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Interaction between parathyroid hormone and the Charlson comorbidity index on survival of incident haemodialysis patients

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Abstract

Background. Haemodialysis patients are ageing and have with a high rate of comorbidities. The impact of this novel clinical setting on intact parathyroid hormone (iPTH) is not well established.

Methods. For this observational, prospective multicentre cohort study, incident haemodialysis patients were recruited in 40 Italian centres and followed up for a mean period of 18 ± 6.7 months. Clinical characteristics and biochemistry were recorded at baseline. Comorbid conditions were scored by the Charlson comorbidity index (CCI).

Results. Data of 411 patients (mean age: 66.5 ± 14.8 years; 17.3% >80 years old) were recorded. The mean CCI was 4.17 ± 2.8. In patients with CCI >0, an inverse correlation was observed between CCI (excluding age) and iPTH ($P = 0.00002$). Independently of CCI, patients with iPTH <150 pg/ml had 76% as high as the risk

of all-cause mortality. After multivariable adjustment, the combination of the first tertile of iPTH with second and third tertiles of CCI was significantly associated with all-cause mortality (RR = 3.83, $P = 0.02$; RR = 3.79, $P = 0.01$, respectively).

Conclusions. Incident haemodialysis patients suffer from a high rate of clinical complications. In these patients, low iPTH and high CCI are often associated and very likely responsible for an adverse outcome.

Keywords: Charlson index; elderly; incident ESRD patients; intact parathyroid hormone; survival

Introduction

In most western countries, the median age of patients starting renal replacement therapy (RRT) has increased over the last decade with a concomitant rise in comorbidities and with diabetes as the leading cause of renal failure [1–5]. Other frequent comorbidities are cancer (11%), coronary, cerebral and/or peripheral vascular disease (61%) [6].

Comorbidities in ageing patients represent an emerging problem for nephrologists, and these make the management of patients in RRT even more difficult despite the progress in dialysis techniques [6,7]. Therefore, greater attention and specific research probably should be devoted to the above-mentioned comorbidities, going beyond the traditional role as a statistical adjustment tool in survival studies on patients with chronic kidney disease (CKD). For instance, the impact of comorbidities on some CKD complications such as the CKD-mineral bone disorder is unknown.

Comorbidities can be assessed in several ways. In the general population, the Charlson comorbidity index (CCI) is commonly used. In its original structure as well as in ensuing adaptations, the CCI is considered as a valid and easy to use method for assessing comorbidities and predicting survival also in incident patients with end-stage renal disease (ESRD) [8–12].

The present study aimed at investigating the relationship between comorbidities and intact parathyroid hormone as well as the impact of their interaction on survival in a cohort of incident haemodialysis patients.

Subjects and methods

The present observational cohort study was performed in 411 incident haemodialysis patients who started treatment between 13 January 2005 and 4 September 2007. Data were collected from 40 Italian renal units.

The study has been exclusively managed by nephrologists belonging to the 'Mineral Metabolism and Trace Elements study group' of the Italian Society of Nephrology. The study was completely independent and did not receive support from any pharmaceutical or medical company.

The STROBE recommendations for observational studies (http://www.strobe-statement.org) were taken into account.

Inclusion criteria

Consecutive patients (age >21 years) who started RRT in each participating centre during the 1-year enrolment period were allowed to enter the study. A further inclusion criterion was adequacy of dialysis dose according to K/DOQI guidelines (spKt/V >1.2, assessed using pre-dialysis and post-dialysis blood urea nitrogen sampling). Exclusion criteria were as follows: previous kidney transplant, switch from peritoneal dialysis and spKt/V ≤1.2 in two consecutive monthly measurements. During the 1-year enrolment period, 500 patients started RRT. The median number of patients for each centre was 9 (range 2–59). From the initial cohort, 15 patients did not fit inclusion criteria and 24 did not have complete data. Patients on peritoneal dialysis ($n = 38$) and those on haemodialysis on calcium in dialysate different from 1.50 mmol/l ($n = 12$) were excluded. Thus, 411 patients were recruited.

Data collection

Baseline data were as follows: patient identifying code, birth date, gender, underlying kidney disease, dialysis start date, duration of pre-dialysis follow-up, smoking habit, co-morbid conditions, ability to walk without assistance, systolic and diastolic blood pressure, anti-hypertensive drugs, treatment and dosages of vitamin D receptor activators (VDRA), calcimimetic and phosphate-binding drugs. In addition, the following laboratory data were recorded: serum calcium, phosphate, albumin and haemoglobin (determined within 1 month from the beginning of dialysis), concentration of serum intact parathyroid hormone (iPTH) (assayed within the first 2 months of dialysis using second generation methods) and C-reactive protein (C-rp) (assayed within the first 3 months of dialysis). The blood samples were collected using uniform techniques before the start of the first dialysis session of the week and were sent to the laboratory within 2 h, with the iPTH sample on ice. Serum total calcium was corrected for albuminaemia according to the formula: albumin − corrected calcium = measured calcium + (4.0 − serum albumin in g/dl) × 0.8) [13].

Patients with a positive history of hyperglycaemia and/or on chronic treatment with insulin or anti-diabetic drugs were regarded as diabetic. In accordance with the JNC-7 guidelines, hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg [14]. Patients with systolic pressure ≤90 mmHg were arbitrarily recorded as hypotensive. Patients with a pre-dialysis follow-up <4 months were labelled as 'late referrals' to the nephrology service [15].

The presence and degree of comorbid conditions were assessed using the CCI at the beginning of dialysis [8]. The CCI includes age (weight 1 for every 10 years starting from 40 years of age) and contains 17 categories of comorbidities including congestive heart failure (weight 1), myocardial infarction (weight 1), chronic pulmonary disease (weight 1), cerebrovascular disease (weight 1), haemiplegia or paraplegia (weight 2), dementia (weight 1), diabetes (weight 1), diabetes with complication (weight 2), malignancy (weight 2), metastatic solid tumour (weight 6), mild liver disease (weight 1), moderate or severe liver disease (weight 3), peptic ulcer disease (weight 1), peripheral vascular disease (weight 1), rheumatologic disease (weight 1), renal disease (weight 2) and AIDS (weight 6). In this study, the CCI score for the presence of kidney disease was not taken into account being all patients were on RRT.

The following cardiovascular events were recorded: stroke or transient ischaemic attack, angina pectoris or acute myocardial infarction, congestive heart failure, haemodynamically significant tachyarrhythmias or bradyarrythmias, and dissecting aneurysm of the aorta.

Death due to one of the above events was recorded as death from cardiovascular causes. Other deaths were considered not due to cardiovascular causes.

The diagnosis of cardiovascular events was based on medical records obtained from participating centres and reviewed by the principal investigator of the study (L.F.M.).

Statistics

All data are presented as proportions of the patient population, mean ± standard deviation or median and range, as appropriate. Differences between groups were evaluated using the Kruskal–Wallis test, one-way ANOVA or χ^2 analysis, where necessary.

Due to the multicentre nature of the study, iPTH levels were assayed in different laboratories and with different commercial kits. Accordingly, we have applied a hierarchical multilevel regression approach that enabled us to take into account the centre and method effects. The multilevel model used included random intercepts and fixed slopes. The assumption is that the effects are fixed for centres and methods, whereas the mean effect of each hospital is allowed to vary [16]. A likelihood ratio (LR) test was used to evaluate the suitability of the single level versus multilevel regression approach. When the LR test was not applicable, the Wald test was used.

Table 1. Patient characteristics

Number of patients	411
Male/female ratio	1.66
Age over 65 years, *n* (%)	235 (57.2)
Age over 80 years, *n* (%)	71 (17.3)
Diabetes, *n* (%)	96 (23.4)
Arterial hypertension, *n* (%)	242 (58.9)
Late referral, *n* (%)	144 (35.0)
Autonomous walking impairment, *n* (%)	84 (20.4)
Aetiology of ESRD, *n* (%)	
Diabetic nephrophathy	88 (21)
Nephroangiosclerosis	82 (20)
Glomerulonephritis	45(11)
Interstitial nephritis	41 (10)
Vasculitis	8 (2)
Others and unknown	147 (36)
Comorbidities, *n* (%)	
CCI above 0	372 (91)
CCI above 1	343 (83)
Age (decades over 4th)	353 (86)
Diabetes with complications	96 (23)
Cardiovascular disease	53 (13)
Chronic pulmonary disease	38 (9)
Neurologic disease	21 (5)
Rheumatologic disease	19 (5)
Liver disease	19 (5)
Neoplasms	11 (3)
Peptic ulcer	7 (2)

The multilevel procedure was statistically able to exclude any confounding effect of centres and assay methods on iPTH variable, when it was included in a regression model together with the CCI regressor.

Spearman's regression analysis was used to evaluate the CCI values with respect to age and iPTH. Multiple regression models were applied to examine whether the CCI was related to the logarithm of iPTH, after adjustment for several covariates. Survival curves were derived with the Kaplan–Meier method using the log-rank test to evaluate the differences between the curves. The Cox procedure was used to model death as a function of serum iPTH levels alone or in combination with the CCI score, both expressed as tertiles. Therefore, the Cox model for all-cause survival was adjusted for age, gender, diabetes, arterial hypertension, late referral, vitamin D administration, circulating levels of haemoglobin, albumin, calcium and phosphate. Estimated relative risk (RR) and their 90% confidence limits were calculated using estimated regression coefficients and their standard errors. To evaluate potential interactions among age, iPTH and CCI, a multivariate regression model was built where dependent variable was all-cause mortality and independent variables were iPTH, age, CCI and their interaction terms. Interaction (product) terms were given by iPTH × CCI, iPTH × age and CCI × age. In this model, age was excluded from the CCI and analysis was restricted only to patients with comorbidities.

A two-sided P-value <0.05 was considered statistically significant.

Statistical procedures were performed using the statistical packages NCSS 2007, PASS 2005 (NCSS, Kaysville, UT, USA) and STATA 10 (Stata Corp., College Station, TX, USA).

Results

Study population

A total of 260 males and 151 females (mean age: 66.5 ± 14.8 years) were enrolled. The patient characteristics at the start of RRT are presented in Table 1. Most patients were elderly and had multiple co-morbidities. A few diabetic patients did not have diabetic nephropathy (2%), but a renal biopsy was performed only in 12% of all patients. Underlying kidney diseases and most frequent comorbidities are also reported in Table 1. Figure 1 shows the distribution of the CCI score in the whole cohort.

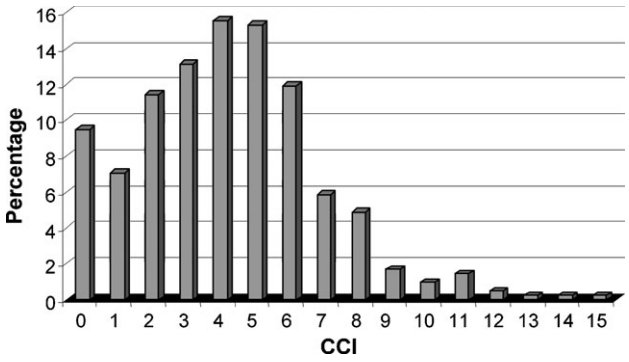

Fig. 1. Distribution of the CCI.

Baseline clinico-laboratory characteristics according to iPTH levels

Tables 2 and 3 show the clinico-laboratory characteristics of patients at the dialysis initiation according to iPTH. Patients with low-to-normal iPTH levels had a significantly higher rate of the CCI (excluding age) ($P = 0.01$) and diabetes ($P = 0.03$). Patients with low iPTH displayed the highest frequency of late referral ($P = 0.005$), high serum calcium ($P = 0.01$) and low serum phosphate ($P = 0.02$). Patients with iPTH >300 pg/ml had more frequently low serum calcium levels ($P = 0.001$), and they were more frequently treated with active forms of vitamin D ($P = 0.0003$). Among patients with iPTH > 300 pg/ml, 25% (9% of the entire cohort) had iPTH >600 pg/ml.

Correlation between iPTH levels and CCI

Non-significant correlation between iPTH and CCI was observed in the entire cohort. In contrast, the correlation became significant when data of patients without comorbidities were not taken into account (rho $= -0.12$, $P = 0.02$). Of note, the statistical significance increased (rho $= -0.25$, $P = 0.00001$) when age was excluded from the CCI. The inverse correlation persisted (rho $= -0.31$, $P = 0.001$) when analysis was repeated in the subgroup of patients with comorbidities but younger than 65 years old. Finally, the inverse correlation was confirmed in a multiple regression model adjusted for serum calcium and phosphate and active vitamin D administration; the highest correlation (beta $= -0.20$, $P = 0.0004$) was observed in patients with a CCI >0 when age was excluded from CCI calculation; the significance remained high (beta $= -0.16$, $P = 0.004$) when diabetes and serum albumin were added as adjustment covariates.

Survival analysis

The mean follow-up was of 18.8 ± 6.7 months. During the observational period, 77 out of 411 patients (18.8%) died: 31 (40.3%) and 46 (59.7%) because of cardiovascular events and other causes, respectively. Figure 2 shows the

Table 2. Characteristics of incident chronic haemodialysis patients subdivided according to circulating iPTH levels

	iPTH < 150 pg/ml	iPTH 150–300 pg/ml	iPTH > 300 pg/ml	*P*-value
Patients (%)	132 (32.1)	126 (30.7)	153 (37.2)	
Male gender (%)	62.9	69.0	58.8	N.S.
Age: median (range)	68.0 (22–90)	70.5 (23–92)	69.0 (21–96)	N.S
CCI: median (range)	4.0 (0–14)	5.0 (0–13)	4.0 (0–15)	N.S.
CCI excluding age: median (range)	2 (0–10)	2 (0–10)	1 (0–11)	0.01
Diabetic patients (%)	26.5	28.6	16.3	0.03
Hypertensive patients (%)	53.8	56.5	65.5	N.S.
Hypotensive patients (%)	0.8	0.9	1.4	N.S.
Late referred patients (%)	45.5	33.3	27.5	0.005
Cigarette smoking (%)	29.7	24.6	20.5	N.S.
Haemoglobin < 11 g/dl (%)	78.6	75.4	71.9	N.S.
C-rp = 3.11 mg/dl (%)	40.2	34.0	32.4	N.S.
Serum albumin = 3.2 g/dl (%)	34.4	22.4	23.9	N.S.
Corrected calcium > 9.5 mg/dl (%)	44.8	38.3	27.8	0.01
Corrected calcium < 8.4 mg/dl (%)	6.4	13.9	21.8	0.001
Phosphorus > 5.5 mg/dl (%)	32.1	42.9	43.8	N.S.
Phosphorus < 3.5 mg/dl (%)	17.6	7.9	9.2	0.02
All active vitamin D administration (%)	25.0	35.7	48.0	0.0003
Oral calcitriol administration (%)	22.7	29.4	27.7	N.S.
Phosphate binders administration (%)	67.4	76.0	73.9	N.S.
Calcium salts administration (%)	40.2	44.0	52.9	N.S.

C-rp 3.11 mg/dl= third tertile; serum albumin 3.2 g/dl= first quartile; haemoglobin, iPTH, calcium and phosphate concentrations are categorized according to K/DOQI recommendations for stage 5 CKD.

Table 3. Clinical and laboratory characteristics (mean ± standard deviation) of incident chronic haemodialysis patients subdivided according to circulating iPTH levels

	iPTH < 150 pg/ml (mean ± SD)	iPTH 150–300 pg/ml (mean ± SD)	iPTH > 300 pg/ml (mean ± SD)	*P*-value
Age (years)	66.1 ± 13.4	66.5 ± 15.9	66.8 ± 15.0	N.S.
Systolic blood pressure (mmHg)	144 ± 22	144 ± 23	142 ± 24	N.S.
Diastolic blood pressure (mmHg)	77 ± 11	80 ± 12	78 ± 12	N.S.
Corrected calcium (mg/dl)	9.43 ± 0.85	9.27 ± 0.80	9.06 ± 0.86	0.003
Phosphorus (mg/dl)	4.91 ± 1.53	5.32 ± 1.62	5.36 ± 1.46	0.01
Haemoglobin (g/dl)	9.72 ± 1.39	9.96 ± 1.53	10.1 ± 1.39	N.S.
C-rp (mg/dl)	4.80 ± 6.81	3.95 ± 6.27	3.64 ± 6.40	N.S.
Serum albumin (g/dl)	3.38 ± 0.57	3.55 ± 0.52	3.60 ± 0.54	0.02

CCI-adjusted (CCI as continuous variable) relative risk of death for all-cause, non-cardiovascular and cardiovascular causes, grouping patients on iPTH concentration and assuming iPTH = 150–300 pg/ml as reference. The relative risk of death increased in patients with iPTH <150 pg/ml, but reached the statistical significance only for all-cause mortality.

The Kaplan–Meier survival curves for all-cause mortality (Figure 3) point out a significantly ($P < 0.00001$) worse survival for patients with a combination of highest tertile of CCI and lowest one of iPTH.

The results of multivariable-adjusted Cox analysis to test the effect on survival of several combinations between tertiles of CCI and tertiles of iPTH are shown in Figure 4. The worst combination for all-cause mortality was second and third tertiles of CCI with first tertile of iPTH (RR = 3.83, $P = 0.02$; RR = 3.79, $P = 0.01$, respectively). Finally, the interaction between iPTH and CCI on patient survival was underlined in the interaction test where the interaction term iPTH × CCI was significantly associated with all-cause mortality (beta = −0.20, $P < 0.05$).

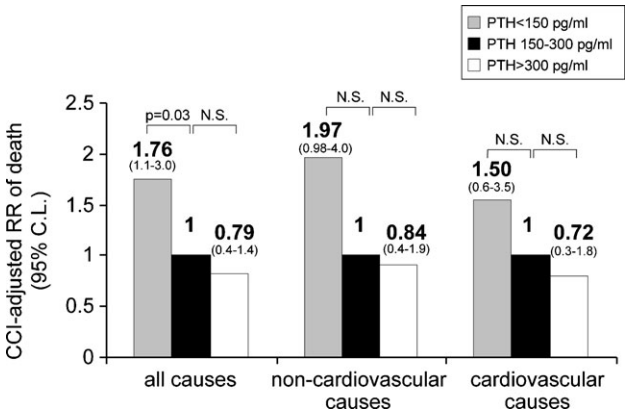

Fig. 2. CCI-adjusted risk of death and 95% confidence limits (C.L.) in patients with iPTH outside the K/DOQI target range, considering patients with PTH in a range as the reference group.

Discussion

The increased serum concentration of phosphate and calcium has adverse effects on survival of patients on chronic

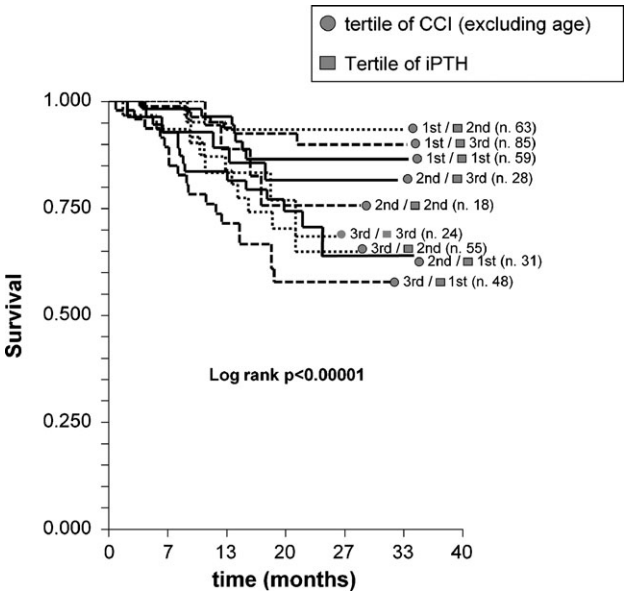

Fig. 3. Kaplan–Meier survival curves for all-cause mortality in patients subdivided according to combinations between tertiles of the CCI (excluding age) and tertiles of iPTH.

RRT [17–20]. PTH has been often associated with higher mortality rate [17–20]. Instead, survival analyses have yielded conflicting results on the effects of low PTH [17–23].

The incident dialysis population represents an interesting cohort to identify potential causes of high mortality observed within the first year of dialysis. In this population, both high and low PTH were correlated with a significant reduction in the quality of life, while low PTH had no detrimental effect on survival [20,24].

In the present study, we have evaluated the data of 411 incident haemodialysis patients and found a very high overall rate of clinical complications.

Late referral and low concentration of serum albumin were frequently found in patients with low iPTH; the latter finding may indicate sub-optimal clinical care of patients in pre-dialysis stages and consequent malnutrition.

An inverse relationship between the CCI and iPTH was observed in comorbid patients, and it was independent of diabetes, active vitamin D administration and concentrations of serum calcium, phosphate and albumin. Potential links between the CCI and iPTH may be the limitation in skeletal mobilization and/or the malnutrition frequently observed in patients with high-grade comorbidities. In fact, the limitation in skeletal mobilization may increase serum calcium with consequent reduced secretion of iPTH. Despite the fact that high serum calcium and low serum albumin were more frequently found in our patients with low iPTH, the inverse association between the CCI and iPTH was independent of both variables. However, it is difficult to deduce from PTH levels the metabolic state of bone. Not all patients with low iPTH have reduced bone turnover; at the same time, patients with high iPTH do not have increased turnover [25].

The lack of an increased risk of death in patients with iPTH > 300 pg/ml should be viewed with caution because only 9% of the entire cohort had iPTH > 600 pg/ml which has been associated with an increased mortality in prevalent dialysis patients [18]. The weak statistical association between low iPTH and CCI-adjusted risk of death and the presence of inverse correlation between iPTH and CCI prompted us to look for more distinctive interactions between both factors and evaluate the impact of their combinations on all-cause mortality. The attained data highlighted the hazardousness of the combinations of lowest tertile of iPTH and highest tertiles of the CCI. Remarkably, the detrimental effect of high CCI on survival was mostly evident in patients with low iPTH. However, a trend between rising CCI and risk of death was observed also in patients with high tertiles of iPTH; the lack of statistical significance may be due once more to the low percentage of patients with very high iPTH.

From the standpoint of the clinical implications, more attention should be devoted to all interventions aiming at attenuating the high mortality risk present in haemodialysis

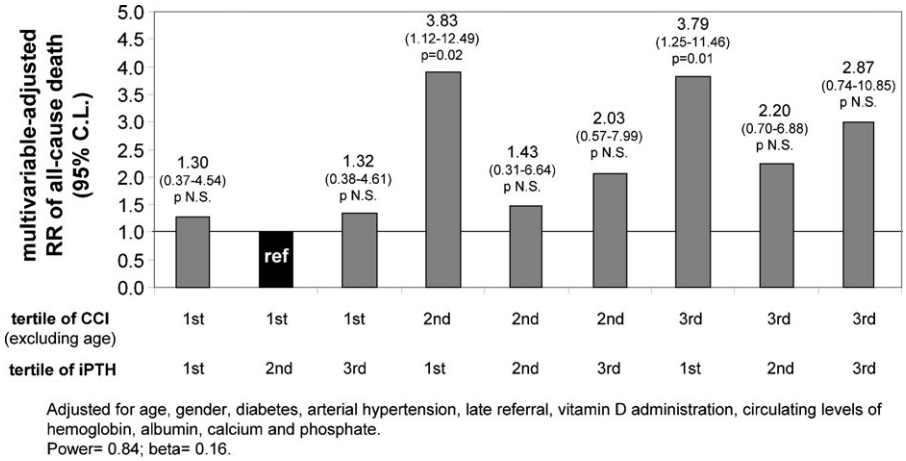

Fig. 4. Multivariable-adjusted risk of all-cause death and 95% confidence limits (C.L.) in patients subdivided according to combinations between tertiles of the CCI (excluding age) and tertiles of iPTH. Subjects with lowest tertile of the CCI and second tertile of iPTH were considered as the reference group.

patients with low iPTH and high CCI. The first step is a better management of the alterations in mineral metabolism, an aspect that showed some inadequacies. In fact, at the start of RRT vitamin D and calcium salts were still administered to 25.0% and to 40.2% of our patients with a low concentration of serum iPTH, respectively. Despite observational studies which have shown a beneficial effect of vitamin D compounds on patients' survival, in our patients the detrimental effect of low iPTH and high CCI on survival was independent of vitamin D administration, at least at the start of RRT.

The present study has some limitations. iPTH was obtained at several renal units with different second generation assay methods. Nonetheless, the regression model multilevel analyses did not show any significant influence of the nested levels method and centre. Survival analysis based on a single baseline value of iPTH may be questioned, but this is the case of many other studies. Furthermore, the mortality risk was not different when iPTH was analysed at baseline, as a standard time-dependent covariate and as a cumulative time-dependent covariate [24]. Data analysis took into account only drugs administered at the start of RRT but not the variations occurring during the observation period. In some patients the follow-up might appear too short, but only 5% and 1% of patients had censoring time shorter than 12 and 6 months, respectively. Of note, these patients were free from events; their influence on the outcome analysis may be regarded as negligible.

In conclusion, incident haemodialysis patients suffer from a high rate of clinical complications. In these patients, low iPTH and high CCI are often associated and their interaction affects survival negatively.

Conflict of interest statement. None declared.

Appendix: investigators of the CPCP (Comorbidity–Parathormone–Calcium–Phosphate) study

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