Int J Clin Exp Med 2017;10(7):10333-10341
www.ijcem.com /ISSN:1940-5901/IJCEM0054740

Original Article

Parathyroidectomy improves overall survival in hemodialysis patients with severe secondary hyperparathyroidism: a two-year's follow-up result

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Received April 6, 2017; Accepted May 25, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: The aim of this study was to investigate the effect of parathyroidectomy (PTX) on 2-year survival and other clinical variables in hemodialysis patients with severe secondary hyperparathyroidism (sHPT), and to explore the factors influencing overall survival. A total of 363 hemodialysis patients with severe sHPT was recruited in this prospective cohort study. According to whether PTX were performed, the participants were divided into two groups: PTX group and non-PTX group. Serum sample were collected at baseline and fibroblast growth factor 23 (FGF-23) expression was measured by enzyme-linked immunosorbent assay (ELISA). All participants were followed up for 24 months. 2-year survival rate in PTX group (84.4%) was increased compared with non-PTX group (52.8%) ($P < 0.001$). And Kaplan-Meier curves analysis illuminated PTX group displayed a longer overall survival ($P < 0.001$). Change of serum FGF-23, intact parathyroid hormone (iPTH) and calcium (Ca) from M0 to M24 were greatly elevated In PTX group compared with those in non-PTX group (all $P < 0.001$). Besides, baseline high FGF-23 expression was associated with worse overall survival compared to low expression ($P < 0.001$). In addition, univariate and multivariate Cox's proportional hazards regression analysis showed that PTX was an independent protective factor for overall survival ($P < 0.001$), while high FGF-23 expression, high CRP, hypertension and cardiac disease were independent risk factor for overall survival ($P < 0.001$, $P < 0.001$, $P = 0.010$ and $P = 0.005$, respectively). This study indicated PTX could dramatically improve overall survival independently in hemodialysis patients with severe sHPT, and high FGF-23 expression could be served as a biomarker for poor prognosis.

Keywords: Parathyroidectomy, severe secondary hyperparathyroidism, hemodialysis, FGF-23

Introduction

In spite of great improvement in hemodialysis treatment, patients with end-stage renal disease (ESRD) still displays unsatisfied high mortality rate worldwide [1]. Secondary hyperparathyroidism (sHPT), as one of the most critical complications in ESRD patients, correlates with disturbances in mineral and bone metabolism as well as parathyroid hormone (PTH), which results in cardiovascular events and death [2, 3].

Conventional therapy of sHPT includes phosphate binders and vitamin D receptor activators (VDRAs) [4, 5]. But these medications may not manifested sufficient control of sHPT, especially in patients with severe sHPT which defined as intact PTH (iPTH) value persistently exceeding 800 pg/mL or complicated with hypercalcemia or hyperphosphatemia refractory to medical therapy according to The Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines [6].

Parathyroidectomy (PTX), as an established and satisfied concept in the treatment of sHPT, could tremendously reduce iPTH levels and simultaneously inhibit extraosseous calcification stress by lowering serum calcium (Ca), phosphorus (P) and fibroblast growth factor 23 (FGF-23), and improve patients' survival and cardiovascular outcomes [7, 8]. However, few studies have been reported about the effect of PTX on survival in severe sHPT patients of Chinese population.

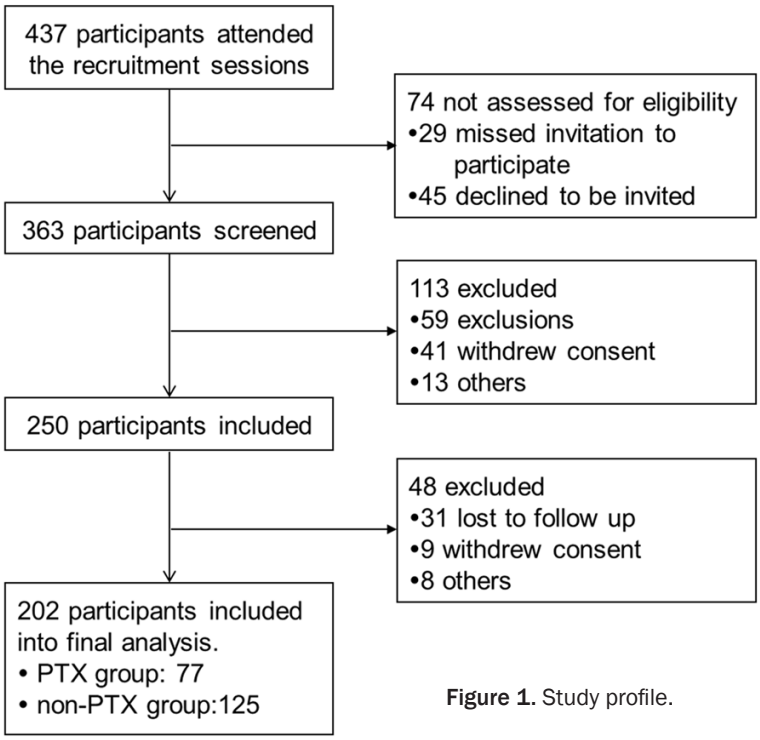

Figure 1. Study profile.

The aim of this study was to investigate the effect of PTX on 2-year survival and other clinical variables in hemodialysis patients with severe sHPT, and to explore the factors influencing overall survival.

Materials and methods

Participants

Totally, 363 hemodialysis patients with severe sHPT were recruited in this prospective cohort study during the period between Jan. 2013 and Apr. 2014 in Cangzhou People's Hospital.

The eligibility criteria were: 1) Age between 18 and 75 years. 2) CKD stage 5, and duration of hemodialysis was no less than 12 months. 3) iPTH level persistently over 800 pg/mL or complicated with hypercalcemia and hyperphosphatemia (hypercalcemia was defined as serum Ca > 2.54 mmol/L, and hyperphosphatemia as serum P > 1.78 mmol/L). The exclusive criteria were: 1) Previous kidney transplantation. 2) History of PTCA or bypass surgery. 3) History of malignant tumor. 4) Serious infection. 5) Malignant hypertension. 6) Pregnancy or lactation. 7) Cognitive impairment, or poor adherence and could not understand the study protocol.

All participants provided the written informed consents. This study was approved by the Ethics Committee of the Cangzhou People's Hospital.

Treatments and follow-up

This study did not intervene in the therapy of all participants, the treatments were decided based on clinical needs and patients' condition as well as willing. According to whether PTX were performed, the participants were divided into two groups: PTX group and non-PTX group.

PTX group patients were followed at month 0 (M0) (in the preoperative hours), M1, M2, M3, M6, M12, M18 and M24. And non-PTX group patients were also followed at baseline (M0), M1, M2, M3, M6, M12, M18 and M24.

Endpoints

The primary endpoint was: 2-year overall survival rate in two groups. The secondary endpoints were: Change of serum iPTH, Ca, P, FGF-23 at M24 from baseline (M0).

Samples and ELISA assay

Serum samples were collected from all participants at M0, M1, M6, M12 and M24. FGF23 expression level was measure by enzyme-linked immunosorbent assay (ELISA) with commercial Human ELISA Kits (No. DY2604-05, R&D systems, Bio-Techne China Co.,Ltd.) according to the instructions of manufacturers.

Statistics

Statistical analysis was performed using the SSPS 21.0 program. Data were mainly presented as mean ± standard deviation (SD), median and (25^{th}-75^{th}) and count (percentage). Difference between two groups was compared by

Table 1. Demographic, clinical and biological characteristics of hemodialysis patients with severe sHPT at Baseline

Parameters	PTX group (n = 77)	non-PTX group (n = 125)	*P* Value
Age (years)	59 ± 13	56 ± 14	0.131
Gender-Male (%)	39 (51%)	87 (70%)	0.088
BMI (kg/m^2)	23.4 ± 7.6	21.9 ± 7.8	0.179
Duration of dialysis (months)	42 (31-68)	36 (28-59)	0.047
Kt/V	1.7 ± 0.5	1.6 ± 0.5	0.169
Ultrafiltration rate (ml/min)	7.4±1.9	6.8 ± 2.0	0.034
iPTH (pg/mL)	1509 ± 490	1111 ± 315	< 0.001
Ca (mmol/L)	3.11 ± 0.94	2.74 ± 0.82	0.004
P (mmol/L)	2.40±0.38	2.31 ± 0.41	0.121
FGF-23 (pg/mL)	635 ± 181	589 ± 190	0.093
Albumin (mg/L)	36.8 ± 6.3	38.1 ± 5.9	0.140
Blood urea nitrogen (mmol/L)	25.9 ± 6.2	26.5 ± 5.9	0.492
Serum creatinie (mmol/L)	962.6 ± 219.4	995.1 ± 208.8	0.294
Serum uric acid (mmol/L)	516 ± 104	485 ± 96	0.032
ALP (U/L)	385.1 ± 109.7	286.9 ± 96.3	< 0.001
Hb (g/dL)	11.9 ± 2.7	11.6 ± 2.8	0.454
CRP (mg/L)	11.6 (6.2-19.4)	10.1 (3.2-16.6)	0.352
Complications			
Hypertension	45 (58%)	71 (57%)	0.819
Diabetes mellitus	14 (18%)	20 (16%)	0.114
Hyperuricemia	32 (42%)	35 (28%)	0.047
Cardiac disease	3 (4%)	6 (5%)	0.762
Cerebrovascular disease	2 (3%)	1 (2%)	0.305

Data were presented as Mean values ± SD, median and 25th-75th or count (percentages). A *P* Value < 0.05 was considered statistically significant. Significance of the comparison was determined by Student t test, Wilcoxon rank sum test or Chi-square test. BMI, body mass index; iPTH, intact parathyroid hormone; Ca, calcium; P, phosphorus; FGF-23, fibroblast growth factor 23; ALP, alkaline phosphatase; Hb, hemoglobin; CRP, C-reactive protein.

Student *t* test, Wilcoxon rank sum test or Chi-square test; Difference between each visit and baseline was compared by paired t test. Kaplan-Meier curve and Log-rank test were established to analyze OS in different groups. The influence of each factor on OS was measured by univariate Cox's proportional hazards regression, while all factors with a *P* value < 0.1 were further analyzed by multivariate Cox's proportional hazards regression. A *P* value < 0.05 was considered significant.

Results

Characteristics

Four hundred and thirty-seven participants were invited to attend the recruitment session, while 363 were screened for eligibility. And 250 participants met the criteria were enrolled in this cohort study, among which 31 cases lost to follow up, 9 cases withdrew informed consents, and 8 cases excluded for other reasons, so 202 cases were included into the final analysis, as presented in **Figure 1**. On the basis of whether PTX were performed, patients were divided into two groups: PTX group (n = 77) and non PTX group (n = 125).

Patients in PTX group exhibited a longer duration of dialysis (P = 0.047), evaluated ultrafiltration rate (P = 0.034), increased iPTH (P < 0.001), Ca (P = 0.004), serum uric acid (P = 0.032) and ALP (P < 0.001) compared to non-PTX group (**Table 1**). Other detailed demographic, clinical and biological characteristics of hemodialysis patients with severe sHPT at Baseline were presented in **Table 1**.

Primary endpoint

2-year survival rate in PTX group (84.4%) was increased compared with that in non-PTX group (52.8%, P < 0.001; **Figure 2A**). So as to 1-year survival rate, PTX group (93.5%) was also higher than non-PTX group (75.2%, P = 0.001). Besides, Kaplan-Meier curves analysis illuminated PTX group had a longer overall survival than non-PTX group with P < 0.001 (**Figure 2B**).

Secondary endpoints

Serum FGF-23, iPTH, Ca and P level in PTX group were all decreased at M24 compared to baseline (M0) (P < 0.001, **Figure 3**). While in non-PTX group, serum Ca and P level were declined at M24 than baseline (M0) (both P < 0.001), but no difference were found in FGF-23 and iPTH level (P = 0.065 and P = 0.268, respectively).

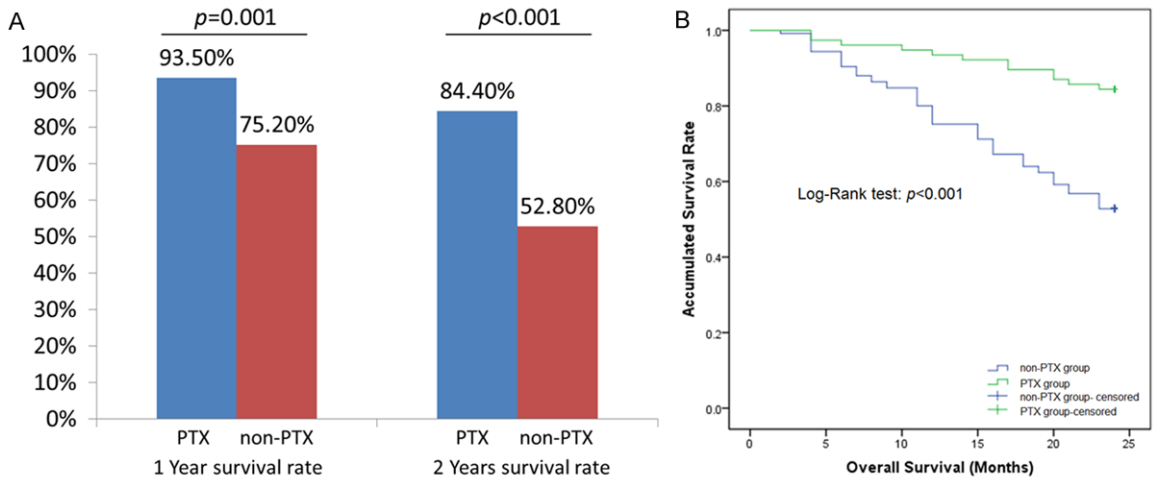

Figure 2. Survival analysis of patients in PTX and non-PTX group. A. One year and two years survival rate in two groups; B. K-M curve of PTX and non-PTX for overall survival.

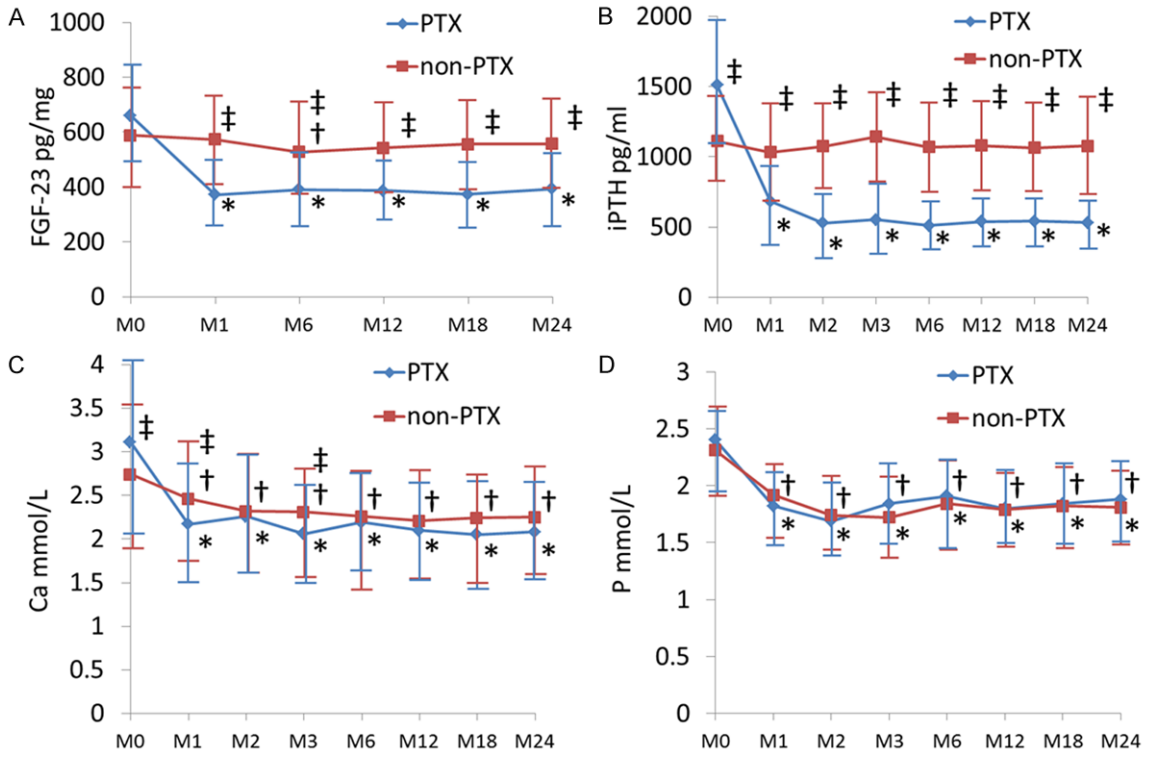

Figure 3. Serum FGF-23, iPTH, Ca and P level in PTX and non-PTX group at each visit. A. FGF-23; B. iPTH; C. Ca; D. P. *P < 0.05, comparison between each visit to baseline (M0) in PTX group. †P < 0.05, comparison between each visit to baseline (M0) in non-PTX group. ‡P < 0.05, comparison at each visit between PTX and non-PTX groups.

Change of serum FGF-23, iPTH and Ca from M0 to M24 in PTX group was greatly elevated compared with that in the non-PTX group, (P < 0.001; **Figure 4A** and **4C**). However, no difference was exhibited in change of P level from M0 to M24 between groups (P = 0.599; **Figure 4D**).

Serum FGF-23 on overall survival

Further analysis has been carried out to investigate the effect of serum FGF-23 level on prognosis of participants whether PTX was performed or not performed, and patients were divided into two groups by cut off as median

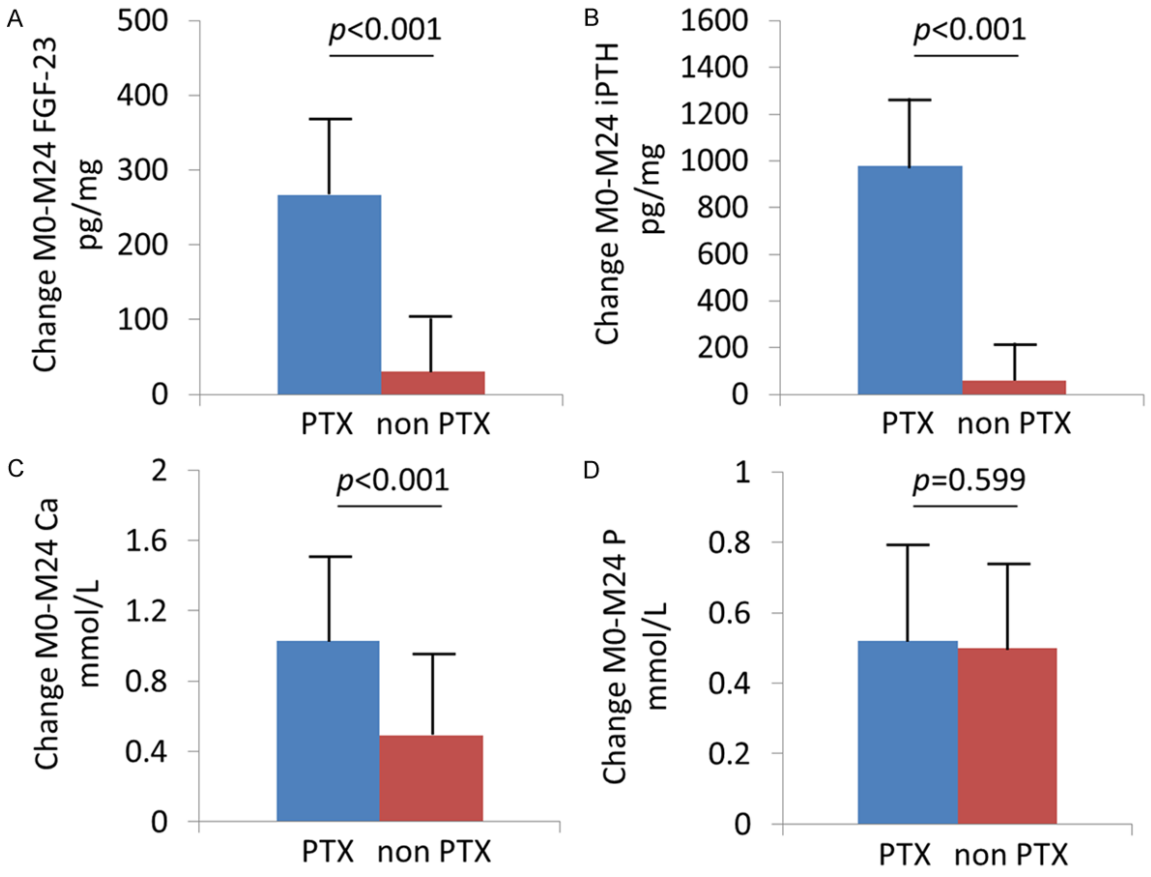

Figure 4. Change of serum FGF-23, iPTH and Ca from M0 to M24 in PTX group and non-PTX group. A. FGF-23; B. iPTH; C. Ca; D. P.

value of FGF-23. As presented in **Figure 5** by K-M curve analysis, patients with high serum FGF-23 expression showed a shorter overall survival compared with those with low serum FGF-23 expression (P < 0.001, **Figure 5A**). As to PTX group and non-PTX group, we found in non-PTX group, patients with high FGF-23 expression also disclosed worse overall survival than those with low FGF-23 expression (P < 0.001, **Figure 5B**), but no difference was observed in PTX group (P = 0.054, **Figure 5C**).

Overall survival analysis

Factors at baseline as quantitative value were divided into two groups by their median value, and univariate Cox's proportional hazards regression was performed to evaluate factors at baseline (M0), which influence overall survival in hemodialysis patients with severe sHPT. As shown in **Table 2**, patients in PTX group illustrated a lower mortality risk than those in non-PTX group (P < 0.001), while patients with high FGF-23 expression, high CRP and hypertension showed a higher mortality risk (P < 0.001, P = 0.001 and P = 0.010, respectively).

All factors with *P*-value ≤ 0.1 were further analyzed by multivariate Cox's proportional hazards regression, as presented in **Table 2**, PTX was an independent protecting factor for overall survival compare to non-PTX (P < 0.001), while high FGF-23 expression, high CRP, hypertension and cardiac disease were independent risk factor for overall survival (P < 0.001, P < 0.001, P = 0.010 and P = 0.005, respectively).

Discussion

This study observed: (1) hemodialysis patients with severe sHPT receiving PTX illuminated decreased mortality in two years compared to patients not receiving PTX, and PTX was an independent factor for longer overall survival. (2) PTX dramatically decreased serum FGF-23, iPTH and Ca compared to non-PTX (3) high

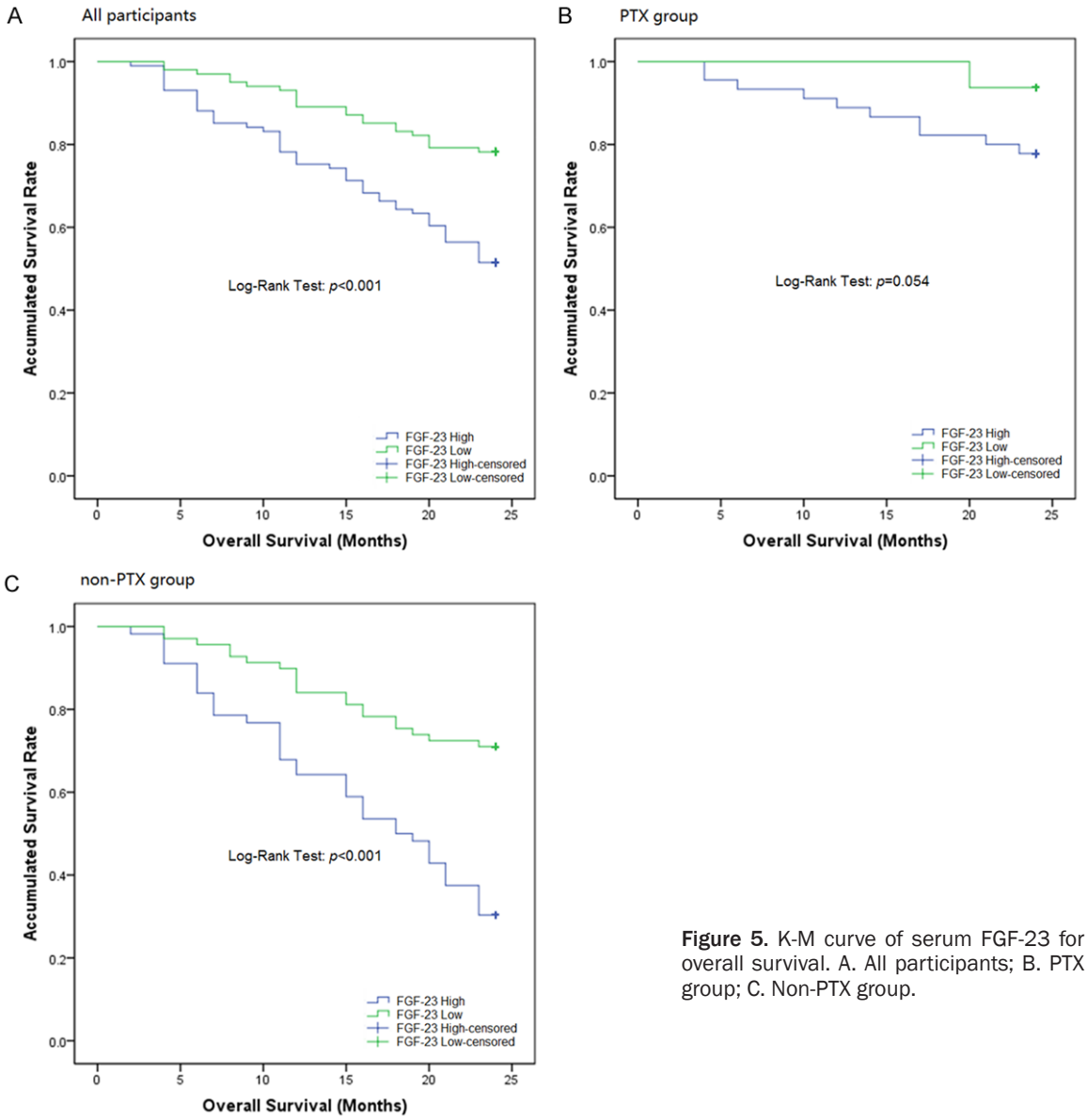

Figure 5. K-M curve of serum FGF-23 for overall survival. A. All participants; B. PTX group; C. Non-PTX group.

serum FGF-23 expression was found to be associated with increased mortality independently, especially in patients not receiving PTX.

sHPT, as an adaptive (in many cases ultimately maladaptive) process that develops in response to declining kidney function, is one of the most common complications of hemodialysis patients with chronic kidney disease (CKD) particularly with ESRD, which could led to the metabolic bone disease, severe cardiovascular events and significantly decreased life quality of hemodialysis patients as well as increasing death risk [9, 10]. Earlier medical therapy such as phosphate binders and VDRAs may mitigate the disease in some patients developing sHPT, but they still lack satisfactory effect on sHPT and correlated complications in a large proportion of patients, especially severe sHPT patients [5, 11]. For these, PTX surgery represents an effective way for definitive treatment [12].

Our previous study has demonstrated that PTX reduces one year mortality in patients of Chinese population with sHPT (iPTH > 300 pg/mL) independently [13]. A national wide registry study with large sample in Japan which includes 4428 PTX patients and 4428 matched non-PTX patients with sHPT, reports patients undergone PTX has a 34% lower risk for one year all-cause

Table 2. Univariate and multivariate Cox's proportional hazards regression analysis of the factors for overall survival in hemodialysis patients with severe sHPT

	Univariate Cox's				Multivariate Cox's			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
PTX (vs non-PTX)	< 0.001	0.269	0.145	0.502	< 0.001	0.206	0.109	0.388
FGF-23 (high vs low)	< 0.001	2.640	1.596	4.368	< 0.001	4.132	2.336	7.309
Age (old vs young)	0.613	1.128	0.707	1.798	-	-	-	-
Gender (male vs female)	0.187	0.729	0.456	1.165	-	-	-	-
BMI (high vs low)	0.660	1.110	0.697	1.768	-	-	-	-
Duration of dialysis (long vs short)	0.100	1.485	0.927	2.379	0.209	1.365	0.840	2.216
Kt/V (high vs low)	0.442	0.833	0.522	1.328	-	-	-	-
Ultrafiltration rate (high vs low)	0.309	0.785	0.492	1.252	-	-	-	-
iPTH (high vs low)	0.182	1.376	0.861	2.200	-	-	-	-
Ca (high vs low)	0.584	1.139	0.715	1.817	-	-	-	-
P (high vs low)	0.302	1.279	0.801	2.041	-	-	-	-
Blood urea nitrogen (high vs low)	0.144	0.704	0.440	1.128	-	-	-	-
Serum creatinie (high vs low)	0.090	1.495	0.939	2.382	0.150	1.420	0.881	2.290
Serum uric acid (high vs low)	0.214	1.346	0.842	2.152	-	-	-	-
ALP (high vs low)	0.730	1.085	0.681	1.729	-	-	-	-
Hb (high vs low)	0.242	0.756	0.474	1.207	-	-	-	-
CRP (high vs low)	0.001	2.310	1.412	3.780	< 0.001	2.568	1.565	4.212
Hypertension (Yes vs No)	0.010	1.932	1.168	3.197	0.010	1.983	1.176	3.343
Diabetes mellitus (Yes vs No)	0.388	1.285	0.727	2.273	-	-	-	-
Hyperuricemia (Yes vs No)	0.242	1.332	0.824	2.151	-	-	-	-
Cardiac disease (Yes vs No)	0.079	2.119	0.916	4.900	0.005	3.894	1.502	10.097
Cerebrovascular disease (Yes vs No)	0.269	2.212	0.541	9.039	-	-	-	-

Data were presented as *P* value, HR (hazard ratio) and 95% CI. A *P* Value < 0.05 was considered statistically significant. Significance was determined by univariate Cox's proportional hazards regression analysis, and all factors with a P < 0.1 were further analyzed by multivariate Cox's proportional hazards regression. BMI, body mass index; iPTH, intact parathyroid hormone; Ca, calcium; P, phosphorus; FGF-23, fibroblast growth factor 23; ALP, alkaline phosphatase; Hb, hemoglobin; CRP, C-reactive protein.

mortality and 41% lower risk for cardiovascular mortality [7]. As to severe sHPT, few studies on the effect of PTX are reported. Diana Moldovan, et al illustrated non-PTX increases 2.5 fold risk of overall survival compare to PTX in chronic hemodialysis patients with severe sHPT (defined as Ipth > 700 pg/mL) by a cohort study with two years follow up in Romania [14]. In accordance to the previous studies, our present study found hemodialysis patients with severe sHPT receiving PTX manifested a decreased mortality in two years compared to patients not receiving PTX, and PTX decreased 73% lower risk for shorter overall survival by multivariate Cox analysis. This mainly results from the effect of PTX on reducing iPTH and inhibiting xtraosseous calcification stress by down regulation of serum Ca, P and FGF-23 levels as also presented in this present study [14, 15]. Besides, the influence of PTX on increasing erythropoietin response to anemia treatment, improvement of cardiac function as well as left ventricular hypertrophy, remittance of skin itching, decreasing facture risk, improving of hypertension, immune system and so on may contributes to the lower mortality likewise [16-19].

FGF-23, as a member of peptide hormones into fiber growth factor, decreases 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$) synthesis in kidney which contributes to the secondary hyperparathyroidism of CKD, and regulates serum mineral homeostasis and derives from bone [20, 21]. Several studies have disclosed serum FGF-23 expression is elevated in CKD patients and correlates with iPTH level [22-24]. And increased

serum FGF-23 level could predict higher mortality among patients undergoing hemodialysis [25]. However, the role of FGF-23 expression in the prognosis of hemodialysis patients with severe sHPT was obscure. In this study, we found serum FGF-23 high expression was independently associated with a worse overall survival in all analyzed hemodialysis patients with severe sHPT, which may due to its effects on bone metabolism and iPTH expression [22, 26]. Furthermore, we observed only in non-PTX treated patients, FGF-23 was displayed as a prognostic biomarker for overall survival, but not in PTX treated patients. This might because: 1. PTX decreases FGF-23 greatly which reduces long term influence of FGF-23 high expression on prognosis. 2. Comparatively small sample in PTX group (only 12 deaths out of 77 cases within 2 years in PTX treated group).

There were some limitations in this study: firstly, although we had set a strict inclusion and exclusive criteria to reduce the bias, unmeasured confounders or potential sources of bias might exist which influence the outcomes of PTX, such as the possibility that patients with less healthy condition who could not tolerate surgery were more likely to be included into non-PTX group. Secondly, drug treatments were not analyzed in this study due to data missing which may have some impact on the outcomes. However, Patients included in this study exhibited more similar characteristics, and drug used for ESRD are usually the same. This factor might not affect much on overall results.

In conclusion, our study indicated PTX could dramatically improve overall survival independently in hemodialysis patients with severe sHPT, and high FGF-23 expression could be served as a biomarker for poor prognosis.

Disclosure of conflict of interest

None.

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