

## Original Article

# Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study

José Luis Fernández-Martín<sup>1</sup>, Pablo Martínez-Cambor<sup>2,3</sup>, María Paula Dionisi<sup>1</sup>, Jürgen Floege<sup>4</sup>, Markus Ketteler<sup>5</sup>, Gérard London<sup>6</sup>, Francesco Locatelli<sup>7</sup>, José Luis Gorriz<sup>8</sup>, Boleslaw Rutkowski<sup>9</sup>, Aníbal Ferreira<sup>10</sup>, Willem-Jan Bos<sup>11</sup>, Adrian Covic<sup>12</sup>, Minerva Rodríguez-García<sup>13</sup>, José Emilio Sánchez<sup>13</sup>, Diego Rodríguez-Puyol<sup>14</sup> and Jorge B. Cannata-Andía<sup>1</sup>, on behalf of the COSMOS group\*

<sup>1</sup>Bone and Mineral Research Unit, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Asturias, Spain, <sup>2</sup>Oficina de Investigación Biosanitaria de Asturias (OIB), Asturias, Spain, <sup>3</sup>Universidad Autónoma de Chile, Chile, <sup>4</sup>Department of Nephrology and Clinical Immunology, RWTH Aachen University, Aachen, Germany, <sup>5</sup>Division of Nephrology, Klinikum Coburg, Coburg, Germany, <sup>6</sup>Centre Hospitalier FH Manhes, France, <sup>7</sup>Department of Nephrology, Dialysis and Renal Transplant, Alessandro Manzoni Hospital, Lecco, Italy, <sup>8</sup>Hospital Universitario Dr. Peset, Valencia, Spain, <sup>9</sup>Department of Nephrology, Transplantology and Internal Medicine, Gdańsk Medical University, Gdansk, Poland, <sup>10</sup>Nephrology Department, Hospital Curry Cabral and Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal, <sup>11</sup>Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands, <sup>12</sup>University of Medicine 'Gr. T. Popa', Iasi, Romania, <sup>13</sup>Department of Nephrology, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Hospital Universitario Central de Asturias, Universidad de Oviedo, Oviedo, Asturias, Spain and <sup>14</sup>Department of Medicine, Universidad de Alcalá Nephrology Section and Research Unit Foundation, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Spain IRSIN REDinREN (Instituto de Salud Carlos III), Madrid, Spain

Correspondence and offprint requests to: Jorge B. Cannata-Andía; E-mail: cannata@hca.es

\*Other Collaborators (COSMOS Group): Miha Benedik, Juan Jesus Carrero, David Goldsmith, Reinhard Kramar, Pierre-Yves Martin, Dimitrios Memmos, Judit Nagy, Drasko Pavlovic, Vladimir Teplan, Christian Tielemans, Dierik Verbeelen, Rudolf P. Wüthrich.

## ABSTRACT

**Background.** Abnormalities in serum phosphorus, calcium and parathyroid hormone (PTH) have been associated with poor survival in haemodialysis patients. This COSMOS (Current management Of Secondary hyperparathyroidism: a Multi-centre Observational Study) analysis assesses the association of high and low serum phosphorus, calcium and PTH with a relative risk of mortality. Furthermore, the impact of changes in these parameters on the relative risk of mortality throughout the 3-year follow-up has been investigated.

**Methods.** COSMOS is a 3-year, multicentre, open-cohort, prospective study carried out in 6797 adult chronic haemodialysis patients randomly selected from 20 European countries.

**Results.** Using Cox proportional hazard regression models and penalized splines analysis, it was found that both high and low serum phosphorus, calcium and PTH were associated with a higher risk of mortality. The serum values associated with the minimum relative risk of mortality were 4.4 mg/dL for serum phosphorus, 8.8 mg/dL for serum calcium and 398 pg/mL for serum PTH. The lowest mortality risk ranges obtained using as base the previous values were 3.6–5.2 mg/dL for serum

phosphorus, 7.9–9.5 mg/dL for serum calcium and 168–674 pg/mL for serum PTH. Decreases in serum phosphorus and calcium and increases in serum PTH in patients with baseline values of >5.2 mg/dL (phosphorus), >9.5 mg/dL (calcium) and <168 pg/mL (PTH), respectively, were associated with improved survival.

**Conclusions.** COSMOS provides evidence of the association of serum phosphorus, calcium and PTH and mortality, and suggests survival benefits of controlling chronic kidney disease-mineral and bone disorder biochemical parameters in CKD5D patients.

**Keywords:** calcium, chronic kidney disease, CKD-MBD, cosmos, hemodialysis, phosphorous, PTH, survival

## INTRODUCTION

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a common complication of CKD5D [1], which has been associated with a higher risk of mortality [2, 3]. In 2003, the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guideline recommended for CKD5D to maintain serum phosphorus between 3.5 and 5.5 mg/dL (1.13–1.78 mmol/L), albumin-corrected serum calcium between 8.4 and 9.5 mg/dL (2.10–2.37 mmol/L) and serum parathyroid hormone (PTH) between 150 and 300 pg/mL (16.5–33.0 pmol/L) [4]. Six years later, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline suggested to maintain serum phosphorus and calcium within the normal range and serum PTH in the range of two to nine times the upper normal limit of the assay. However, the level of evidence for the K/DOQI and KDIGO recommendations was relatively low [5].

All studies assessing the association between the risk of mortality and abnormalities of CKD-MBD serum parameters have been observational in nature and therefore they do not prove causality. Unfortunately, due to the high cost and the current clinical-epidemiological and experimental evidence, it is unlikely that large clinical trials addressing this issue will be performed in the future. Thus, according to Hill's criteria for causation [6], consistency among different observational studies performed at different places, circumstances and times is one of the minimal conditions required to provide adequate evidence of a causal effect between incidence factors and consequences.

Previous studies looking for the association between serum biochemical parameters of CKD-MBD and mortality risk have been carried out in the USA [3, 7, 8], Latin America [9], some European countries [10–13] and worldwide including USA, Asia and European countries [14]. However, no prospective studies representative of the European haemodialysis population have been carried out up to COSMOS [15, 16].

This COSMOS paper analyse the association between serum phosphorus, calcium, PTH and mortality risk with the aim to describe the lowest mortality serum values and the safest ranges for each of these three parameters. Furthermore, in patients

outside the described ranges, the outcome impact of variations in these CKD-MBD biochemical parameters was assessed.

## MATERIALS AND METHODS

COSMOS is a 3-year, multicentre, open-cohort, prospective observational study surveying bone and mineral disturbances in 227 dialysis centres from 20 European countries including patients undergoing maintenance haemodialysis older than 18 years. A total number of 4500 patients were randomly recruited for COSMOS. The number of patients recruited per country was proportional to the haemodialysis population of each country. The larger countries were divided into different geographic areas, and haemodialysis sites were randomly selected within the predefined areas. Within each site 20 patients were randomly selected. During the 3-year follow-up period, 2297 patients were additionally recruited to replace those patients leaving the study for any reason, making a total number of 6797 patients. These replacement patients were not randomly selected but they should have been on haemodialysis for <1 year. Facilities were identified using a stratified, random selection methodology, the detailed study protocol design has been previously published [15, 16]. Recruitment of sites and patients began in February 2005 and finished in July 2007 and data collection ended in July 2010.

At baseline and every 6 months, clinical, biochemical and therapeutic relevant information was collected [15, 16]. Intact PTH levels from sites measuring bio-intact assay were corrected as it has been already described in detail [16]. Serum PTH values higher than 3000 pg/mL were removed from the present analysis (0.4% of observations).

Patients were followed for survival until they died or were censored because they underwent renal transplantation, left the study (i.e. referred to other haemodialysis unit or lost by other reasons) or reached the end of the study, whichever happened first, and they were replaced by new incident patients. The design of this open-cohort guaranteed the same number of patients over the 3-year follow-up by replacing lost baseline randomly selected patients by new incident patients. The outcome was all-cause mortality and the exposure serum levels of phosphorus, calcium and PTH. Differences in the characteristics of patients according to serum phosphorus, calcium and PTH were assessed by using quartiles and one-way analysis of the variance for continuous variables and chi-squared test for categorical variables.

Cox proportional hazard regression analysis with time-dependent variables was used to assess the association between all-cause mortality and serum phosphorus, calcium and PTH. The exposure variables were introduced in the Cox models as continuous variables and fitted by using penalized splines smoothing. The optimal degree of smoothness was selected using the Akaike Information Criterion.

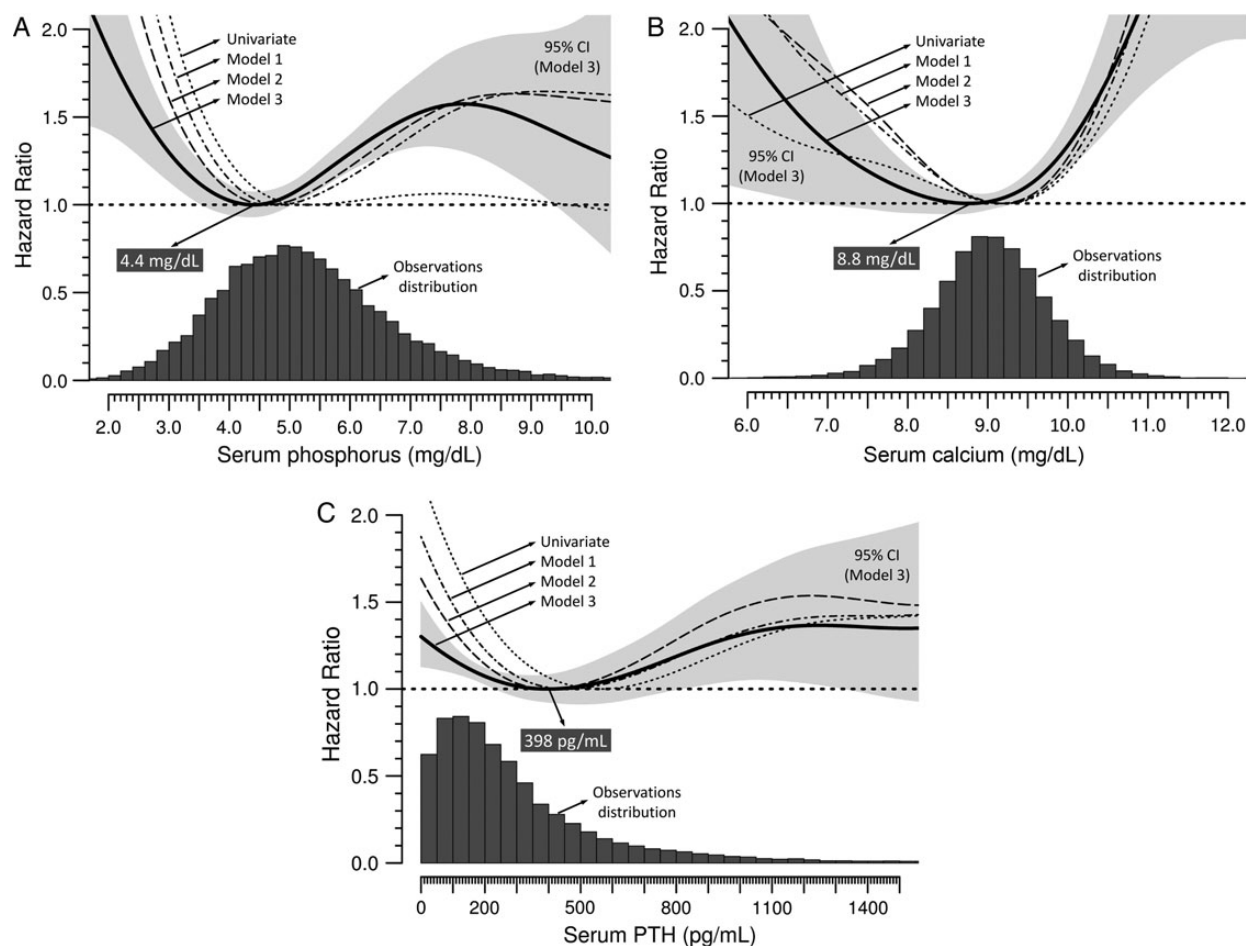
Three different multivariate models were used for adjustment containing a total number of 22 variables in the full model. Model 1 included demographic characteristics and comorbidities: age, sex, body mass index (BMI), smoking habit, time on haemodialysis, aetiology of chronic kidney disease,

diabetes, cardiovascular disease history and parathyroidectomy. Model 2 included the variables of Model 1 plus the treatment variables: dialysis type, calcium concentration in the dialysate, hours of haemodialysis per week, treatment with erythropoietin stimulating agents (ESAs) and prescription of vitamin D metabolites/analogues (calcitriol, alfacalcidol or paricalcitol), native vitamin D or calcidol, phosphate binding agents (PBAs) (calcium-containing PBAs, sevelamer, aluminium-containing PBAs, lanthanum carbonate or other PBAs) and calcimimetics. Model 3 (full model) included all previous variables plus five biochemical parameters haemoglobin, albumin, phosphorus, calcium and PTH. All multivariate models were stratified by centre. All variables included in Models 2 and 3 as well as BMI and parathyroidectomy in Model 1 were used as time-varying covariates.

The serum values of phosphorus, calcium and PTH with the minimum log (hazard ratio, HR) were used as reference (HR = 1.0) (Figure 1). The lowest mortality risk ranges or 'safest ranges' were estimated as those serum ranges with a hazard ratio  $\leq 1.1$  ( $\leq 10\%$  increase in the relative risk of mortality).

Afterwards, serum values of all patients were categorized as below, within and above the lowest mortality risk ranges, and the association of these categories with mortality was assessed. Serum categories were used as time-varying variables, and the reference (HR = 1.0) was the serum values within the estimated ranges. The multivariate models used for adjustments were the same as described earlier.

During the 3-year follow-up, every 6 months, taking as reference the baseline serum values, the association between changes in serum phosphorus, calcium and PTH and relative risk of mortality was specifically assessed in the three groups of patients in whom previous studies have shown a higher risk of mortality. The mean serum value of each 6-month period minus the baseline values was calculated and used as a time-varying variable. Thus, negative and positive values meant decrease and increase from baseline values, respectively. Crude and adjusted relative mortality risk was calculated by using penalized splines smoothing, using the same three multivariate models described earlier. All statistical analyses were done using R Statistical Software version 3.0.1 with the 'survival'



**FIGURE 1:** Relative risk of mortality with serum phosphorus, calcium and PTH. Grey boxes show the serum values with the minimum risk of mortality. Multivariate Model 1 (general and demographic characteristics) included the following variables: sex, age, BMI, aetiology of CKD, time on haemodialysis, diabetes, cardiovascular disease, parathyroidectomy and smoking habit; Model 2 (treatments): variables from Model 1 plus prescription of vitamin D receptor activators (calcitriol, alfacalcidol or paricalcitol), native vitamin D, PBAs, calcimimetics, ESAs, type of dialysis (low flux, high flux, other), hours of haemodialysis per week and dialysate calcium concentration; Model 3 (laboratory parameters): variables from Model 2 plus serum phosphorus, calcium, PTH, albumin and haemoglobin. Number of observations: 28 167.

package (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

After excluding patients who had only baseline data (no follow-up), the final analysis was carried out in 6307 patients (4318 randomly selected and 1989 replacements) from the following countries (number of patients and percentages): Germany (1288, 20.4%), France (858, 13.6%), Italy (727, 11.5%), Spain (660, 10.5%), Poland (462, 7.3%), Portugal (313, 5.0%), Greece (252, 4.0%), Czech Republic (219, 3.5%), the Netherlands (205, 3.3%), Hungary (187, 3.0%), Romania (180, 2.9%), Austria (167, 2.6%), UK (135, 2.1%), Sweden (133, 2.1%), Belgium (132, 2.1%), Denmark (102, 1.6%), Croatia (97, 1.5%), Finland (69, 1.1%), Switzerland (62, 1.0%) and Slovenia (59, 0.9%). The main characteristics of patients are shown in Table 1.

After 3-year follow-up, 1642 patients had died (26.0%), 642 were transplanted (10.2%), 239 referred to other haemodialysis units (3.8%) and 75 were lost to follow-up for other reasons (1.2%). The mean time of follow-up was 23.5 months (median 24.0 months). Overall, the crude all-cause mortality rate was 13.3 deaths per 100 patient years.

### Association between serum markers of bone metabolism and risk of mortality

Supplementary Tables S1–S3 show patient baseline characteristics by quartiles of serum phosphorus, calcium and PTH as potential confounders. Most demographic characteristics,

**Table 1. Main baseline characteristics of patients**

Sex ( <i>n</i> , % males)	6307	60.7
Age (years) ( <i>n</i> , mean $\pm$ SD)	6307	64.0 $\pm$ 14.4
BMI (kg/m <sup>2</sup> ) ( <i>n</i> , mean $\pm$ SD)	6302	25.3 $\pm$ 5.1
Current smokers ( <i>n</i> , %)	6299	13.9
Diabetics ( <i>n</i> , %)	6306	30.7
CVD history ( <i>n</i> , %)	6300	72.1
Parathyroidectomy ( <i>n</i> , %)	6307	4.9
Months on HD ( <i>n</i> , mean $\pm$ SD)	6307	38.9 $\pm$ 49.5
Hours of dialysis per week ( <i>n</i> , mean $\pm$ SD)	6307	12.0 $\pm$ 2.1
Dialysis technique ( <i>n</i> )	6307	
HD conventional low flux (%)		54.1
HD conventional high flux (%)		37.1
Haemodiafiltration and other (%)		8.8
Calcium conc. in dialysate ( <i>n</i> )	6088	
2.5 mEq/L (%)		30.0
3.0 mEq/L (%)		50.0
3.5 mEq/L (%)		19.9
Treated with PBAs ( <i>n</i> , %)	6297	85.0
Treated with VDRAs ( <i>n</i> , %)	6305	47.5
Treated with calcimimetics ( <i>n</i> , %)	6270	6.2
Treated with ESAs ( <i>n</i> , %)	6300	90.4
Phosphorus (mg/dL) ( <i>n</i> , mean $\pm$ SD)	6291	5.4 $\pm$ 1.4
Calcium (mg/dL) ( <i>n</i> , mean $\pm$ SD)	6087	9.1 $\pm$ 0.7
PTH (pg/mL) ( <i>n</i> , median [IQR])	6221	210.8 [269.0]
Albumin (g/dL) ( <i>n</i> , mean $\pm$ SD)	6164	3.8 $\pm$ 0.5
Haemoglobin (g/dL) ( <i>n</i> , mean $\pm$ SD)	6258	11.4 $\pm$ 1.4

*n*, number of patients; BMI, body mass index; HD, haemodialysis; CVD, cardiovascular disease; PBAs, phosphate binding agents; VDRAs, Vitamin D receptor activators; ESAs, erythropoietin stimulating agents; IQR, interquartile range.

comorbidities and laboratory parameters varied among the different quartiles of serum phosphorus, calcium and PTH.

After adjustment with the three multivariate models, both high and low levels of serum phosphorus, calcium and PTH were associated with a higher risk of mortality (Figure 1), but the 95% confidence interval (95% CI) for low serum calcium and high serum PTH was wider.

The minimum relative risk of mortality (HR = 1.0) was found at 4.4 mg/dL for serum phosphorus, 8.8 mg/dL for serum calcium and 398 pg/mL for serum PTH (Figure 1). The lowest mortality risk ranges or safest ranges (HR  $\leq$  1.1 in Figure 1) were 3.6 (95% CI: 3.1–4.1) to 5.2 (95% CI: 4.9–5.5) mg/dL for serum phosphorus, 7.9 (95% CI: 5.8–8.4) to 9.5 (95% CI: 9.3–9.7) mg/dL for serum calcium and 168 (95% CI: 85–238) to 674 (95% CI: 450–not estimable) pg/mL for serum PTH. Serum values below and above these ranges were associated with a higher relative risk of mortality (Table 2), except for serum calcium below the range which did not reach statistical significance. At baseline, the highest percentages of patients outside the safest risk ranges were found in serum phosphorus and calcium above ranges (50.9 and 25.7% respectively, Table 3) and PTH below the range (40.7%, Table 3). These three groups also represent the three situations more frequently associated with a higher risk of mortality. Only 14.9% of patients were within the safest mortality risk ranges considering all three serum values simultaneously.

### Association between changes in serum phosphorus, calcium and PTH and risk of mortality

In patients with baseline serum phosphorus or calcium values within the lowest mortality ranges [3.6–5.2 mg/dL for serum phosphorus (Figure 2A), 7.9–9.5 mg/dL for serum calcium (Figure 3A)], the phosphorus or calcium increases or decreases from baseline values were associated with a higher risk of mortality.

In patients with baseline serum phosphorus and calcium values above the lowest mortality risk ranges, i.e. >5.2 mg/dL for serum phosphorus (Figure 2B) and >9.5 mg/dL for serum calcium (Figure 3B), the reduction in serum phosphorus or calcium towards the safest range was associated with a lower relative risk of mortality. However, a decrease in serum phosphorus or calcium beyond the safest range was associated with increment in the relative risk of mortality (Figures 2B and 3B).

In patients with baseline serum PTH within the lowest and safest mortality range (168–764 pg/mL), increases or decreases in serum PTH did not show significant association with the risk of mortality (Figure 4A). In contrast, in patients with baseline serum PTH below the COSMOS safest ranges (<168 pg/mL), increases in serum PTH were associated with lower mortality risk (Figure 4B).

## DISCUSSION

In COSMOS, the first 3-year prospective study surveying CKD-MBD parameters in CKD5D patients, which due to its design fully represents the haemodialysis European



**Table 2. Relative risk of mortality [HR (95% CI)] and serum values below, within and above the lowest mortality ranges of serum biochemical parameters**

Serum phosphorus (mg/dL)	<3.6	3.6–5.2	>5.2
Univariate ( <i>n</i> = 6291)	1.87 (1.63–2.14)	1.0	0.96 (0.86–1.07)
Model 1 ( <i>n</i> = 6278)	1.80 (1.55–2.09)	1.0	1.21 (1.08–1.37)
Model 2 ( <i>n</i> = 6015)	1.59 (1.36–1.86)	1.0	1.28 (1.14–1.45)
Model 3 ( <i>n</i> = 5590)	1.34 (1.13–1.59)	1.0	1.34 (1.18–1.53)
Serum calcium (mg/dL)	<7.9	7.9–9.5	>9.5
Univariate ( <i>n</i> = 6087)	1.13 (0.92–1.40)	1.0	1.17 (1.05–1.32)
Model 1 ( <i>n</i> = 6074)	1.32 (1.05–1.66)	1.0	1.18 (1.05–1.34)
Model 2 ( <i>n</i> = 5811)	1.40 (1.11–1.78)	1.0	1.23 (1.07–1.40)
Model 3 ( <i>n</i> = 5590)	1.13 (0.87–1.46)	1.0	1.32 (1.14–1.52)
Serum PTH (pg/mL)	<168	168–674	>674
Univariate ( <i>n</i> = 6221)	1.63 (1.47–1.80)	1.0	1.16 (0.97–1.37)
Model 1 ( <i>n</i> = 6209)	1.46 (1.31–1.64)	1.0	1.30 (1.08–1.58)
Model 2 ( <i>n</i> = 5951)	1.35 (1.20–1.53)	1.0	1.48 (1.22–1.81)
Model 3 ( <i>n</i> = 5590)	1.17 (1.02–1.33)	1.0	1.39 (1.13–1.72)

Intermediate category (used as reference—HR = 1.0) was the serum range of each parameter with a hazard ratio  $\leq 1.10$  ( $<10\%$  increase in the relative risk of mortality) in Figure 1. Each serum parameter was categorized as indicated and used as a time-varying variable in the univariate and the three multivariate models.

**Table 3. Number and percentage of patients within each serum biochemical parameter category at baseline**

Serum phosphorus (mg/dL)	<3.6	3.6–5.2	>5.2
Number of patients (%)	523 (8.3)	2569 (40.8)	3199 (50.9)
Serum calcium (mg/dL)	<7.9	7.9–9.5	>9.5
Number of patients (%)	326 (5.4)	4199 (69.0)	1562 (25.7)
Serum PTH (pg/mL)	<168	168–674	>674
Number of patients (%)	2529 (40.7)	3079 (49.5)	613 (9.9)

Intermediate category was the serum range of each parameter with the lowest mortality risk (HR  $\leq 1.1$  in Figure 1,  $\leq 10\%$  increase in the relative risk of mortality).

population [16], a significant association between high and low serum phosphorus, calcium and PTH levels and mortality was observed. In addition, we identified the serum values of the three biochemical parameters in which the minimum mortality risk was observed and also the ranges in which the lowest relative risk of mortality was observed (for serum phosphorus: 4.4 mg/dL, range 3.6–5.2 mg/dL, for serum calcium 8.8 mg/dL, range: 7.9–9.5 mg/dL, for PTH 398 pg/mL, range 168–764 pg/mL). The serum value ranges found in COSMOS are proposed as a complement or alternative to the existing KDOQI and KDIGO ranges, provided they can be confirmed in other non-European populations. Furthermore, the mortality risk impact of changes in these three serum CKD-MBD parameters during the 3-year follow-up was analysed showing that decreases in serum phosphorus and calcium and increases in serum PTH towards safest ranges were associated with a lower relative risk of mortality. These new COSMOS results provide important and novel information related to possible benefits on outcomes achieved through a better control of the main CKD-MBD parameters in CKD5D patients.

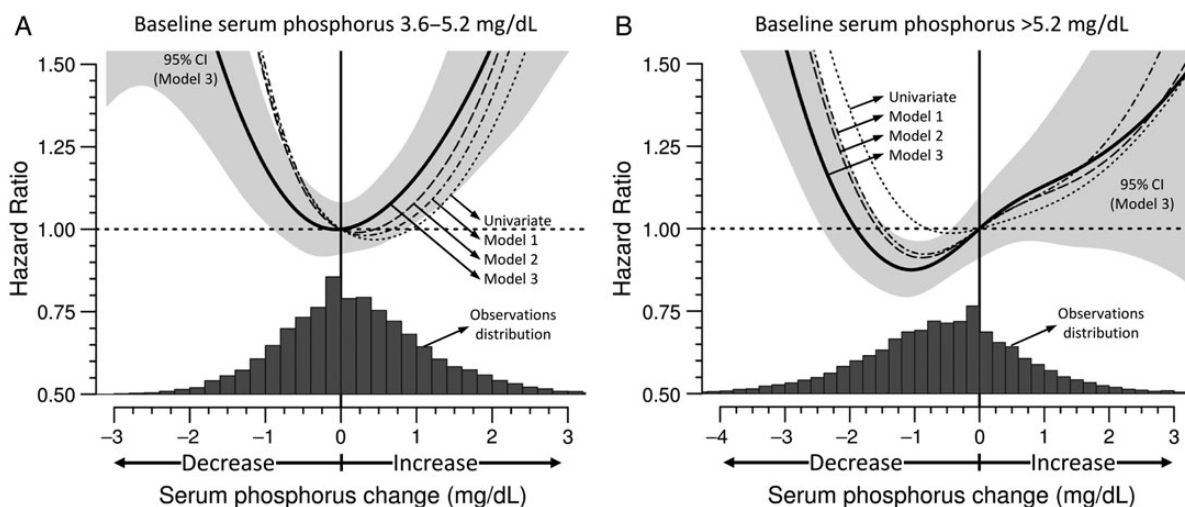
The association between CKD-MBD biochemical parameters and mortality has been the subject of numerous observational studies and reviews [2, 3, 7, 8, 10, 13, 14, 17–33]. The bulk of evidence including the present results from COSMOS [9, 11–14, 34–39] has shown that both high and low levels of serum phosphorus, calcium and PTH are associated with an increased risk of mortality. In most of these studies, the assessment of the association of the CKD-MBD serum parameters

and mortality has been carried out by categorization of the exposure variable using arbitrary cut-off values, mostly guideline-based, and establishing one of them as the reference in the Cox regression models [2, 3, 7, 8, 10, 14, 26, 27, 29, 33]. In some studies, the exposure variable was introduced in the Cox models as numeric covariate assuming a linear effect on the outcome [23, 24, 32, 33, 40]. Categorization of a continuous variable causes loss of information, and the relationship between the hazard ratio and serum biochemical parameters of bone metabolism has been found to be non-linear, currently describing a U-shaped curve.

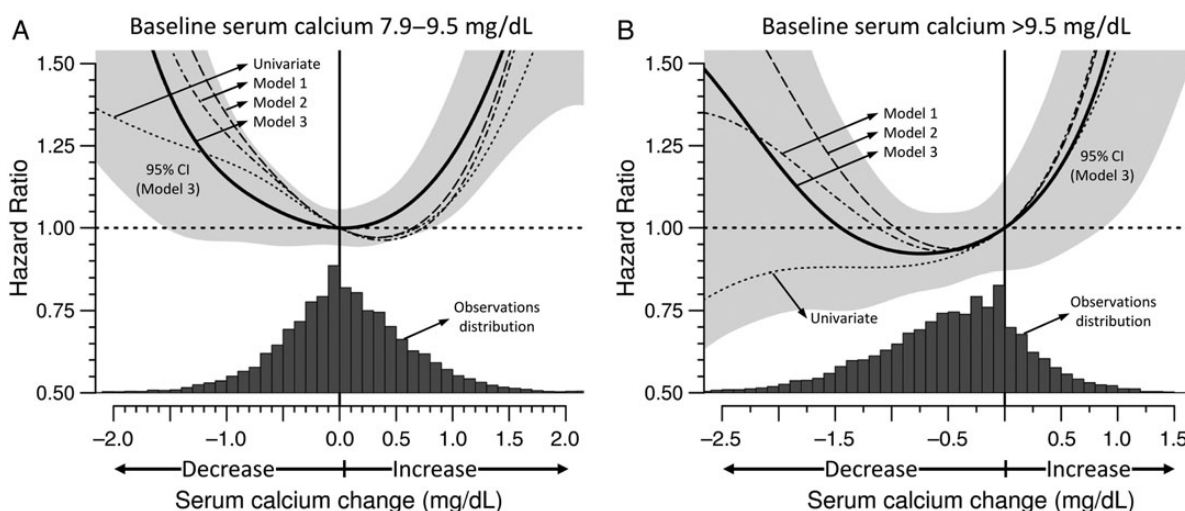
For the previous reason, the most recent studies have used regression models that allow modelling non-linear relationships between continuous variables and relative risk of mortality, i.e. fractional polynomials [12, 13] and the multivariate spline regression models [35, 39]; in the present study, penalized splines smoothing analyses were used. For large sample sizes, multivariate fractional polynomials, restricted cubic splines and penalized splines often provide similar smoothing results [41]. However, the penalized splines smoothing analyses used in this analysis of COSMOS are able to detect and correctly model non-linear effects [42], providing the most consistent fit for the Cox regression models [43] with a great flexibility [44].

Fouque *et al.* [12] used fractional polynomials and found a 10% increase in the relative risk of mortality for serum phosphorus  $<2.2$  and  $>6.1$  mg/dL, calcium  $<6.4$  and  $>9.7$  mg/dL and PTH  $<100$  and  $>1090$  pg/mL. In the present study, more than 10% increase in the relative risk of mortality was found when serum phosphorus was  $<3.6$  and  $>5.2$  mg/dL, calcium  $<7.9$  and  $>9.5$  mg/dL and PTH  $<168$  and  $674$  pg/mL. The differences among the optimal ranges in the CKD-MBD serum parameters found in the study of Fouque and COSMOS could be mainly explained by the different methodology used.

The identification of risk using categorization of serum values, which has been mostly used in the past, is more difficult to interpret and compare due to the heterogeneity of the different cut-off reference values used in each study [33]. Tentori *et al.* [14] used narrower ranges for serum phosphorus and calcium (0.5 mg/dL increments) and PTH (50 pg/mL



**FIGURE 2:** Serum phosphorus changes from baseline and relative risk of mortality. (A) Patients with baseline serum phosphorus between 3.6 and 5.2 mg/dL (patients with <10% increase in the relative risk of mortality at baseline, HR < 1.1 in Figure 1A, number of observations: 9176). (B) Patients with baseline serum phosphorus higher than 5.2 mg/dL (number of observations: 11 630). Multivariate models were the same described in Figure 1. Serum phosphorus changes were considered as a time-varying variable. The multivariate Model 3 included serum calcium and PTH (both as time-varying variables). Serum phosphorus changes from baseline equal to 0 (no change) were used as reference (HR = 1.0) in both graphs.

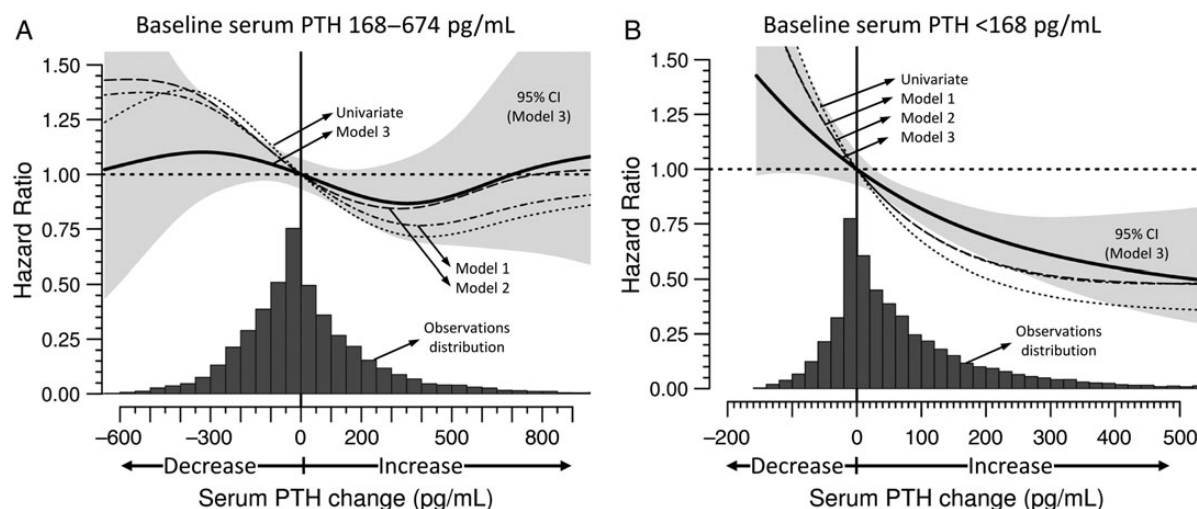


**FIGURE 3:** Serum calcium changes from baseline and relative risk of mortality. (A) Patients with baseline serum phosphorus between 7.9 and 9.5 mg/dL (patients with a HR < 1.1 in Figure 1B, number of observations: 15 254). (B) Patients with baseline serum calcium higher than 9.5 mg/dL. Multivariate models were the same described in Figure 1 (number of observations: 6171). Serum calcium changes were considered as a time-varying variable. The multivariate Model 3 included serum phosphorus and PTH (both as time-varying variables). Serum calcium changes from baseline equal to 0 (no change) were used as reference (HR = 1.0) in both graphs.

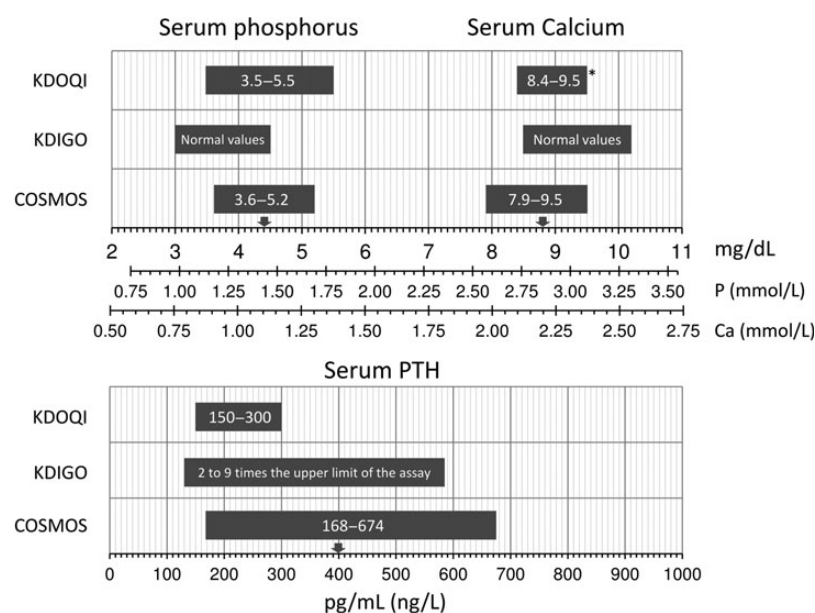
increment) compared with others [2, 3, 8–10, 12, 13, 17, 21, 22, 26–29, 31]. However, despite several approaches (baseline or time-dependent values), different outcomes (all-cause and cardiovascular mortality) and the use of different strategies, Tentori *et al.* obtained results similar to this study with the lowest risk of mortality with serum phosphorus 3.6–5.0 mg/dL, calcium 8.6–10.0 mg/dL and PTH 101–600 pg/mL.

One of the most attractive and practical contributions of this new data from COSMOS is related to the strategy used to find the lowest mortality risk ranges for serum phosphorus, calcium and PTH, which differs from the previous studies. In fact,

instead of using arbitrary categories, we determined as cut-off value a predefined percentage of HR increase (10%), which represents quite a reasonable strategy that allows the use as a reference the lowest mortality risk values of the COSMOS population. Furthermore, these figures were the base to obtain what we called ‘the optimal or the safest serum ranges’ of the CKD-MBD parameters in CKD5D patients. We decided to fix the limit of our range in a 10% increase of HR, but this strategy offers the possibility of changing the percentage of increase in HR allowing to wider or narrower the serum ranges in order to relax or harden the recommended targets; in fact, even a 20%



**FIGURE 4:** Serum PTH changes from baseline and relative risk of mortality. (A) Patients with baseline serum PTH between 168 and 674 pg/mL (patients with a HR < 1.1 in Figure 1C, number of observations: 11 070). (B) Patients with baseline serum PTH lower than 168 pg/mL. Multivariate models were the same described in Figure 1 (number of observations: 9271). Serum PTH changes from baseline were considered as a time-varying variable. The multivariate Model 3 included serum phosphorus and calcium (both as time-varying variables). Serum PTH changes from baseline equal to 0 (no change) were used as reference (HR = 1.0) in both graphs.



**FIGURE 5:** Comparison of KDOQI and KDIGO recommended targets and COSMOS lowest mortality ranges. Grey arrows show the serum values with the minimum risk of mortality. \*Albumin-corrected serum calcium.

increase is fully acceptable to define these safest ranges from an epidemiological point of view.

Despite the safest serum ranges were obtained after adjustment for treatments of CKD-MBD, to further study if these safest ranges were applicable also to patients without therapeutic intervention, as other authors did recently for serum PTH [45], additional analyses were performed in a subcohort of patients ( $n = 1771$ ) not treated with VDRA or calcimimetics at any time during follow-up. The results obtained in this subcohort suggest that the safest ranges used in this analyses for serum phosphorus and PTH were valid (data not shown). However,

the analyses with patients not treated with any drug (PBAs, VDRA or calcimimetics) did not allow any kind of comparisons due to the reduced number of patients ( $n = 213$ ).

So far, as Figure 5 shows, the serum ranges recommended by the two widely used guidelines (K/DOQI and KDIGO) showed important differences between them with the consequent important impact on the management of CKD patients. The COSMOS results are not recommendations, but they can be used as a practical test to know if the current guideline targets are in agreement with real new data of outcomes in CKD patients. The serum phosphorus values associated with a lower risk of

mortality found in COSMOS were similar and closer to K/DOQI but higher than KDIGO recommendations (Figure 5). With respect to calcium, the upper limit of the lowest mortality range found in COSMOS was exactly the same as the K/DOQI recommendation despite albumin-corrected values were used in the latter; however, the lower limit was below the K/DOQI recommendation (7.9 mg/dL in COSMOS and 8.4 mg/dL in K/DOQI, Figure 5). Finally, regarding serum PTH, COSMOS results, in agreement with the KDIGO recommended values, showed a wide and similar range in serum PTH values in which there was no increase in the relative risk of mortality.

To better interpret the differences between the K/DOQI and KDIGO PTH recommendations, it is necessary to remember the approaches used by the two guidelines to obtain their serum PTH targets. In KDOQI, the recommended serum PTH values were based on bone turnover criteria with bone biopsies as gold standard [46], meanwhile the KDIGO recommendations were based on the relative risk of mortality associated with serum PTH levels, the latter has also been the approach used in COSMOS.

The present study also analysed the association between improvement of the CKD-MBD parameters and mortality. This is a field where solid information is urgently needed. However, due to ethical reasons, it is unlikely that randomized long-term large scale clinical trials will be performed despite the lack of information on survival benefits with the control of these parameters. In COSMOS, the 3-year follow-up divided into six periods of 6 months, allowed a great number of observations every 6 months ( $n = 28\,167$ ), a fact that may partly mimic the follow-up of a clinical trial and gives the possibility to evaluate if there are benefits in outcomes in patients moving from the dangerous to the recommended ranges.

The three most frequent risk groups of patients that were specifically analysed in the present study; patients with high serum phosphorus ( $>5.2$  mg/dL, mean 6.5 mg/dL) or serum calcium ( $>9.5$  mg/dL, mean 10.0 mg/dL) at baseline (Figure 2B and 3B) showed that decreases in serum phosphorus and calcium towards the 'safest ranges' were associated with a lower relative risk of mortality. Similarly, patients with low baseline serum PTH levels ( $<168$  pg/mL, mean 88.8 pg/mL) showed that increases in serum PTH were associated with a lower risk of mortality. These are very promising results which reinforce the fact that the better control of the CKD-MBD biochemical parameters may positively impact on survival. The association of serum changes in patients below the safest ranges for serum phosphorus and calcium and above the safest range for serum PTH was not assessed because the reduced number of patients did not allow the analysis.

In the three groups of patients at higher risk in whom the analysis was performed, the reduction of the relative risk of mortality was 12% for phosphorus and 8% for calcium (Figures 2B and 3B) while it was 31% for an increase of 200 pg/mL in serum PTH (Figure 4B).

The impact of changes in serum CKD-MBD biochemical parameters and outcomes has been already addressed by other investigators but in shorter periods. One study with a follow-up of between 6 and 18 months [8] and categorization

of serum phosphorus and calcium changes from baseline intervals of 0.5 mg/dL for phosphorus and 0.2 mg/dL for calcium, found that in patients within K/DOQI ranges both, increases or decreases in serum phosphorus and calcium were associated with an increased risk of mortality. Another study [29] in incident haemodialysis and peritoneal dialysis patients, found that patients with low levels of serum phosphorus at baseline that remained low after 6 months showed a better survival than those with high serum phosphorus levels at baseline that subsequently decreased in the following 6 months. At first sight, the previous results may appear in disagreement with the present study; however, in COSMOS, the reference ( $HR = 1.0$ ) was patients with no changes in serum phosphorus during follow-up (Figure 2B) which renders the comparisons difficult.

A limitation of the study is its observational nature, which does not allow to make causal statements. In addition, as it has been explained, in some groups of patients there was not enough number of patients to investigate if increments in patients with serum values of serum phosphorus and calcium  $<3.6$  and  $7.9$  mg/dL, respectively, or reductions serum PTH from values  $>674$  pg/mL were associated with changes in the relative risk of mortality. In addition, the low number of patients not receiving any kind of drugs to control CKD-MBD serum parameters did not allow to investigate separately if spontaneous changes in serum parameters (not related to medical intervention) were associated with an improved risk of mortality. Besides limitations, COSMOS also has great strengths, which mainly relies on its careful design explained in brief in the methods section of this paper but in detail in previous papers [15, 16]. COSMOS used random selection of centres and patients with a proportional sampling according to the haemodialysis patients of each country.

In summary, in COSMOS, a non-linear relationship between serum CKD-MBD biochemical parameters and mortality risk was found. Low and high serum levels of serum phosphorus, calcium and PTH were associated with a higher relative risk of mortality. New mortality risk ranges were described:  $3.6$ – $5.2$  mg/dL for serum phosphorus,  $7.9$ – $9.5$  mg/dL for serum calcium and  $168$ – $674$  pg/mL for serum PTH. In addition, in the three groups of patients with a higher risk of mortality (serum phosphorus  $>5.2$  mg/dL, serum calcium  $>9.5$  mg/dL and serum PTH  $<168$  pg/mL), decreases in serum phosphorus and calcium and increases in serum PTH during the follow-up were associated with a significant lower risk of mortality. The latter, together with new serum targets described, makes this COSMOS analysis a relevant contribution to better know the impact of the control of serum CKD-MBD parameters on survival. In addition, this new information can be of help for the preparation of future CKD-MBD guidelines.

## SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.



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