pressures [19], suggesting that it may reflect advanced myocardial remodeling with interstitial fibrosis, possibly more prominent in the high-PTH group; and (iii) this distribution pattern has rarely been systematically described in the MHD population with SHPT.

PSD reflects electromechanical dispersion in SHPT: a new dimension of the myocardial toxicity of PTH

Beyond the decline in global contractility, this study used peak strain dispersion (PSD) to assess electromechanical synchrony [11,20]. PSD was similar between controls and the low-PTH group ($P = 0.254$) but markedly elevated in the high-PTH group (both $P < 0.001$); this stepwise pattern, however, was not synchronous with GLS: GLS had already decreased significantly in the low-PTH group ($P = 0.014$) whereas PSD had not yet risen, suggesting that impairment of mechanical synchrony lags behind the decline in global contractility — PSD is less sensitive than GLS for early impairment, and its elevation more likely marks a later stage of impairment. It should be noted that the absolute PSD values of the control group were relatively high overall (7/43 cases > 80 ms), which may have masked the difference between normal and mildly abnormal values (see Limitations). PSD was positively correlated with iPTH ($rho = 0.441$, $P < 0.001$), but this association disappeared after GLS was included, suggesting that PSD lies downstream of GLS; as a third dimension beyond EF and GLS, PSD provides complementary evidence for the direct myocardial toxicity of PTH [21].

Cox proportional-hazards regression for cardiovascular events: a marker of impairment is not necessarily an independent prognostic factor

Cox proportional-hazards regression was performed with cardiovascular events as the endpoint (n = 84, median follow-up 22.0 months, 53 events). In univariable analysis, each 10 ms increase in PSD was associated with an approximately 14% higher event risk, and age and systolic blood pressure were also significant predictors, whereas GLS, EF, PTH group, sex and albumin did not reach statistical significance; after multivariable adjustment, only age remained independently predictive, while the effect of PSD attenuated to borderline significance (HR = 1.088, P = 0.094) (Table 7, Fig. 4). Kaplan-Meier curves showed no significant differences in event-free survival by iPTH group (log-rank P = 0.397) or by PSD $\geqslant$ 65 ms (P = 0.229).

It must be emphasized that this study was designed primarily for cross-sectional assessment of impairment and that the prognostic analysis is exploratory: cardiovascular events were a composite endpoint with a high event rate and a broad definition, and a follow-up of only 22.0 months and the limited sample size were insufficient to confirm or exclude a moderate association. Although GLS has been shown to independently predict cardiovascular events in dialysis patients [22], the prognostic information of iPTH and PSD in this cohort attenuated markedly after adjustment for age, suggesting that their value lies more in identifying established impairment and informing the timing of intervention; this information may be partly carried by age and transmitted through the impairment phenotype [11,12], consistent with the experience from PTH-targeted intervention trials in which lowering PTH did not concurrently reduce cardiovascular events [23-25].

Specific myocardial toxicity of PTH: multiple pathways

Multivariable linear regression confirmed that iPTH was an independent negative determinant of GLS ($\beta = -0.0044$, $P < 0.001$). Systolic blood pressure

(147.5 vs. 144.5 mmHg) and E/e′ (13.1 vs. 12.3) differed only minimally between the high- and low-PTH groups (P > 0.05), suggesting that the PTH-dependent decline in GLS is not a byproduct of blood pressure or diastolic dysfunction. The multiple mechanistic pathways by which PTH injures the myocardium (calcium overload, PKC activation, FGF23/Klotho axis dysregulation, etc.) [1-7,26-28] are not reiterated here; this study adds the PSD dimension: elevated PSD suggests that PTH may affect myocardial electrical conduction, thereby disrupting electromechanical synchrony [11].

Practical value of the clinical cutoff and its limitations

ROC analysis showed an AUC of 0.859 (95% CI 0.772–0.932) for iPTH in predicting myocardial impairment (GLS < 16%), with an optimal cutoff of 190.8 pg/mL (sensitivity 82.5%, specificity 92.0%), almost identical to the stratification cutoff used in this study (3× ULN, 195 pg/mL) [14,15]: the two values were derived by different approaches yet nearly coincide. It should be noted that patients were stratified at 195 pg/mL at enrollment, so the ROC optimum may have been partly drawn toward this cutoff by the stratification itself, and the concordance should be verified in an independent, unstratified cohort.

Nutritional status and myocardial impairment

Serum albumin was an independent positive predictor of GLS (β = +0.1840, P = 0.004) and was not correlated with iPTH (P = 0.719), suggesting that nutritional status is a myocardial protective factor independent of PTH; uremic myocardial impairment is often accompanied by protein-energy wasting and a microinflammatory state, and hypoalbuminemia may contribute to myocardial remodeling through oxidative stress and endothelial dysfunction. Serum calcium showed an association that emerged only after adjustment (β = −3.1057, P = 0.015): its univariable correlation was not significant (P = 0.280) because approximately 40%–50% of serum calcium is bound to albumin (r = 0.292), causing opposing effects to cancel; after adjustment, the adverse effect of calcium load became apparent, suggesting that

calcium overload and myocardial calcification may participate in SHPT-related myocardial impairment.

Limitations

(1) The design was retrospective and primarily cross-sectional, allowing associations to be suggested but not causality to be established, with potential selection bias; (2) the proportion of women in the control group was high (76.7%), and residual bias is possible despite regression adjustment; (3) vascular calcification was not directly assessed and was indirectly represented by dialysis vintage and serum phosphate; (4) the death endpoint comprised only 4 events (0 in the low-PTH group), precluding reliable modeling, and the main conclusions are based on cardiovascular events (n = 53); (5) constrained by the number of events, the Cox model could accommodate only six variables, albumin and serum calcium were not included, and the effect of PSD was diluted by age; (6) the 17-segment analysis was based on two-dimensional STE, and three-dimensional STE is more comprehensive but less accessible [29]; (7) four patients had established cardiovascular disease diagnosed before the echocardiographic examination and were excluded from the survival analysis. In addition, the absolute PSD values of the control group were relatively high overall (median 52.5 ms, 7 cases > 80 ms), so extrapolation of the reference range requires caution.

Conclusions

This study shows that patients with MHD complicated by SHPT already have widespread subclinical myocardial impairment while EF remains normal (71.6% of patients with GLS < 16%), presenting a triad of reduced global GLS, a basal-predominant segmental pattern with relative apical preservation, and impaired synchrony (elevated PSD). This combination suggests that SHPT-related myocardial impairment is a diffuse process led by impaired longitudinal strain and subsequently extending to electromechanical synchrony, and that its early detection depends on GLS rather than EF.

iPTH is an independent determinant of this impairment, and its association with GLS is threshold-like rather than simply linear: as a continuous variable, iPTH explained only about 18% of the variance in GLS, yet each 100 pg/mL increase was associated with an approximately 3.8-fold higher odds of crossing the myocardial impairment threshold (multivariable-adjusted OR = 4.531, 95% CI 1.978 – 10.380, P < 0.001), and the optimal ROC cutoff of 190.8 pg/mL was almost identical to the stratification cutoff of 195 pg/mL adopted in this study, suggesting a reference time point for initiating or intensifying intervention [30].

PSD rises later than GLS declines and is better suited to marking the stage of impairment than to early screening; the exploratory Cox analysis did not confirm an independent predictive value of iPTH or PSD, and their roles should be positioned as markers of the severity of impairment and of the timing of intervention rather than as independent prognostic factors. Incorporating GLS combined with 17-segment strain and PSD into the routine echocardiographic follow-up of dialysis patients may help identify SHPT-related myocardial impairment earlier; their independent prognostic value awaits verification in prospective, multicenter cohorts.

List of abbreviations

2D-STE: two-dimensional speckle-tracking echocardiography
AUC: area under the curve
BMI: body mass index
CI: confidence interval
CKD: chronic kidney disease
CKD-MBD: chronic kidney disease-mineral and bone disorder
EF: ejection fraction
ESRD: end-stage renal disease
FGF23: fibroblast growth factor 23
GLS: global longitudinal strain
HR: hazard ratio
iPTH: intact parathyroid hormone
KDIGO: Kidney Disease: Improving Global Outcomes
LV: left ventricular
LVH: left ventricular hypertrophy
MHD: maintenance hemodialysis

OR: odds ratio
PSD: peak strain dispersion
PTH: parathyroid hormone
ROC: receiver operating characteristic
SHPT: secondary hyperparathyroidism

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Nanjing Medical University Affiliated BenQ Hospital (approval no. 2026-KL006) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Availability of data and materials

The datasets generated and analysed during the current study are not publicly available because they contain individually identifiable patient information, but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZF and SHG conceived and designed the study. ZF, DY and YQ performed the echocardiographic examinations and offline image analysis. SL and BJ collected the clinical and laboratory data and contributed to follow-up. ZF performed the statistical analysis and drafted the manuscript. SHG supervised the study, validated the image analysis and critically revised the manuscript. All authors read and approved the final manuscript.

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