Role of parathyroid hormone and vitamin D supplementation in stroke among patients on peritoneal dialysis

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Abstract

Background

Continuous ambulatory peritoneal dialysis (CAPD) patients have a high incidence of stroke and commonly have increased parathyroid hormone levels and vitamin D insufficiency. We seek to investigate the incidence of stroke and the role of parathyroid hormone and vitamin D supplementation in stroke risk among CAPD patients.

Methods

This is a retrospective study enrolled a Chinese cohort of 980 CAPD patients who were routinely followed up in our department. The demographic and clinical data recorded at the time of initial CAPD and during follow-up time are collected. The included cases were separated into nonstroke and stroke groups. The role of parathyroid hormone and vitamin D supplementation for stroke in CAPD patients is evaluated. The primary endpoint is defined as the first-time occurrence of stroke, and composite endpoint events are defined as death or switch to hemodialysis during follow-up.

Results

A total of 757 eligible CAPD patients with a mean follow-up time of 54.7 (standard deviation (SD) 33) months were included in the study. The median incidence of stroke among our CAPD patients was 18.9 (IQR, 15.7 - 22.1) per 1000 person-years. A significant nonlinear correlation between baseline iPTH and hazard of stroke (p value of linear association = 0.2 and nonlinear association = 0.002) was observed in our univariate Cox regression analysis, and low baseline iPTH levels (≤150 pg/ml) were associated with an increased cumulative hazard of stroke. Multivariate Cox regression analysis indicated a significant interaction effect between age and iPTH after adjusting for other confounders. Vitamin D supplementation during follow-up was a predictive factor for stroke in our cohort.

Conclusions

CAPD patients suffered a high risk of stroke. Lower iPTH levels were significantly associated with an increased risk of stroke. Vitamin D supplementation is an independent predictive factor for stroke among CAPD patients.

Background

Continuous ambulatory peritoneal dialysis (CAPD) is a widely accepted and cost-effective therapy for end-stage renal disease (ESRD) patients (1, 2), and the second or third cause of death among these patients is stroke (3). The risk of stroke is more than 3- to 10-fold higher among ESRD patients than among the general population (4–6). However, studies focused on risk factors for stroke among CAPD patients are rare.

Past studies have indicated that ESRD patients share traditional risk factors for stroke with the general population (3, 7). However, it is also recognized that the stroke risk profiles of CAPD patients are slightly different from those of the general population because of the loss of residual renal function, which may contribute to disorders of mineral and bone metabolism, volume overload, irrepressible hypertension, electronic disorder, and treatment with glucose-based dialysis solutions. Commonly, increased serum parathyroid hormone (PTH) levels and vitamin D insufficiency are universal among CAPD patients and are mostly attributed to chronic kidney disease-mineral and bone disorder (CKD-MBD) (8–10). Accumulating evidence has indicated that vitamin D deficiency or insufficiency significantly increased cardiovascular disease (CVD) events among the general or dialysis population (11–14). However, the relationship between serum PTH levels and CVD events is not consistent (15–18). Studies have indicated that serum PTH levels may increase cardiovascular risk (15, 19). However, a prospective study that recruited a cohort of 15,792 people in four U.S. communities with a median follow-up of 19 years failed to show that elevated PTH is an independent risk marker for incident cardiovascular disease (16). Conversely, a weak but significant inverse association (p value = 0.02 to 0.04) of incident heart failure, peripheral artery disease, and CVD mortality with PTH was observed in this study, and these findings were also consistent with those of studies among patients with dialysis (17, 20).

Few studies have focused on the relationship between stroke and CAPD, especially the role of PTH and vitamin D supplementation for stroke in patients with CAPD. Our study investigated the prevalence of stroke among patients with CAPD and the role of serum PTH levels and vitamin D supplementation in stroke risk via a retrospective study with a long-term, single-center follow-up.

Methods

Participants

This is a retrospective study based on a large cohort of CAPD patients that was conducted at a single center of the First Affiliate Hospital of Wenzhou University. A total of 1,024 cases were identified and reviewed from our hospital information system and peritoneal dialysis database between Jan 2006 and Dec 2018. The inclusion criteria were as follows: 1. ESRD patients with CAPD and 2. Routine follow-up for more than 3 months in our peritoneal dialysis center. The exclusion criteria were as follows: 1. History of continuous hemodialysis for more than 6 months prior to CAPD or combination of continuous hemodialysis and CAPD, 2. History of kidney transplant, and 3. Missing important laboratory data or medicine data. The study protocol was reviewed and approved by the Ethics Committee of the First Affiliate Hospital of Wenzhou University before the collection of any data, but additional informed consent was not obtained.

Clinical Data

At the initiation of CAPD, age; sex; blood pressure; serum creatinine; hemoglobin; serum albumin; serum intact parathyroid hormone (iPTH); serum uric acid; serum calcium; serum phosphorus; and history of diabetes, hypertension, chronic heart disease, and stroke were recorded as baseline values. During follow-

up, medications including calcium channel blockers (CCBs), renin–angiotensin–aldosterone system (RAAS) blockades (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), vitamin D supplements, calcium agents, and antiplatelet agents, as well as laboratory data and first-time occurrence of stroke, were recorded. The log-transformed, time-averaged and median absolute deviation (MAD) of iPTH were calculated for every case during follow-up. Patients who received medications for more than three months were assigned to the treatment group.

Definitions

Stroke is defined as an episode of focal neurological deficit persisting for more than 24 hours that is presumed to be caused by cerebral ischemia or hemorrhage. The diagnosis of stroke is verified by computer tomography or magnetic resonance imaging and evidence from the patients' medical records. The primary endpoint is defined as the first-time occurrence of stroke, and composite endpoint events are defined as death or switch to hemodialysis during follow-up. Hypertension is defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg. Chronic heart disease is defined as evidence in medical records; treatment for coronary artery disease, arrhythmia, or congestive heart failure; or the presence of valvular heart disease. Patients lost to follow-up or those who did not reach an endpoint event during follow-up were censored. Survival time is defined from the initial time of CAPD until the date of the last follow-up at our peritoneal dialysis center or the time of occurrence of the endpoint event.

Statistical Analysis

Numerical data are expressed as the mean (standard deviation) for normally distributed data or median [interquartile range] for skewed data, and categorical data are expressed as a count with a percentage (%). The included cases were divided into two groups by stroke status (nonstroke and stroke), and the differences between groups were examined using Student's t-test or Kruskal-Wallis test for numerical data and chi-square test for categorical data. The Kaplan-Meier analysis was performed to calculate the cumulative hazard of stroke. A log-rank test and a pairwise comparison was performed to compare the survival differences between the groups. A spline term of iPTH was constructed to fit a nonlinear Cox regression model. The relationships between clinical characteristics and stroke were investigated by univariate and multivariate Cox regression analyses, and an interaction item of age and iPTH was constructed. A nonlinear regression was performed to fit the iPTH levels with follow-up times using the local polynomial regression for displaying the difference in iPTH levels between the stroke and nonstroke groups. A subgroup analysis was performed to assess the effects of vitamin D supplementation on stroke in different subgroups of age (≤ 65, and > 65 years), sex (male, and female), serum calcium (≤ 2.1, and > 2.1 mmol/l), serum phosphorus (≤ 1.5, and > 1.5 mmol/l), and serum iPTH (< 150, 150–300, 300–600, and > 600). Plots were constructed and smoothed using the R package of ggplot2 (21). All reported p values are two-tailed, and p values less than 0.05 are considered to indicate statistical significance. R (3.6.0, R Core Team) and R packages were used for data processing and statistical analyses (22).

Results

A total of 757 eligible CAPD patients with a mean follow-up time of 54.7 (standard deviation (SD), 33) months were included in the study (Fig. 1). The median age of our cohort was 49 (interquartile range (IQR), 38–60) years, and the proportion of men was 55.1%. A total of 91 (12%) patients experienced stroke during a median follow-up time of 15 months and with a median occurrence age of 61.5 years, and the counts of ischemic stroke and hemorrhagic stroke were 74 (83.1%) cases and 23 (25.8%) cases, with median ages of 64.5 and 55 years, respectively. The median incidence of stroke among our CAPD patients was 18.9 (IQR, 15.7–22.1) per 1000 person-years. An obvious phenomenon was noticed in which patients at the initiation and 5 years and 10 years after CAPD had a high incidence of stroke (Supplemental Fig. 1). A total of 153 (20%) patients in our cohort experienced composite endpoints, and the proportion of composite endpoint events increased significantly in the stroke group compared to that of the nonstroke group (39.6% vs 17.6%, respectively; p value < 0.001).

A few significant differences at the initiation of CAPD were observed between the stroke and nonstroke groups in our cohort. The median age in the stroke group was significantly older (62 vs 48 years; p value < 0.001), and the stroke group had lower levels of serum albumin (33.6 vs 35.7 g/l, p value = 0.002), serum phosphorus (1.6 vs 1.7 mmol/l, p value = 0.001), iPTH (167.7 vs 269.0 pg/ml, p value = 0.001) and DBP (76.6 vs 84.6 mmHg, p value < 0.001). Furthermore, the prevalence of chronic heart disease (97.8% vs 25.8%, p value < 0.001) and diabetes (53.8% vs 24.3%, p value < 0.001) was significantly higher in the stroke group. Interestingly, the prevalence of vitamin D supplementation was significantly lower in the stroke group than in the nonstroke group (53.8% vs 70.9%, respectively; p value = 0.002). The results of the comparison between the stroke and nonstroke groups are shown in Table 1.

Table 1

Comparing the clinical characteristics and laboratory measurements of the included CAPD patients with and without stroke.

Characteristics	Nonstroke	Stroke	p
Patients (n)	666	91	
Male (n, %)	368 (55.3)	49 (53.8)	0.9
Age (years, median [IQR])	48.0 [37.0, 58.0]	62.0 [52.5, 68.5]	< 0.001
Serum albumin (g/l, median [IQR])	35.7 [32.0, 39.1]	33.6 [31.2, 37.1]	0.002
Hemoglobin (g/l, median [IQR])	81.3 (18.7)	80.0 (19.2)	0.5
Serum creatinine (μmol/l, median [IQR])	748.0 [571.0, 946.2]	583.7 [470.0, 790.5]	< 0.001
Serum calcium (mmol/l, median [IQR])	2.1 [1.9, 2.2]	2.1 [1.9, 2.2]	0.7
Serum phosphorus (mmol/l, median [IQR])	1.7 [1.5, 2.0]	1.6 [1.3, 1.9]	0.001
iPTH (pg/ml, median [IQR])	269.0 [154.7, 422.0]	167.7 [87.7, 346.2]	0.001
SBP (mmHg, mean (SD))	140.7 (25.1)	143.6 (26.6)	0.3
DBP (mmHg, mean (SD))	84.6 (14.9)	76.6 (16.4)	< 0.001
MAP (mmHg, mean (SD))	103.3 (16.7)	99.0 (17.6)	0.02
Follow-up time (month, mean (SD))	54.6 (32.7)	55.5 (35.4)	0.8
Ischemic stroke (n, %)		74 (83.1)	
Hemorrhagic stroke (n, %)		23 (25.8)	
Composite endpoints (n, %)	117 (17.6)	36 (39.6)	< 0.001
Combined Diseases			
Chronic heart disease (n, %)	172 (25.8)	89 (97.8)	< 0.001
Hypertension (n, %)	645 (96.8)	91 (100.0)	0.2
Diabetes (n, %)	162 (24.3)	49 (53.8)	< 0.001
Treatments			
Calcium agents (n, %)	538 (80.8)	66 (72.5)	0.09
Antiplatelet agents (n, %)	208 (31.2)	62 (68.1)	< 0.001

iPTH: intact parathyroid hormone; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; Vitamin D: alfacalcidol or calcifediol; RAAS: renin–angiotensin–aldosterone system; CCBs: calcium channel blockers

Characteristics	Nonstroke	Stroke	p
Statins (n, %)	399 (59.9)	67 (73.6)	0.02
Vitamin D (n, %)	472 (70.9)	49 (53.8)	0.002
RAAS blockades (n, %)	529 (79.4)	71 (78.0)	0.9
CCBs (n, %)	597 (89.6)	88 (96.7)	0.05

iPTH: intact parathyroid hormone; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; Vitamin D: alfacalcidol or calcifediol; RAAS: renin–angiotensin–aldosterone system; CCBs: calcium channel blockers

Relationship between baseline iPTH and stroke

Our data showed a significantly skewed distribution of baseline serum iPTH, and the probability density distribution was markedly different between the nonstroke group and the stroke group, with a significant left-shift peak in the stroke group, which means that the levels of serum iPTH were significantly lower in the stroke group (Supplemental Fig. 2a). Our nonlinear Cox regression analysis indicated a significant nonlinear correlation between baseline iPTH and hazard of stroke (p value of linear part = 0.2, and nonlinear part = 0.002). The curve of the relative stroke rate by baseline iPTH levels (referred to as 152 pg/ml) was J-shaped, which means that patients with low and markedly high levels of iPTH had a higher risk of stroke (Supplemental Fig. 2b).

A Kaplan-Meier analysis of stroke among patients with different levels of baseline serum iPTH (cases were separated into four groups based on iPTH levels: ≤150, 150–300, 300–600, and > 600 pg/ml) showed a significant difference in cumulative hazard of stroke between the groups (log-rank test, p value < 0.001), and patients with low baseline iPTH levels (≤ 150 pg/ml) had an increased cumulative hazard of stroke. The pairwise comparison between groups showed that there were significant differences between the ≤ 150 group and the 150–300 group and the 300–600 group (p value = 0.002 and < 0.001, respectively), and there were no significant differences between the ≤ 150 group and the > 600 group (p value = 0.1, Fig. 2).

Risk factors for stroke and composite endpoints

Our univariate Cox regression analysis showed that increased age, decreased DBP and iPTH levels combined with chronic heart disease and diabetes, receiving antiplatelet agents and not taking vitamin D supplements are common risk factors for stroke and composite endpoints. However, male sex is a risk factor for composite endpoints but not for stroke, and taking calcium agents is a protective factor for stroke but not for composite endpoints (Table 2).

Table 2

Univariate Cox regression for stroke and composite endpoints.

Variables	Model 1		Model 2	
	HR [95% CI]	p value	HR [95% CI]	p value
Age (years)	1.07 [1.05, 1.09]	< 0.001	1.05 [1.04, 1.06]	< 0.001
Male	0.72 [0.44, 1.18]	0.2	1.67 [1.19, 2.34]	0.003
Serum albumin (g/l)	0.96 [0.92, 1.00]	0.06	0.96 [0.93, 0.98]	0.002
Serum UA (mg/dl)	0.97 [0.86, 1.10]	0.6	0.99 [0.91, 1.07]	0.7
Hemoglobin (g/l)	1.00 [0.99, 1.01]	0.9	1.00 [1.00, 1.01]	0.3
Serum calcium (mmol/l)	1.44 [0.57, 3.63]	0.4	1.10 [0.61, 1.97]	0.8
Serum phosphorus (mmol/l)	0.55 [0.30, 1.02]	0.06	0.60 [0.40, 0.90]	0.01
iPTH levels				
<150	Ref	-	Ref	-
150–300	0.43 [0.23, 0.81]	0.01	0.86 [0.57, 1.28]	0.5
300–600	0.38 [0.20, 0.73]	0.003	0.53 [0.34, 0.82]	0.004
>600	0.58 [0.25, 1.33]	0.2	0.69 [0.38, 1.22]	0.2
SBP (mmHg)	1.00 [0.99, 1.01]	0.6	1.00 [0.99, 1.01]	1
DBP (mmHg)	0.97 [0.95, 0.98]	< 0.001	0.98 [0.97, 0.99]	< 0.001
Chronic heart disease	3.19 [1.95, 5.22]	< 0.001	2.96 [2.14, 4.10]	< 0.001
Diabetes	2.81 [1.72, 4.59]	< 0.001	2.52 [1.82, 3.49]	< 0.001
Calcium agents	0.53 [0.31, 0.92]	0.02	0.73 [0.50, 1.08]	0.1
Vitamin D	0.38 [0.23, 0.63]	< 0.001	0.47 [0.34, 0.66]	< 0.001
Antiplatelet agents	3.33 [1.99, 5.58]	< 0.001	1.75 [1.26, 2.42]	0.001
Statins	1.38 [0.80, 2.37]	0.3	0.87 [0.62, 1.21]	0.4

HR: hazard ratio; CI: confidence interval; UA: uric acid; SBP: systolic blood pressure; DBP: diastolic blood pressure; Model 1: Univariate model for stroke; Model 2: Univariate model for composite endpoints.

Our data showed a significant inverse correlation between serum iPTH and age (Kendall's rank correlation coefficient = -0.15, p value < 0.001). We hypothesize that interaction effects may exist between age and iPTH. Thus, an interaction item of serum iPTH and age was constructed in the multivariate Cox models

for stroke and composite endpoints. In the stroke model (Table 3, model 1), there was a significant interaction effect between serum iPTH levels and age. Surprisingly, the baseline serum iPTH levels were still significantly associated with stroke, but age was not associated after adjusting for other confounders. In regard to stroke risk, there was no significant interaction effect between serum iPTH and age, and age but not iPTH was significantly associated with composite endpoints (Table 3, model 2). A plot of interaction effects showed that iPTH levels between 150 and 300 pg/ml are appropriate for patients younger than 65 years and between 300 and 600 pg/ml for patients older than 65 years (Supplemental Fig. 3).

Table 3

Multivariate Cox regression of iPTH with interest endpoints.

Variables	Model 1		Model 2	
	HR [95% CI]	p value	HR [95% CI]	p value
Age (years)	1.03 [1.00, 1.06]	0.08	1.03 [1.01, 1.06]	0.009
Male			1.61 [1.11, 2.35]	0.01
Serum albumin (g/l)	0.99 [0.93, 1.04]	0.6	0.98 [0.95, 1.01]	0.2
Serum UA (mg/dl)	1.07 [0.93, 1.23]	0.3	0.99 [0.91, 1.08]	0.8
Serum calcium (mmol/l)	0.93 [0.29, 3.03]	0.9	1.29 [0.60, 2.75]	0.5
Serum phosphorus (mmol/l)	1.12 [0.56, 2.27]	0.7	1.16 [0.72, 1.87]	0.5
iPTH levels				
<150	Ref	-	Ref	-
150–300	0.01 [0.00, 0.49]	0.02	0.52 [0.08, 3.59]	0.5
300–600	0.16 [0.01, 3.49]	0.2	0.20 [0.03, 1.51]	0.1
>600	0.34 [0.01, 19.77]	0.6	0.25 [0.02, 3.48]	0.3
SBP (mmHg)	1.01 [1.00, 1.02]	0.09	1.00 [0.99, 1.01]	0.9
DBP (mmHg)	0.99 [0.97, 1.01]	0.2	1.00 [0.99, 1.02]	0.8
Chronic heart disease	2.03 [1.20, 3.42]	0.008	2.35 [1.64, 3.37]	< 0.001
Diabetes	1.12 [0.64, 1.96]	0.7	1.46 [1.00, 2.13]	0.05
Calcium agents	0.52 [0.29, 0.93]	0.03		
Vitamin D	0.42 [0.24, 0.74]	0.002	0.47 [0.32, 0.68]	< 0.001
Antiplatelet agents	1.71 [0.96, 3.04]	0.07	0.90 [0.62, 1.30]	0.6
Interaction term				
Age: iPTH < 150	Ref	-	Ref	-
Age: iPTH 150–300	1.07 [1.01, 1.14]	0.03	1.01 [0.98, 1.05]	0.5
Age: iPTH 300–600	1.02 [0.97, 1.08]	0.4	1.02 [0.99, 1.06]	0.2

HR: hazard ratio; CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure; Covariables with a p value less than 0.1 in univariate Cox regressions were selected to build the multivariate Cox regression models. Model 1: multivariate model for stroke; Model 2: multivariate model for composite endpoints.

Variables	Model 1		Model 2	
	HR [95% CI]	p value	HR [95% CI]	p value
Age: iPTH > 600	1.03 [0.95, 1.10]	0.5	1.04 [0.99, 1.09]	0.1

HR: hazard ratio; CI: confidence interval; SBP: systolic blood pressure; DBP: diastolic blood pressure; Covariables with a p value less than 0.1 in univariate Cox regressions were selected to build the multivariate Cox regression models. Model 1: multivariate model for stroke; Model 2: multivariate model for composite endpoints.

The difference in iPTH levels during follow-up between the stroke and nonstroke groups

Compared to the nonstroke group, the median values of the original, log-transformed and time-averaged iPTH levels during follow-up decreased significantly in the stroke group (p value = 0.001, < 0.001 and 0.001, respectively). Furthermore, the median absolute difference in serum iPTH levels also decreased significantly in the stroke group (52.9 [34.4, 93.2] vs 66.2 [41.7, 106.5], p value = 0.03), which indicates that serum iPTH was significantly reduced in the stroke group compared with that in the nonstroke group during follow-up (Supplemental Table 1).

The nonlinear regression curves displayed markedly different trends in iPTH levels during follow-up in the stroke group and the nonstroke group; the iPTH levels gradually decreased in the stroke group but increased in the nonstroke group as the number of dialysis months increased (Fig. 3).

Subgroup analysis for vitamin D supplementation

Our multivariate Cox regression analysis indicated that the receiving vitamin D supplementation during follow-up was an independent protective factor both for stroke and the composite endpoints (model 1: HR, 0.42, 95% CI 0.24–0.74, p value = 0.002; model 2: HR, 0.47, 95% CI 0.32–0.68, p value < 0.001; Table 3). To further investigate the effects of vitamin D supplementation among different populations of CAPD patients, a subgroup analysis was performed. Regardless of the levels of serum calcium or phosphate, vitamin D supplementation was a significant protective factor for stroke. Interestingly, vitamin D supplementation was an independent predictive factor for stroke in male patients and older patients (HR 0.38, 95% CI 0.2–0.72, and HR 0.24, 95% CI 0.1–0.58, respectively). Additionally, vitamin D supplementation may decrease the risk of stroke in patients with serum iPTH levels lower than 600 pg/ml (Supplemental Fig. 4).

Discussion

As studies have revealed, stroke is a serious complication associated with high rates of hospitalization, transfer to hemodialysis, and death (3, 23). The median incidence of stroke was 18.9 per 1000 person-years in our cohort, which is markedly increased compared to the incidence among the general population of China (3.5 per 1000 person-years) (24), and a significantly increased proportion of composite endpoints among patients with stroke during follow-up. Furthermore, we noticed an interesting

phenomenon in our cohort in which patients at the time of initiation and 5 years and 10 years after CAPD had a higher incidence of stroke. After these peaks, the incidence of stroke decreased gradually. Murray et al. found a peak incidence of stroke 1 to 2 months before and after initiation of hemodialysis or peritoneal dialysis, and the incidence of stroke decreased gradually during follow-up (25). However, to our knowledge, the other two peaks over the CAPD period have not been described in previous studies. Based on our clinical practice, we presumed that these peaks may be attributed to the loss of residual renal function five years after CAPD and the gradually decreased peritoneal function at ten years.

Hyperparathyroidism is a common complication in patients with CAPD, and a modest increase in iPTH may represent an appropriate adaptive response to declining kidney function (26). The target range of PTH levels for dialysis patients was suggested by the Kidney Disease Outcome Quality Initiative (K/DOQI) guidelines and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines based on studies of bone and mineral disorders in CKD patients (26, 27). Our study demonstrated that the relationship between baseline iPTH levels and the risk of stroke appeared to be J-shaped, indicating that low or markedly elevated baseline iPTH levels are associated with an increased risk of stroke. Furthermore, iPTH levels were significantly lower in the stroke group than in the nonstroke group, and a notable inverse trend of iPTH levels between stroke and nonstroke patients was observed during follow-up. Previous studies have demonstrated that lower iPTH levels are significantly associated with vascular calcification, cardiovascular disease and mortality in dialysis patients (17, 18, 28, 29). However, whether the decreased iPTH level is a cause or just a phenomenon associated with stroke in CAPD patients is still unclear.

Our study indicated a significant interaction effect between age and baseline iPTH levels for stroke. Importantly, distinct from age, baseline iPTH levels are still a significant risk factor for stroke after adjusting for the interaction term and other confounders in the multivariate Cox regression model. Although age is a significant predictor of stroke (23, 30), the interaction effect of age and PTH cannot be ignored, and PTH may play a more important role in stroke in CAPD patients.

Vitamin D supplementation is widely used to treat vitamin D deficiency or insufficiency, secondary hyperparathyroidism, and hypocalcemia in CAPD patients. However, treatment with vitamin D agents in dialysis patients is still controversial. In our study, regardless of any strategies of vitamin D supplementation during follow-up, vitamin D supplementation was an independent predictive factor for stroke in our CAPD patients, and the predictive effects were more significant in male and younger patients and even in patients with lower iPTH levels. Studies have demonstrated that vitamin D supplementation can downregulate the activity of the RAAS, decrease inflammation, and improve endothelial function, and its deficiency is significantly associated with stroke (11). However, the benefit of vitamin D supplementation for cardiovascular disease has not been demonstrated (31). Thus, individualized treatment with vitamin D supplements may be more important for CAPD patients due to the complex dynamic equilibrium of the calcium-parathyroid hormone-vitamin D axis.

However, our results should be interpreted cautiously. First, a key limitation is that the study cohort was from a single Chinese center; thus, the findings may not be suitable for generalizing to other populations

and should be validated in different centers. Second, due to the retrospective study design, a high proportion of patients withdrew from the study. Third, approximately 3% of included patients died of unknown causes at home, and some of the deaths could have been attributed to stroke but were not counted in the stroke group, which may lead to an underestimation of the incidence of stroke.

Conclusions

CAPD patients suffered a high risk of stroke, especially at the initiation and five years and ten years after CAPD. Lower iPTH levels were significantly associated with an increased risk of stroke, especially the baseline iPTH level, which was an independent risk factor for stroke that was stronger than age. Vitamin D supplementation was an independent predictive factor for stroke in our cohort; however, individualized therapy may be important for CAPD patients.

Declarations

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Authors' contributions

Research idea and study design: XHY, YZ, RRS, and JZ; data acquisition: JNZ, QXZ, and YLS; data analysis/interpretation: XHY, YZ and JZ; statistical analysis: JZ; and supervision or mentorship: ZS, CSC, and RRS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Availability of data and materials

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

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of the First Affiliate Hospital of Wenzhou University before the collection of any data,Approval number: 2018 (093).Verbal informed

consent was obtained from all subjects before the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no relevant competing interests.

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Figures

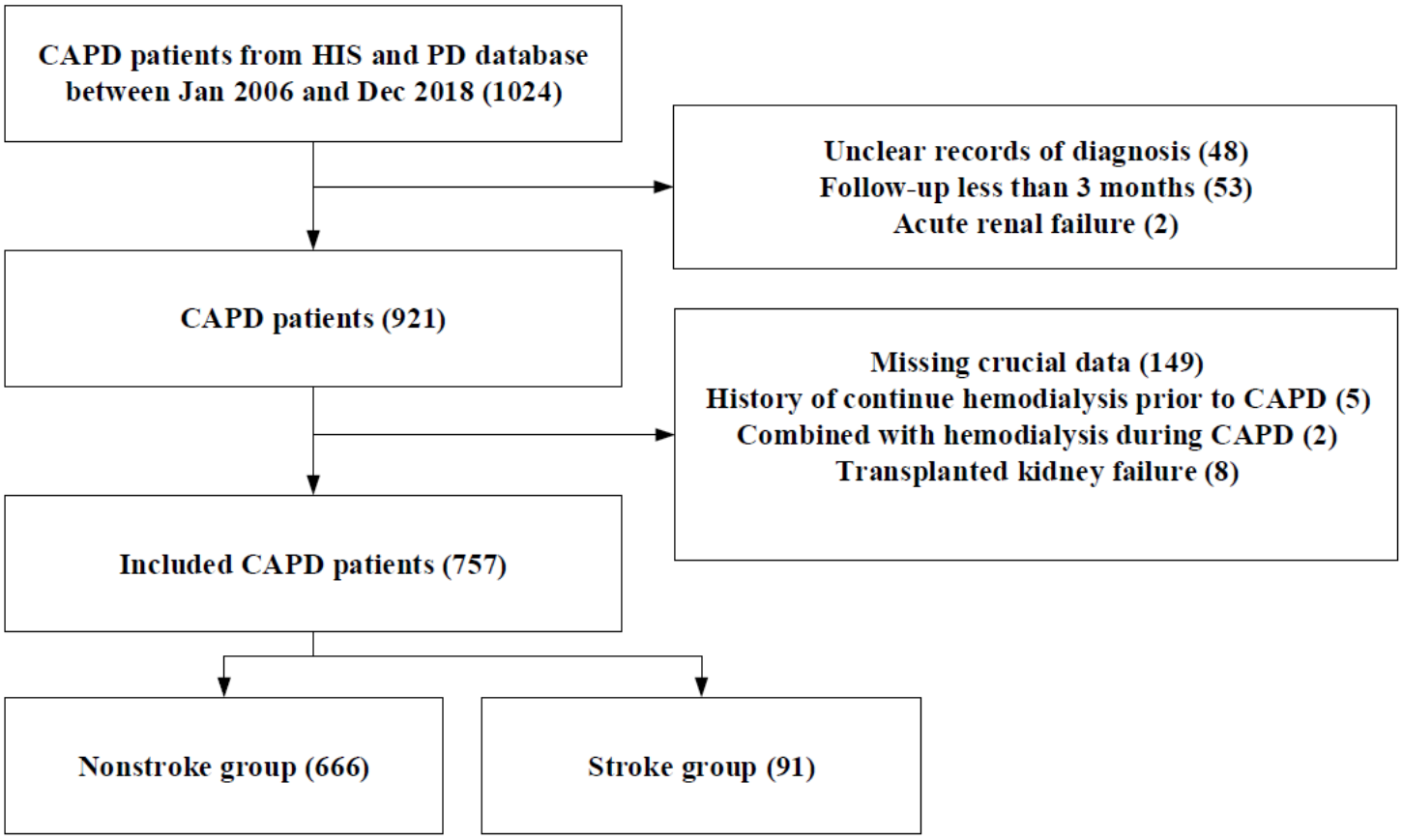

Figure 1

Flow chart of the patient inclusion process. Abbreviations: CAPD, continuous ambulatory peritoneal dialysis.

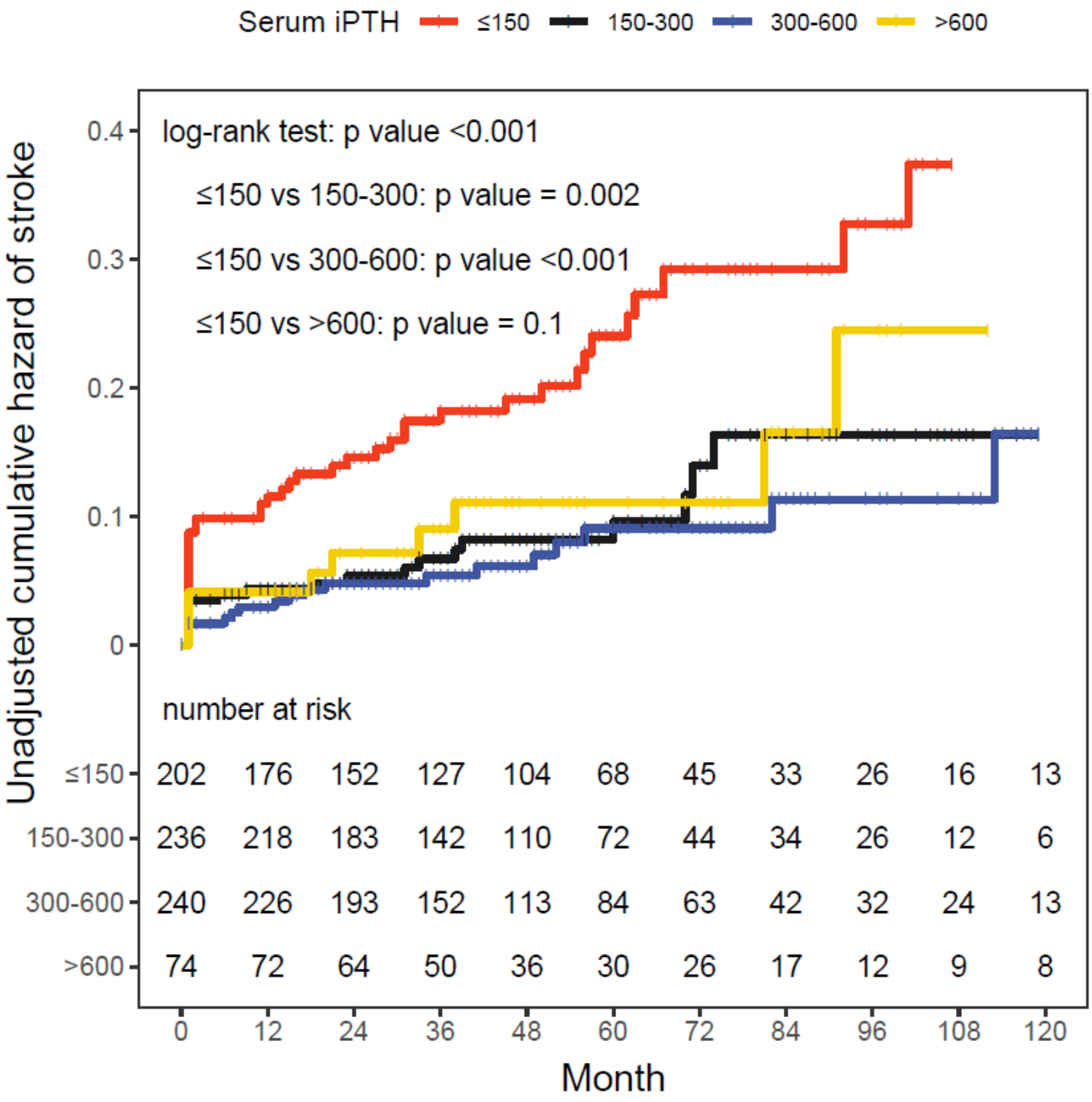

Figure 2

Kaplan-Meier analysis of stroke hazard by different levels of serum iPTH. Serum iPTH was separated into four groups: <150, 150-300, 300-600, and >600 pg/ml.

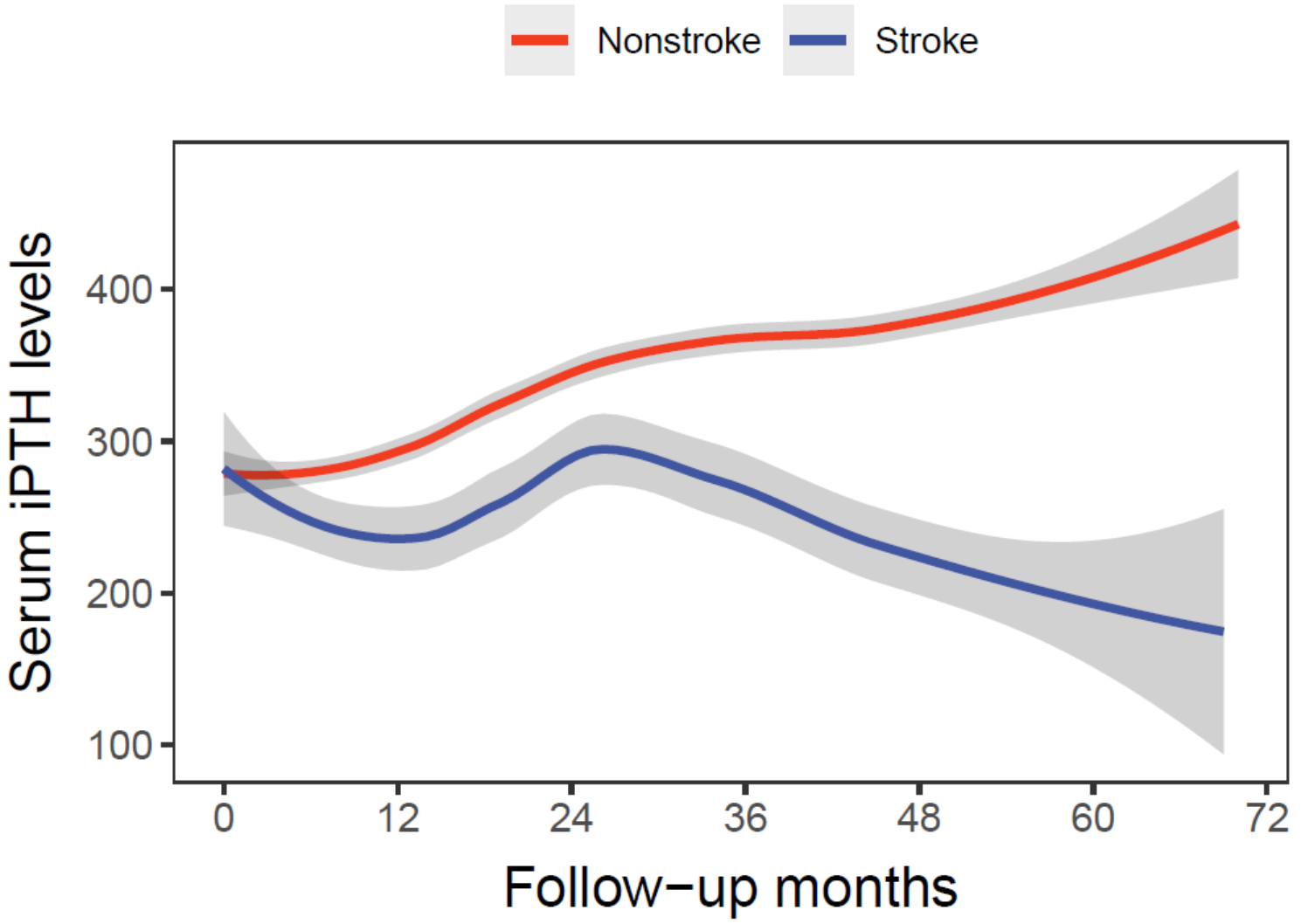

Figure 3

The difference in serum iPTH levels during follow-up between the stroke and nonstroke groups. The curves were fitted using the local polynomial regression, and the gray region denotes the 95% confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure2distributionandCoxipth.pdf
- SupplementaryFigure3interactionAgeiPTH.pdf
- SupplementaryFigure4strokeforest.pdf
- SupplementaryFigure1ggplotstrokerate.pdf
- SupplementalTable1.pdf