

CALCIUM, PHOSPHORUS, PTH AND DEATH RATES IN A LARGE SAMPLE OF DIALYSIS PATIENTS FROM LATIN AMERICA. THE CORES STUDY.

Authors: M Naves-Díaz, associate biologist^{1,4}, J Passlick-Deetjen, executive medical consulting², A Guinsburg, consultant², C Marelli, executive medical consultant², JL Fernández-Martín, associate chemist^{1,4}, D Rodríguez-Puyol, professor of medicine^{3,4}, JB Cannata-Andía, professor of medicine^{1,4}.

¹*Bone and Mineral Research Unit. Hospital Universitario Central de Asturias. Universidad de Oviedo. Oviedo, Spain. Julián Clavería s/n. 33006 Oviedo. España.*

²*Fresenius Medical Care. Latin America and Germany. Fresenius Medical Care Deutschland GmbH Else-Kroener-Str. 161352 Bad Homburg v. d. H. Germany.*

³*Nephrology Section and Research Unit. Hospital Príncipe de Asturias.* ⁴*Instituto Reina Sofía de Investigación. REDinREN del ISCIII.*

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Address for correspondence:

Jorge B. Cannata-Andía
Servicio de Metabolismo Óseo y Mineral
Instituto Reina Sofía de Investigación
c/ Julián Clavería s/n
33006 Oviedo. Spain.
Phone #: +34.985.10.61.37
Fax: +34.985.10.61.42
E-mail: cannata@hca.es

ABSTRACT

Mineral metabolism parameters may play a role in the survival of patients with chronic kidney disease (CKD). In the CORES study we analyzed the association between calcium, phosphorus and PTH and mortality (all-cause and cardiovascular) in 16173 haemodialysis (HD) patients over 18 years from 6 Latin American countries, who underwent haemodialysis up to 54 months. Unadjusted, case-mix and time-dependent multivariable-adjusted hazard ratio (HR) of death were calculated for categories of serum albumin-corrected calcium (Ca_{Alb}), phosphorus and PTH using as “reference values” the range in which the lowest death rate was observed. Age, gender, vitamin D treatment, diabetes, vintage, vascular access, weight, blood pressure and laboratory variables (serum albumin, haemoglobin, creatinine, ferritin, and Kt/V) were used as confounding variables.

Low (< 9.5 mg/dL) and high (>10.5 mg/dL) Ca_{Alb} increased the HR for all-cause mortality. Low (<9.0 mg/dL) Ca_{Alb} increased the HR for cardiovascular mortality. High phosphorus (>5.5 mg/dL) increased the HR for both all-cause and cardiovascular mortality. Low phosphorus (< 4.0 mg/dL and < 3.0 mg/dL) increased the HR for both all-cause and cardiovascular mortality. Furthermore, low (<150 pg/mL) and high (>500 pg/mL and >300 pg/mL) PTH increased the HR for both all-cause and cardiovascular mortality.

In addition, only phosphorus higher than 6.0 mg/dL increased the HR for cardiovascular hospitalizations. No effect was observed with Ca_{Alb} or PTH.

In summary, in 16,173 HD patients, elevated and reduced serum levels of albumin-corrected calcium, phosphorus and PTH levels were associated with increments in all-cause mortality. Similar results were obtained when only CV mortality was analyzed.

Keywords: hemodialysis, mortality risk, mineral metabolism, CORES study.

INTRODUCTION

Patients on HD have CKD-MBD¹⁻², several studies have shown an association between high calcium, phosphorus and PTH and all-cause mortality³⁻⁷. However, these studies have examined associations between baseline serum mineral values and subsequent survival without taking into account any changes in the concentrations of these measures and other covariates over time. In fact, recent studies using time-dependent models, not restricted to fixed baseline data but including changes over time, seem to show more realistic clinical scenarios⁸⁻⁹.

In addition, most studies, except the DOPPS carried out in Europe and Asia⁹⁻¹⁰, have been carried out in HD patients from North America. So far, there is not a single large population-based study carried out in Latin America. Thus, in the CORES study, a large observational study from Latin America, a likely different clinical management of bone metabolism markers may contribute to different outcomes.

On the other hand, although the K/DOQI guidelines have assumed ranges of serum mineral parameters as “normality”¹¹, the recently published K/DIGO guidelines¹², take a different approach, opening a new scenario.

This study analysed, using time-dependent Cox models, the risk for all-cause mortality and the risk for cardiovascular mortality according to serum calcium, phosphorus and PTH levels in a large cohort of 16,173 haemodialysis patients from six Latin American countries who were followed-up from January 2000 to June 2004.

RESULTS

Tables 1 to 3 summarize the potential association between the different demographic, laboratory, clinical and treatment variables used in the multivariable adjustment and the categories values of each parameter (serum albumin-corrected calcium, phosphorus, and PTH) analysed at the time of recruitment for 16,173 HD patients from 183 facilities. Mean follow-up was 1.65 ± 1.14 years (median, 1.35 years).

Age was inversely correlated with serum albumin-corrected calcium ($r = -0.063$), serum phosphorus ($r = -0.223$), and serum PTH ($r = -0.114$). Diabetes also inversely correlated with the three variables: $r = -0.121$, $r = -0.046$ and $r = -0.107$, for serum albumin-corrected calcium, phosphorus, and PTH, respectively. Conversely, serum creatinine and vintage directly correlated with serum albumin-corrected calcium ($r = 0.128$ and $r = 0.131$), P ($r = 0.377$ and $r = 0.081$), and PTH ($r = 0.160$ and $r = 0.207$).

The proportion of patients taking active vitamin D was 45.5%. Meanwhile, fistula was the vascular access most used (46% of patients), catheter was used in 21.4% of patients. Unfortunately, data of vascular access was not available in 27% of patients. A total of 3,151 (19.5 %) patients died during the follow-up period (January 2000 - June 2004). From the total amount of deaths, 1,211 (38.4%) were attributable to a cardiovascular cause.

Serum albumin-corrected calcium

Figure 1 shows the unadjusted, case-mix adjusted and time-dependent multivariable adjusted hazard risk (HR) of all-cause and cardiovascular mortality, and 95% confidence intervals (CI) associated with serum albumin-corrected calcium, considering 9.5 to 10.0 and 10.0 to 10.5 mg/dL as the reference range because it showed the lowest mortality. The time-dependent multivariable adjusted all-cause mortality results (Figure 1) showed a bimodal relationship (U-shape curve), with a significant increase in the HR associated with serum calcium concentrations higher than 10.5 mg/dL [10.5-11.0 mg/dL: HR (95% CI): 1.25 (1.02-1.53) and >11 mg/dL: HR (95% CI): 1.78 (1.40-2.26)] and lower than 9.5 mg/dL [9.0-9.5 mg/dL: HR (95% CI): 1.25 (1.09-1.44); 8.5-9.00: HR (95% CI): 1.61 (1.34-1.92) and <8.5 mg/dL: HR (95% CI): 3.92 (2.95-5.21)]. By contrast, only serum calcium concentrations lower than 9.0 were associated with cardiovascular mortality [<8.5 mg/dL: HR (95% CI): 3.30 (2.02-5.38) and 8.5-9.0 mg/dL: HR (95% CI): 1.59 (1.21-2.09)] (figure 1).

According to the results observed in table 1 (the lowest categories for serum albumin-corrected calcium were associated with the lowest frequencies of vitamin D use) and in order to exclude any interaction between serum albumin-corrected calcium and vitamin D, an additional analysis stratifying the cohort between vitamin D users and non users was performed. Both, vitamin D users and non users showed similar results for all cause mortality [<8.5 mg/dL: HR (95% CI): 3.88 (3.06-4.90) and HR (95% CI): 3.95 (2.86-5.47) vs > 11 mg/dL: HR (95% CI): 2.20 (1.77-2.74) and HR (95% CI): 2.11 (1.61-2.77), respectively].

Serum phosphorus

Figure 2 shows the unadjusted, case-mix adjusted and time-dependent multivariable adjusted HR of all-cause and cardiovascular mortality, and 95% CI associated with serum phosphorus, considering the serum phosphorus concentrations of 5.0 to 5.5 mg/dL, where the mortality was lowest, as the reference range. The time-dependent multivariable adjusted all-cause mortality results showed a significant increase in HR associated with serum phosphorus concentrations lower than 4.0 mg/dL. Significant increases in HR for all-cause and cardiovascular mortalities were observed with serum phosphorus concentrations higher than 5.5 mg/dL, particularly when the serum phosphorus concentration was higher than 7.5 mg/dL [HR (95% CI): 2.24 (1.50-3.34) and HR (95% CI): 2.51 (1.34-4.72) for all-cause and cardiovascular mortalities, respectively].

Serum PTH

Figure 3 shows the unadjusted, case-mix adjusted and time-dependent multivariable adjusted HR of all-cause and cardiovascular mortality, and 95% CI associated with categories of serum PTH, considering serum PTH concentrations 150 to 300 pg/mL as the reference range. Both all-cause and cardiovascular mortality showed a significant increase in the HR associated with serum PTH concentrations lower than 150 pg/mL [< 50 pg/mL: HR (95% CI): 2.42 (1.93-3.03) and HR (95%CI): 3.06 (2.13-4.39), respectively; and 50-150 pg/mL: HR (95% CI): 1.27 (1.06-1.53) and HR (95%CI): 1.52 (1.12-2.06), respectively], and higher than 500 pg/mL [500-800 pg/mL: HR (95% CI): 1.33 (1.07-1.66) and HR (95% CI): 1.61 (1.11-2.33), respectively; and > 800 pg/mL: HR (95% CI): 1.57 (1.23-1.99) and HR (95%CI): 2.02 (1.37-2.98), respectively]. In

addition, cardiovascular mortality was also significantly associated with serum PTH concentrations between 300-500 pg/mL [HR (95% CI): 1.42 (1.06-1.91)].

Similar results for all parameters analysed (serum albumin-corrected calcium, phosphorus, and PTH) were obtained when incident patients (72.4 % of the patients) and prevalent patients were analysed. Incident patients: [< 8.5 mg/dL: HR (95% CI): 4.14 (2.97-5.77) and >11 mg/dL: HR (95% CI): 1.84 (1.37-2.52) for serum albumin-corrected calcium; < 3.0 mg/dL: HR (95% CI): 1.75 (1.17-2.59) and >7.5 mg/dL: HR (95% CI): 2.17 (1.31-3.60) for serum phosphorus and <50 pg/mL: HR (95% CI): 2.24 (1.72-2.92) and >800 pg/mL: HR (95% CI): 1.67 (1.20-2.33) for serum PTH]. Prevalent patients: [< 8.5 mg/dL: HR (95% CI): 3.72 (2.14-6.48) and >11 mg/dL: HR (95% CI): 1.61 (1.09-2.36) for serum albumin-corrected calcium; < 3.0 mg/dL: HR (95% CI): 2.01 (1.11-3.62) and >7.5 mg/dL: HR (95% CI): 2.62 (1.36-5.05) for serum phosphorus and < 50 pg/mL: HR (95% CI): 2.93 (1.89-4.53) and >800 pg/mL: HR (95% CI): 1.44 (1.00-2.09) for serum PTH]. In addition, the stratification by phosphate binders showed identical results for all parameters of mineral metabolism (data not shown).

Cardiovascular hospitalization

There were 1,787 cardiovascular hospitalizations recorded. Significant increases in the HR for cardiovascular hospitalizations were observed with serum phosphorus concentrations higher than 6.0 mg/dL [6.0-7.0 mg/dL: HR (95% CI): 2.51 (1.06-5.94) and > 7.0 mg/dL: HR (95% CI): 3.96 (1.17-13.38), respectively]. No associations were found with low phosphorus. There was no association between serum calcium and PTH and the risk of cardiovascular hospitalization.

DISCUSSION

This retrospective observational study performed on 16,173 HD patients from Latin America from January 2000 to June 2004 sought to examine the relationship between different parameters of mineral metabolism and the risk of all-cause and cardiovascular mortality. In the last years, several studies have shown an increase in the risk of death of CKD patients on HD likely favoured by serum calcium, phosphorus and PTH disturbances^{3-6, 8, 10}. However, less attention has been paid to cardiovascular mortality. Moreover, previously published studies have been performed on North American, Japanese and European populations, and there was no data available from the Latin American CKD population^{10, 13-16}.

As we explained in the Methods section, one of the main strength of our approach was not to analyse the data based on the K/DOQI ranges, which is the comparison with the assumed “normality”¹⁷. We were interested in knowing within which ranges of this cohort, with all their intrinsic characteristics, we observe the lowest death rates; then we assumed that range was the safest and we used it as the “reference range”. This different approach has been described previously by others⁹ and our results confirmed previous data in different cohorts^{3, 8}. For serum calcium and phosphorus we found that our reference range (lowest range of mortality) was different to the serum calcium and phosphorus K/DOQI target ranges. By contrast, in the serum PTH the lowest range of mortality coincides with the serum PTH K/DOQI target range.

Other advantage of the CORES study is that it investigates also the cardiovascular mortality in a multiracial cohort of dialysis patients never studied before, an important aspect not addressed by many previous studies^{9, 16}.

Serum albumin-corrected calcium

Serum albumin-corrected calcium higher than 10.5 mg/dL significantly increased the HR of mortality after adjusting for several confounding variables (time-dependent multivariable adjustment)¹⁸. Additionally, serum albumin-corrected calcium lower than 9.0 mg/dL also increased the HR of mortality in the time-dependent multivariable adjusted analyses. When we compare these figures with previous studies it seems clear that in our study the reference range of serum albumin-corrected calcium, which is the lowest range of mortality, is higher than most previously recommended values. Some characteristics of the Latin America cohort, with HD practice patterns similar to those

used in Europe and USA before, might explain the reasons for finding higher serum calcium levels in this cohort. In fact, the mean dialysate calcium concentration used in this cohort was very high (3.07 ± 0.51 mEq/L), 69% of the patients were dialysed with more than 3 mEq/L of calcium and second, a high percentage of patients (74%) received calcium acetate or calcium carbonate as phosphate binders. These practice patterns are not the ones recommended by KDIGO which propose a calcium dialysate between 2.5 and 3.0 mEq/L and to restrict the dose of calcium-based phosphate binder¹². However, these facts do not explain why we have observed the lowest death range at serum calcium levels slightly higher than previous published studies^{4, 8-9}.

The negative effect of high serum calcium levels on the cardiovascular system and on mortality has been already demonstrated in several studies, and it seems there is evidence to support several deleterious effects of high serum calcium^{4, 8, 10}. Nevertheless, the results are less homogeneous in the range of low serum calcium levels, for which the association with mortality has been contradictory. While Block et al.⁴ and Young et al.¹⁰ found a protective effect of low serum calcium levels on all-cause mortality, Kalantar-Zadeh et al.⁸, Tentori et al.⁹ and others¹⁹⁻²⁰ have found, like us, an increased risk of mortality associated to low serum calcium levels.

It seems clear that this is still an issue open for discussion. Physiologically, there is no reason to justify a better survival due to low serum calcium levels, especially in the very low ranges. Quite the contrary: it is easier to relate low levels of serum calcium to higher morbidity and mortality mainly due to factors such as its association with secondary hyperparathyroidism, osteoporotic bone fractures, neurological sequelae and myocardial dysfunction due to abnormal cardiac contractility²¹⁻²⁴.

Serum Phosphorus

In epidemiologic^{3-4, 8-10} and experimental studies²⁵⁻²⁶, high serum phosphorus levels have been consistently associated with aortic calcifications and other poor cardiovascular outcomes. Our study also showed that high serum phosphorus was associated with a higher risk of mortality. These results are not surprising, since high serum phosphorus levels have been consistently related to all-cause and cardiovascular mortality. In fact, reducing serum phosphorus with phosphate binders has shown a better survival, even in the normal ranges of serum phosphorus²⁷. Furthermore, recent

studies have proven several cardiovascular advantages are obtained after an adequate serum phosphorus control in CKD 5 patients ²⁸, and experimental studies have also demonstrated that phosphorus inversely correlated with survival ²⁹.

Regarding low serum phosphorus, our results, like those in previously published studies, demonstrated an increase in the risk of all-cause and cardiovascular mortality, particularly with serum phosphorus levels is lower than 3 mg/dL ^{4, 8, 10}, likely due to undernutrition ³⁰⁻³¹.

Serum PTH

One of the more controversial issues is the association of serum PTH levels with morbidity and mortality. The normal K/DOQI ranges were selected as such based mainly on the correlation between serum PTH and bone histological parameters. The main objective was to have a useful surrogate bone marker to separate high and low bone turnover. Because of the relationship between bone turnover, calcium and phosphorus uptake and release from bone and their possible implications in hard outcomes, the so-called “normal” PTH ranges also began to be used in the analysis of morbidity and mortality.

Serum PTH values lower than 150 pg/mL showed higher HR values and, consequently, a higher risk of mortality than PTH values higher than 300 pg/mL. In fact, the highest HR values (2.4 and 3.1 for all-cause and cardiovascular mortality, respectively) were found with serum PTH values lower than 50 pg/mL, whereas in the highest serum PTH values (> 500 pg/mL) mortality risk increased up to 1.6 and 2.0 for all-cause and cardiovascular mortality, respectively. The importance of low serum PTH values has already been stressed, showing that patients who start dialysis with very low PTH levels were more likely to die ³²⁻³³.

Previous studies using the same ranges showed similar trends, but the results can not be fully compared as the authors used different cut-off values and also the adjustments were not exactly the same ^{4, 8, 10}. As an example, despite active vitamin D treatment being involved in changes in survival ³⁴⁻³⁵, Block et al. ⁴ did not mention any active vitamin D treatment adjustment, whereas other authors did ^{4, 8, 10}. Tsuchihashi et al. ³⁶ found that HD patients with serum PTH levels below 60 pg/mL experienced greater cardiovascular complications than patients with PTH values between 60-200 pg/mL. However, the number of patients was small (48) and the results were not calcium-adjusted. The NECOSAD study showed no effect of either high or low PTH levels on

cardiovascular mortality¹⁶. The DOPPS study showed no relationship between low PTH and cardiovascular mortality⁹; yet, as they were not able to control the different PTH assays used, the results are difficult to interpret. In our study, we found a clear relationship between cardiovascular mortality and extreme PTH serum values, both high and low, particularly in the latter. The strength of our study resides not only in the sample size, but in the fact that all centres used the same PTH assay. This fact minimizes any variability related to the assay, which has proven to be a relevant factor³⁷. Interestingly, our findings agree with those from the ARO CKD Research Initiative study (authors unpublished data) that showed reduced and elevated iPTH (< 150 pg/mL and > 500 pg/mL, respectively), albumin-corrected calcium and phosphorus levels were all associated with an increase in all-cause mortality using time-dependent analysis.

To conclude, a few words on cardiovascular outcomes. Similarly to the results observed by others^{4,13}, high serum phosphorus was associated with an increased relative risk of death and cardiovascular hospitalization. On the other hand, there was no association between serum calcium and PTH and the risk of cardiovascular hospitalization.

Limitations of the study

One of the limitations of our study is its retrospective and observational nature. However, the fact that it was conducted in a large database of 16,173 patients minimizes any probable selection bias.

Since only HD patients were included in the analysis, no extrapolation is possible to patients on peritoneal dialysis or renal patients with less advanced CKD stages 3-5. In addition, unmeasured confounding variables could increase or decrease the HR for mortalities and/or hospitalization. A recent prospective study has showed an association between vitamin D deficiency and increased cardiovascular mortality in hemodialysis patients³⁸. Physiological doses of active vitamin D have shown protective cardiovascular effects reducing the inflammatory response to cardiovascular injury, the myocardial cell hypertrophy and proliferation, and the renin-angiotensin system activation³⁹. Although Latin America has an adequate sunshine availability, the vitamin D deficiency/insufficiency in Latin America is as endemic as in the Northwestern hemisphere⁴⁰⁻⁴¹, probably due the low intake of vitamin D supplemented foods. Since levels of 25(OH)D and 1.25(OH)₂ were not available in our population, the main effect of serum PTH (both low and high) on the risk of death could only be adjusted according

to the presence or absence of an active vitamin D treatment. Finally, a major limitation of the study is the lack of information of outcomes across countries.

To sum up, the CORES study consists in a large database of patients from 6 Latin American countries followed-up for up to 54 months. We have found in the CORES study that elevated and reduced serum levels of albumin-corrected calcium, phosphorus, and PTH were associated with increments in both all-cause and cardiovascular mortalities. Moreover, we found a significantly higher cardiovascular hospitalization rate in patients with elevated serum phosphorus.

MATERIAL AND METHODS

A historical cohort of chronic haemodialysis patients from six Latin American countries (Argentina, Brazil, Colombia, Chile, Mexico and Venezuela) who underwent haemodialysis three times a week (98.8%) and twice a week (1.2%) in 183 different dialysis facilities associated or operated by Fresenius Medical Care comprises the CORES study. The entire CORES population (n = 22,230) consisted of patients older than 18 years who either initiated haemodialysis (incident patients – 72.4% of the cohort) or were already in haemodialysis (prevalent patients – 27.6% of the cohort) after January 1, 2000. Patients were followed for a maximum period of time of 54 months (median 16 months) until June 30, 2004 or until they were lost to follow-up.

In addition, 6,057 (27.2%) patients who remained less than 90 days on chronic haemodialysis were excluded from the analysis due to the greater instability in the bone and mineral markers in addition to a higher mortality rate, factors that may bias the results. The different reasons for the exclusions were: beginning of haemodialysis after April 2004 (41.8%); death (29.3%); switch to peritoneal dialysis (11.5%); recovery of renal function (7.1%); voluntary withdrawal from therapy (4.7%); unknown circumstances (3.3%); and renal transplantation (2.3%). Therefore, the sample of the study consisted of 16,173 renal patients (over 18 yr) undergoing chronic haemodialysis. During the study period and once the patient was admitted to the haemodialysis centre, demographic, clinical, laboratory and other general data were collected prospectively and entered into a central database updated by medical personnel and stored by Fresenius Medical Care (FME register®). From this database, the following data were analysed: age, gender, weight, country, date of first dialysis, systolic and diastolic pressure, vascular access, primary cause of renal failure, dose of dialysis, medications administered in each haemodialysis session (name, date, dose, and route of administration), and laboratory tests. Two active vitamin D analogues were used; calcitriol was used in the 99.6% of the patients and only 0.4% of the patients used alphacalcidol. The main route of administration of active vitamin D was the oral route (97.7% of patients).

Dialysis vintage was defined as the duration of time between the first day of maintenance dialysis treatment and the last day that the patient was in the study. All missed haemodialysis treatments (e.g. because of hospitalization or non-compliance) and all permanent discharges (e.g. transplantation, voluntary withdrawal from therapy, transfer to a non-Fresenius dialysis unit, change to peritoneal dialysis or loss to follow-

up) were also gathered. All patient hospitalizations were recorded in the database as a type of permanent discharge by each different centre, including the date and cause of hospitalization. The different causes of hospitalization and death were classified according to the International Classification of Diseases (ICD-10). Comorbidities were grouped into vascular, neoplastic, infectious, respiratory, neurological or diabetes according to the table 4. Death causes were grouped as vascular, infectious, neoplastic, neurological, respiratory or unknown. All dialysis facilities underwent a centralized and uniform administrative control. Thus, all the collected data were checked to ensure their accuracy and completeness. The study met the privacy standards implemented by Fresenius with a waiver for informed consent.

For each patient, values of the different parameters studied (calcium, phosphorus and PTH-measured by the Nichols Advantage Chemiluminescence assay) were updated every month (time-dependent). Serum calcium was corrected for serum albumin using a formula already validated for haemodialysis patients: corrected calcium = measured calcium + $[0.0176 \times (34 - \text{serum albumin in g/dL})]$ ¹⁸. Serum albumin-corrected calcium, phosphorus, and PTH were stratified into categories from < 8.5 to > 11.0 mg/dL; < 3.0 to > 7.5 mg/dL, and < 50 to > 800 pg/mL, respectively. The analysis examined only patients who survived for at least 90 days after initiating chronic haemodialysis.

The analyses of hospitalization as outcome included only the cardiovascular hospitalization because previous studies suggested that is a good surrogate marker of mortality in HD patients.

Statistical analyses

Standard univariate analyses (chi-square and ANOVA tests) for the different categories of the three variables analysed (serum albumin-corrected calcium, phosphorus and PTH) were performed. Values were reported as mean or median for continuous variables and as proportions for categorical variables.

Cox proportional-hazards regression was used to estimate all-cause and cardiovascular mortality hazard ratio according to the serum albumin-corrected calcium, phosphorus and PTH. Similarly to the described by Tentori et al⁹ and opposed to previous studies published in this field^{10, 16, 42}, in our study for the three variables analysed (albumin-corrected calcium, phosphorus and PTH), we selected as reference value the serum range of calcium, phosphorus and PTH in which the mortality rate was lower. Patients

contributed person-time until they died, underwent kidney transplantation, voluntarily withdrew from chronic haemodialysis, or reached the end of the follow-up period, whichever occurred first. Cox proportional hazards models were used to calculate hazard ratios for mortality associated with serum albumin-corrected calcium, phosphorus and PTH in models in which laboratory measures were updated every month (time-dependent) or every six months (time-dependent) in the case of serum PTH. For each analysis, three types of models were examined based on the level of multivariate adjustment: (1) unadjusted models included serum albumin-corrected calcium, phosphorus, and PTH as the predicting variable, and mortality as the outcome variable; (2) case-mix adjusted models included additional fixed baseline covariates: age, gender, country, diabetes mellitus, vintage, and vascular access; and (3) case-mix and the following clinical and laboratory time-varying variables (monthly changing) with known associations with survival in haemodialysis patients, such as: weight, albumin, ferritin, haemoglobin, creatinine, systolic and diastolic blood pressure, active vitamin D treatment and Kt/V (delivered dose of dialysis). Kt/V was calculated using the following formula: $\text{Delivered Kt/V} = -\ln(R - 0.008 \times t) + (4 - 3.5 R) \times \text{UF}/W$. Where R= postdialysis/predialysis blood urea nitrogen, t= dialysis hours UF= predialysis-postdialysis weight change, and W= postdialysis weight. Serum albumin-corrected calcium, phosphorus, and PTH were also included as additional time-varying variables. Since it was impossible to obtain a standardized mortality rate in all countries, in order to reduce the country effect on the mortality rate, all the analyses were carried out after adjusting by country. Similarly, a Cox proportional-hazards regression to estimate cardiovascular hospitalization hazard ratio according to the serum albumin-corrected calcium, phosphorus and PTH was carried out. The Cox model included a time-dependent multivariable adjustment which included the same covariates used in the survival analyses.

DISCLOSURE

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Nephrocare Barcelona, Nephrocare La Florida, Nephrocare La Serena.

FME Colombia:

Armenia, Blas de Lezo, Bocagrande, Cedral Cabecera Bucaramanga, Cedral Foscal Bucaramanga 1, Cedral Foscal Bucaramanga 2, Centro Bosque Medirenal, Clínica de los Andes, Clínica de Occidente 1, Clínica De Occidente 2, Cúcut, Dializar, Fray Bartolomé, Hospital San Vicente de Paul, Hospital Universitario, Imbanaco, Instituto del Riñón, Medirrenal Horizonte, Neiva, San José, Sincelejo, Unidad Renal Ibagué, Unidad Renal Popayán, Unirenal.

FME México:

Medica Sur.

FME Venezuela:

Cabimas, Charavalle, Dpac-Cenesuca, Dpac-El Tigre, Dpac- du Valencia, Dpac-Los Cedros, Dpac-Maracaibo, Dpac-Maturin, Dpac-Puerto La Cruz, Dpac-Jnazart Maracay, El Tigre, Hemodiálisis Cenesuca, Jnazart Caracas, Jnazart Maracay, Los Cedros, Madre Emilia, Majestic, Maracaibo Ctro Del Sol, Rómulo Gallegos, Valencia.

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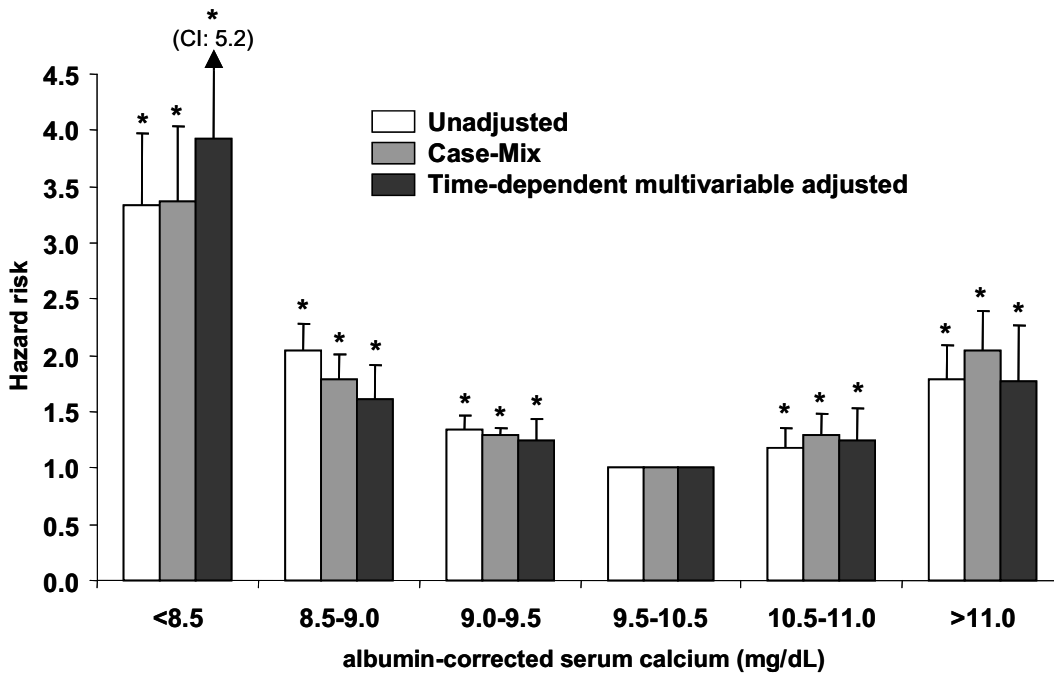
LEGENDS TO FIGURES:

Figure 1: Association between the time-varying serum albumin-corrected calcium values (reference range: 9.50-10.50 mg/dL) in 16,173 haemodialysis (HD) patients followed-up from January 2000 to June 2004 using unadjusted, case-mix and time-dependent Cox models with time-varying repeated measures. * $p < 0.05$ compared with the reference group.

Figure 2: Association between the time-varying serum phosphorus values (reference range: 9.50-10.50 mg/dL) in 16,173 haemodialysis (HD) patients followed-up from January 2000 to June 2004 using unadjusted, case-mix and time-dependent Cox models with time-varying repeated measures. * $p < 0.05$ compared with the reference group.

Figure 3: Association between the time-varying serum PTH values (reference range: 9.50-10.50 mg/dL) in 16,173 haemodialysis (HD) patients followed-up from January 2000 to June 2004 using unadjusted, case-mix and time-dependent Cox models with time-varying repeated measures. * $p < 0.05$ compared with the reference group.

ALL CAUSE MORTALITY



CARDIOVASCULAR MORTALITY

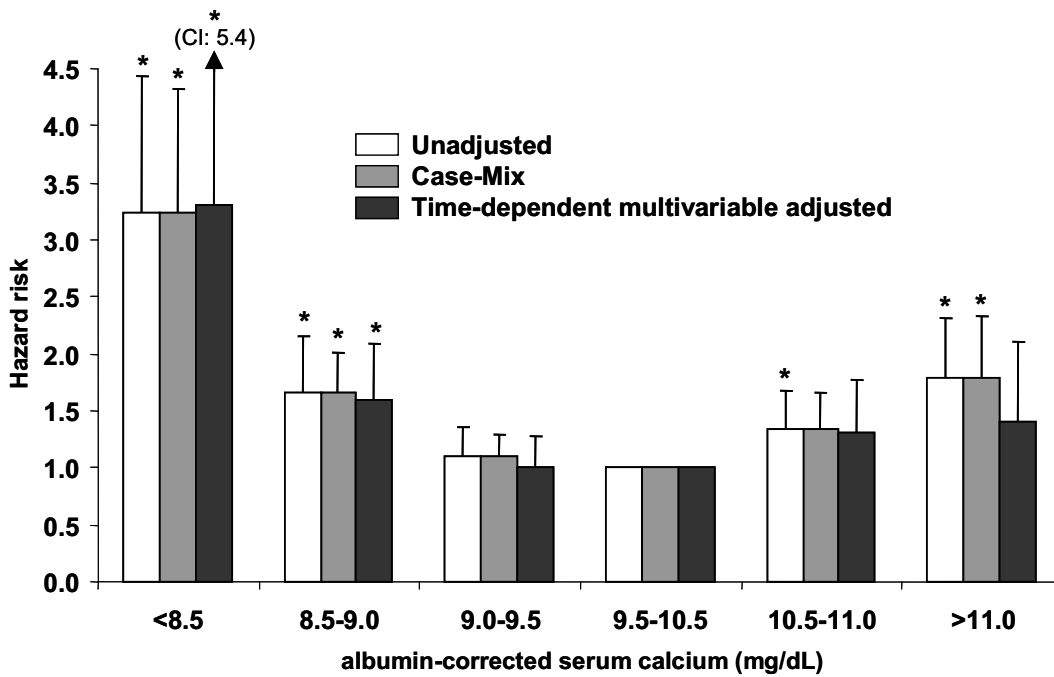
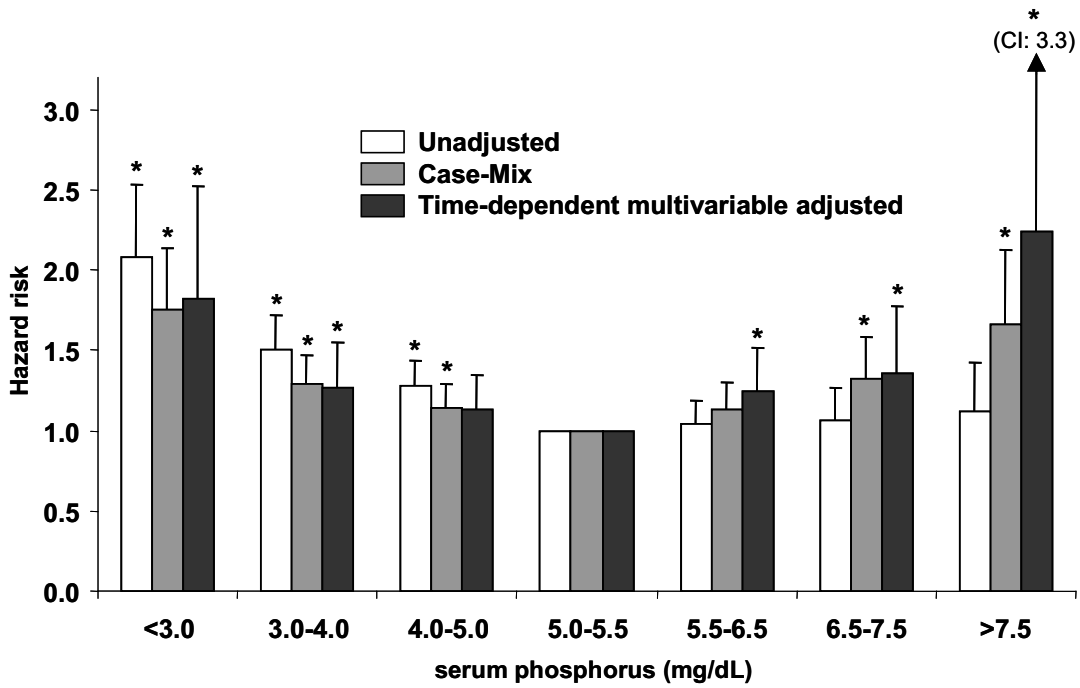


FIGURE 1

ALL CAUSE MORTALITY



CARDIOVASCULAR MORTALITY

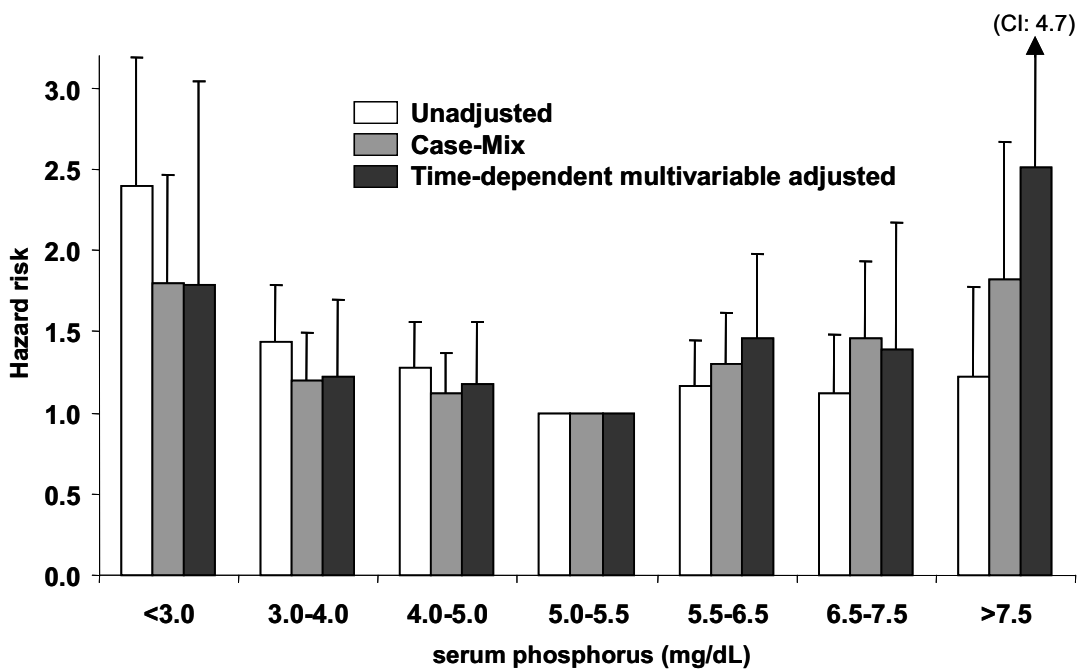
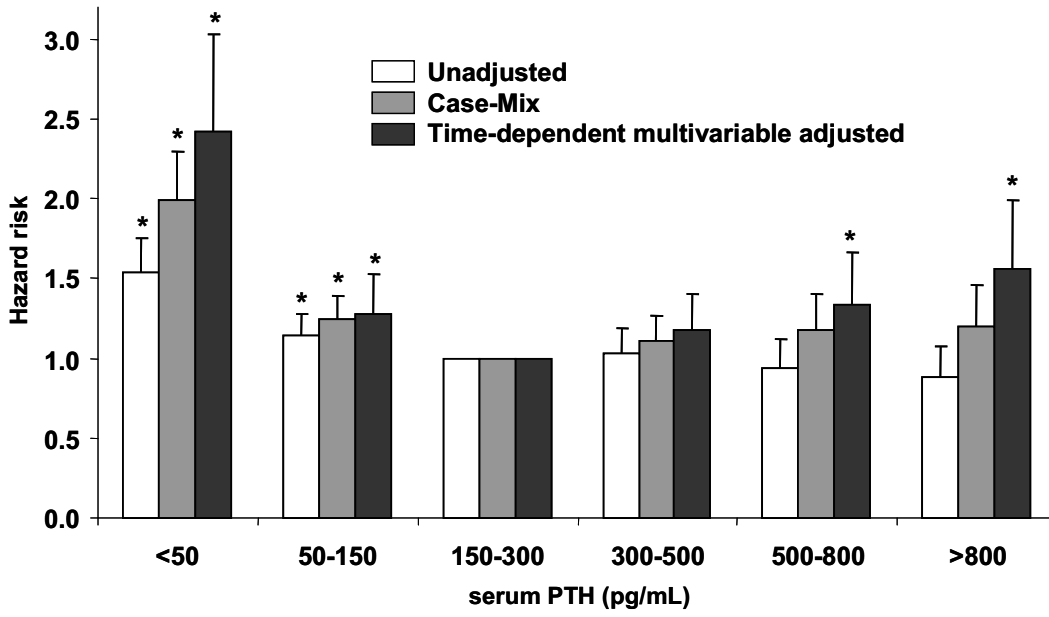


FIGURE 2

ALL CAUSE MORTALITY



CARDIOVASCULAR MORTALITY

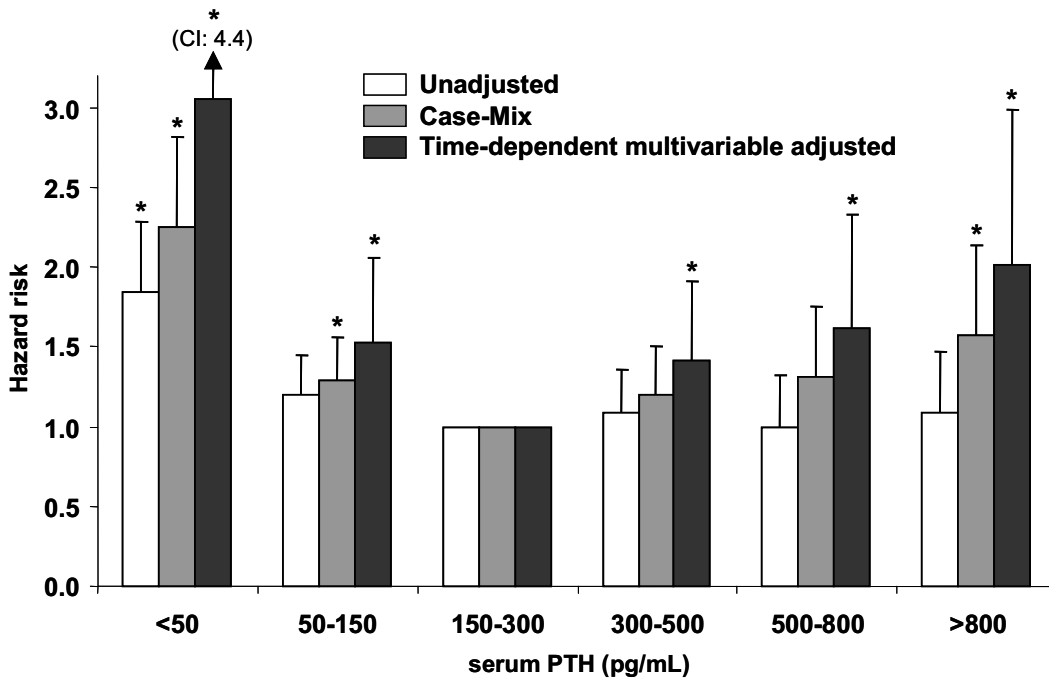


FIGURE 3

Table 1: Patient characteristics by serum albumin-corrected calcium category							
mg /dL (N)	<8.5 (451)	8.5-9.0 (1529)	9.0-9.5 (3433)	9.5-10.5 (6605)	10.5-11.0 (1296)	>11.0 (811)	P-value
Age (years)	55.7	56.1	55.7	54.4	54.1	53.6	<0.001
Gender (% female)	39.2	39.9	42.1	40.6	45.2	44.3	0.010
Diabetes (%)	33.7	35.4	28.6	24.3	18.8	19.2	<0.001
Vintage (years) (median)	1.00	1.48	1.90	2.28	2.55	1.95	<0.001
AV fistula (%)	43.0	46.6	50.9	50.8	50.3	45.3	<0.001
Mortality rate (%)	30.4	25.0	19.5	16.5	19.2	22.9	<0.001
Weight (kg)	64.3	64.6	63.9	64.4	63.9	62.4	0.004
Vitamin D treatment (%)	38.8	46.6	50.8	52.2	51.4	43.9	<0.001
Phosphorus (mg/dL)	4.96	5.04	5.01	5.00	5.07	5.20	< 0.001
PTH (pg/mL)	368	330	294	276	264	293	< 0.001
Albumin (g/dL)	3.48	3.61	3.73	3.82	3.90	3.80	<0.001
KtV	1.27	1.31	1.36	1.35	1.39	1.33	<0.001
Creatinine (mg/dL)	7.76	7.68	7.96	8.38	8.74	8.55	<0.001
Hemoglobin (g/dL)	9.09	9.46	9.78	10.01	10.09	9.92	<0.001
Cholesterol (mg/dL)	173	174	180	183	187	185	<0.001
Ferritin (µg/L) (median)	333	363	372	394	456	429	<0.001
Systolic pressure	138.4	139.3	139.0	139.4	138.1	138.9	0.352
Diastolic pressure	77.77	78.45	78.44	78.94	78.80	78.95	0.082
Phosphate binders (%)	64.8	83.6	81.5	76.9	65.8	53.2	<0.001

Note. P-value represents the chi-square in case of a categorical variable or one way ANOVA among groups in case of a continuous variable.

Table 2: Patient characteristics by serum phosphorus category								
mg /dL (N)	< 3.0 (496)	3.0-4.0 (2466)	4.0-5.0 (4925)	5.0-5.5 (2287)	5.5-6.5 (2907)	6.5-7.5 (1167)	>7.5 (490)	P-value
Age (years)	61.0	58.6	56.9	53.9	51.8	48.6	45.8	<0.001
Gender (% female)	44.4	41.4	42.6	44.6	40.4	37.6	29.0	<0.001
Diabetes (%)	25.6	26.4	28.3	25.4	24.0	21.6	16.7	<0.001
Vintage (years) (median)	1.64	1.77	1.88	2.04	2.16	2.32	2.49	<0.001
AV fistula (%)	36.7	45.0	49.8	50.7	52.2	51.9	46.1	<0.001
Mortality rate (%)	27.8	22.2	20.0	16.3	17.0	17.1	16.9	<0.001
Weight (kg)	58.0	60.0	63.3	64.7	66.8	68.1	70.9	<0.001
Vitamin D treatment (%)	39.1	48.2	49.5	51.7	52.5	44.7	30.8	<0.001
Albumin-corrected calcium (mg/dL)	9.72	9.74	9.74	9.76	9.76	9.81	9.85	0.032
PTH (pg/mL)	162	193	239	300	364	468	531	< 0.001
Albumin (g/dL)	3.57	3.69	3.76	3.80	3.82	3.85	3.89	<0.001
KtV	1.38	1.35	1.34	1.36	1.35	1.32	1.27	<0.001
Creatinine (mg/dL)	6.84	7.13	7.77	8.44	9.05	9.95	10.76	<0.001
Hemoglobin (g/dL)	9.34	9.72	9.88	9.90	9.84	9.97	9.67	<0.001
Cholesterol (mg/dL)	168	177	180	186	186	178	175	<0.001
Ferritin (µg/L) (median)	430	408	379	383	403	384	386	<0.001
Systolic pressure	138.6	137.9	138.2	138.7	140.2	140.8	144.2	<0.001
Diastolic pressure	78.07	78.38	78.19	78.28	79.57	80.49	82.48	<0.001
Phosphate binders (%)	49.2	66.6	75.0	79.6	79.8	72.0	50.2	<0.001

Note. P-value represents the chi-square in case of a categorical variable or one way ANOVA among groups in case of a continuous variable.

Table 3: Patient characteristics by serum PTH category							
mg /dL (N)	< 50 (1663)	50-150 (3446)	150-300 (3125)	300-500 (1862)	500-800 (1003)	>800 (822)	P-value
Age (years)	55.7	56.0	55.9	54.5	51.5	49.6	<0.001
Gender (% female)	40.4	38.5	41.0	42.0	45.5	50.7	<0.001
Diabetes (%)	28.3	27.6	27.8	23.4	17.5	11.2	<0.001
Vintage (years) (median)	1.73	2.01	2.16	2.31	2.73	3.68	<0.001
AV fistula (%)	42.8	51.7	55.6	56.0	56.3	57.3	<0.001
Mortality rate (%)	22.5	19.2	15.2	17.8	16.2	17.4	<0.001
Weight (kg)	60.7	63.3	65.3	67.0	66.2	65.8	<0.001
Vitamin D treatment (%)	38.6	38.1	59.8	72.2	71.3	71.0	<0.001
Albumin-corrected calcium (mg/dL)	10.06	9.80	9.67	9.64	9.67	9.79	< 0.001
Phosphorus (mg/dL)	4.67	4.80	4.97	5.23	5.53	5.86	< 0.001
Albumin (g/dL)	3.75	3.76	3.78	3.82	3.82	3.87	<0.001
KtV	1.37	1.35	1.36	1.35	1.36	1.37	0.519
Creatinine (mg/dL)	7.68	7.97	8.25	8.72	8.98	9.26	<0.001
Hemoglobin (g/dL)	9.90	9.97	10.05	9.98	9.99	9.90	0.009
Cholesterol (mg/dL)	186	182	182	180	180	176	<0.001
Ferritin (µg/L) (median)	423	398	384	382	387	417	<0.001
Systolic pressure	140.7	139.1	138.2	137.0	136.9	137.8	0.023
Diastolic pressure	78.88	78.57	78.23	77.86	77.93	78.69	0.002
Phosphate binders	39.4	77.2	80.2	83.6	80.4	82.0	<0.001

Note. P-value represents the chi-square in case of a categorical variable or one way ANOVA between groups in case of a continuous variable.

Table 4. International Classification of Diseases and Related Health Problems (10th Revision)

Vascular

Diseases of the circulatory system

- I05-I09 Chronic rheumatic fever
- I10-I15 Hypertensive diseases
- I20-I25 Ischaemic heart diseases
- I26-I28 Pulmonary heart disease and disease of pulmonary circulation
- I30-I52 Other forms of heart disease
- I60-I69 Cerebrovascular diseases
- I70-I79 Diseases of arteries, arterioles and capillaries

Infectious

Certain infectious and parasitic diseases

- A00-A09 Intestinal infectious diseases
- A15-A19 Tuberculosis
- A30-A49 Other bacterial diseases
- A50-A64 Infectious with a predominantly sexual mode of transmission
- A65-A69 Other spirochaetal diseases
- A70-A74 Other diseases caused by chlamydiae
- A75-A79 Rickettsioses
- A80-A89 Viral infections of the central nervous system
- A90-A99 Arthropod-borne viral fevers and viral haemorrhagic lesions
- B00-B09 Viral infectious characterized by skin and mucous membrane lesions
- B15-B19 Viral hepatitis
- B20-B24 Human immunodeficiency virus (HIV) disease
- B25-B34 Other viral diseases
- B35-B49 Mycoses
- B50-B64 Protozoal diseases
- B65-B83 Helminthiases
- B90-B94 Sequelae of infectious and parasitic diseases

Diseases of the respiratory system

- J00-J06 Acute upper respiratory infections
- J09-J18 Influenza and pneumonia
- J20-J22 Other acute lower respiratory infectious

Diseases of the skin and subcutaneous tissue

- L00-L08 Infectious of the skin and subcutaneous tissue

Diseases of the musculoskeletal system and connective tissue

- M00-M03 Infectious arthropathies

Diseases of the genitourinary system

- N70-N77 Inflammatory diseases of female pelvic organs

Neoplastic

Neoplasms

- C00-C75 Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue
- C76-C80 Malignant neoplasms of ill-defined, secondary and unspecified sites
- C81-C96 Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue
- D00-D09 In situ neoplasms
- D10-D36 Benign neoplasms
- D37-D48 Neoplasms of uncertain or unknown behaviour

Neurological

Diseases of the nervous system

- G00-G09; G20-G26; G30-G32; G35-G37; G40-G47; G60-G64; G80-G83; G90-G99

Respiratory

Diseases of the respiratory system

- J30-J39; J40-J47; J60-J70; J80-J84; J90-J94; J95-J99

Diabetes

Endocrine, nutritional and metabolic diseases

- E10-E14 Diabetes Mellitus