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BIOMARKERS OF BONE AND MINERAL DISORDERS (FGF-23, FETUIN-A) AND VASCULAR CALCIFICATION SCORES AS PREDICTIVE TOOLS FOR CARDIOVASCULAR DEATH IN DIALYSIS PATIENTS, AT 10 YEARS OF FOLLOW-UP

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Abstract Cardiovascular disorders represent the leading cause of death in dialysis patients. Alterations of bone and mineral metabolism (BMM) and vascular calcifications play a fundamental role in it. The objective of this study was to evaluate the predictive role on cardiovascular mortality of the measurement of biomarkers of BMM and vascular calcifications. A prospective cohort study was performed. All prevalent patients on chronic dialysis in September 2009 at our institution, who completed the total of the complementary studies, were studied. BMM biomarkers were measured (FGF 23, fetuin A, PTH, calcium and phosphorus) and the vascular calcifications were evaluated using the Kauppila and Adragao scores. Follow-up was carried out until 1/1/2019, death or transplant. Of the 30 patients included, 7 (23.3%) died due to cardiovascular causes. The follow-up time was 44.1 ± 30.4 (range = 1.4-112) months. The Adragao score was the only predictive variable of long-term cardiovascular mortality (area under the curve = 0.82; 95% CI 0.64-0.94; p < 0.001). The best cut-off point was 5 (sensitivity = 85.7%; specificity = 78.3%). It was also an independent risk factor for cardiovascular mortality adjusted for age, diabetes mellitus, coronary heart disease, aortic calcifications, time spent on dialysis and follow-up time (adjusted OR = 1.77; 95% CI = 1.06-2.96; p = 0.028). The vascular calcifications quantified from the Adragao score were the only independent predictor of long-term cardiovascular mortality. This score represents a simple, useful and superior tool to the biomarkers of BMM.

Key words: chronic renal failure, bone and mineral metabolism, mortality, vascular calcifications, FGF 23, fetuin A

Resumen ***Biomarcadores del metabolismo mineral óseo (FGF-23, fetuína-A) y calcificaciones vasculares como herramientas predictivas de muerte cardiovascular de pacientes en diálisis, a 10 años de seguimiento***. Los trastornos cardiovasculares representan la primera causa de muerte en los pacientes en diálisis. Las alteraciones del metabolismo óseo y mineral (MOM) y las calcificaciones vasculares juegan un papel fundamental en la misma. El objetivo de este estudio fue evaluar el rol predictor sobre la mortalidad cardiovascular de la medición de los biomarcadores del MOM y las calcificaciones vasculares. Se realizó un estudio de cohorte prospectivo. Se estudiaron todos los pacientes prevalentes en diálisis crónica en septiembre del 2009 en nuestra institución que completaron el total de los estudios complementarios. Se midieron biomarcadores del MOM (FGF 23, fetuína A, PTH, calcio y fósforo) y se evaluaron las calcificaciones vasculares mediante los *scores* de Kauppila y de Adragao. Se realizó un seguimiento hasta el 1/1/2019, la muerte o el trasplante. De los 30 pacientes incluidos, 7 (23.3%) fallecieron por causa cardiovascular. El tiempo de seguimiento fue de 44.1 ± 30.4 (rango = 1.4-112) meses. El *score* de Adragao fue la única variable predictiva de muerte cardiovascular a largo plazo (área bajo la curva = 0.82; IC95% = 0.64-0.94; p<0.001). El mejor punto de corte fue de 5 (sensibilidad = 85.7%; especificidad = 78.3%). Además, fue un factor de riesgo independiente de muerte cardiovascular ajustado por edad, diabetes mellitus, enfermedad coronaria, calcificaciones aorticas, tiempo de permanencia en diálisis y tiempo de seguimiento (OR ajustado = 1.77; IC95% = 1.06-2.96; p = 0.028). Las calcificaciones vasculares cuantificadas a partir del *score* de Adragao fueron el único predictor independiente de mortalidad cardiovascular a largo plazo. Este score representa una herramienta simple, útil y superior a los biomarcadores del MOM.

Palabras clave: insuficiencia renal crónica, metabolismo óseo y mineral, mortalidad, calcificaciones vasculares, FGF 23, fetuína A

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KEY POINTS
Current knowledge

- Cardiovascular disorders represent the leading cause of death in dialysis patients.
- Alteration of FGF 23, fetuin A, PTH, calcium, phosphorus and vascular calcifications play a fundamental role in cardiovascular mortality in these patients.

Contribution of the article to current knowledge

- The vascular calcifications quantified by the Adragao score were the only independent predictor of cardiovascular mortality at 10 years of follow-up in end-stage renal disease patients.
- This score represents a simple, useful and superior tool to the biomarkers of bone and mineral metabolism.

The first cause of death in patients with chronic kidney disease (CKD) is cardiovascular events[1,2]. The risk of their appearance increases progressively according to the stage of CKD, reaching up to 20 times higher than the general population[3]. Data from the Argentine Registry of Dialysis and Transplants reflects something similar, showing that the cardiovascular and cerebrovascular causes represent 46.8% of the total deaths on chronic dialysis in Argentina[4].

Both bone and mineral metabolism (BMM) alterations, and vascular calcifications (VCs) have an important role in long-term mortality in subjects with CKD[5-10].

The VCs detected by simple radiographs of the hands and pelvis have a good correlation with coronary calcifications and vascular territories in dialysis patients. They are also good predictors of hospitalization-free survival, cardiovascular mortality and long-term global mortality[11]. In patients with CKD vascular calcifications occur decades earlier than in the general population and their progression accelerates at the beginning of dialysis treatment[12, 13].

Recent studies found that BMM biomarkers, such as fibroblast growth factor 23 (FGF 23) and fetuin A, can also be predictors of mortality in patients at different stages of CKD[14-16]. In these studies, elevated levels of FGF 23 were associated with mortality, regardless of serum phosphorus values and other known risk factors[14]. Likewise, high levels of fetuin A were significantly associated with lower valve and coronary calcifications and reduced mortality from any cause[17]. However, these biomarkers are not yet available for use in clinical practice in our setting and are used only in the field of research.

It is very useful, for a correct diagnosis and management of these patients, to analyze the risk factors associated with death and cardiovascular events and to know the usefulness of the new BMM biomarkers and the effect of the presence of vascular calcifications to predict events that affect long-term morbidity and mortality.

The objective of this study was to analyze the role of biomarkers of BMM and VCs as predictors of long-term cardiovascular cause mortality, and find the best cut-off point for these biomarkers, in patients with end stage CKD.

Material and methods

A prospective, observational and analytical cohort study was performed.

The inclusion criteria were: patients with end stage CKD in renal replacement therapy for at least three months of permanence prior to inclusion in the study, in the hemodialysis (HD) or peritoneal dialysis (PD) modality, prevalent in September 2009, at the Hospital Privado Universitario de Córdoba.

Subjects under 18 years of age, pregnant women, patients requiring renal replacement therapy for less than three months of stay, or for acute renal failure, or for delayed graft function (in the case of kidney transplants) were excluded. In addition, the patients who were hospitalized at the time of the study, those who refused to participate in it and those who did not complete the total of the required complementary studies were excluded. Among the subjects that met the selection criteria, they were invited to participate voluntarily in the study, after signing the informed consent.

Baseline clinical variables were relieved: age (years), sex, body mass index (kg/m2), modality and time of renal replacement therapy (months), history of arterial hypertension, diabetes mellitus, coronary heart disease, stroke, disease peripheral vascular, etiology of chronic kidney disease and presence of hemodialysis catheter. Biochemical determinations were performed in peripheral blood: hemoglobin (g/dl), albumin (g/dl), calcium (mg/dl), phosphorus (mg/dl), PTH (pg/ml), FGF 23 (pg/ml) and fetuin A (g/l). And different radiographic sets were evaluated to assess the degree of vascular calcifications (Adragao and Kauppila scores).

Each subject was followed up until the kidney transplant, dialysis center change (loss of follow-up), death, until the cut of the study on 1/1/2019 or whichever came first.

Adragao score[18]: It was determined from a simple radiographic set of hands and pelvis, measuring the absence or presence of VCs. Both radiographs were divided into 4 quadrants, giving each quadrant 1 point when the presence of VCs is detected. This score analyzes the presence of VCs of iliac, femoral, radial and digital arteries and the final value ranges between 0 and 8 points (0-4 image of both hands; 0-4 image of hips; where 0 means absence of VCs and 8 presence in all quadrants).

Kauppila score[19]: was determined from a lateral abdominal x-ray that includes from T10 to the first two sacral vertebrae. The aorta is identified as a tubular structure in front of the spine, only the segments of the aorta that are in front of the first four lumbar vertebrae (L1-L4) are analyzed. The score allows to divide into mild calcification (corresponds to 1/3 of the length of the vertebral body), moderate (corresponds to 2/3 of the length of the vertebral body) and severe (more than 2/3 of the vertebral body), according with the length of each calcified plaque detected. The anterior and posterior wall of the aorta is taken into account and a score ranging from 0-24 points is obtained, where 0 means absence of VCs and 24 the presence of these in both walls of the aorta and in the entire length it covers the height of the named vertebrae. All images were evaluated by the same operator.

FGF 23: ALPCO ELISA (enzyme immunosorbent assay) was used, which measures the intact FGF 23 molecule. The assay is a “sandwich” technique that uses two polyclonal antibodies directed towards epitopes of the amino and carboxyl

ends of the FGF23 molecule. Plasma with EDTA is used for the measurement, and samples in freezer were preserved at -70 degrees until measurement.

Ultrasensitive fetuin-A: Ultrasensitive ELISA of ALPCO was used. The assay is a "sandwich" technique that uses two polyclonal antibodies that bind different epitopes of human fetuin-A, for the measurement of fetuin-A serum was used without special preparation of the patient and like the measurement of FGF 23 the samples were preserved in serum at -70 degrees until the time of measurement.

Calcium and phosphorus levels were measured with an autoanalyzer (Hitachi 917; Hitachi, Ltd., Tokyo, Japan) and those of intact PTH with electrochemiluminescence (Nichol`s Institute, San Juan Capistrano, Calif., USA).

To analyze the categorical variables, absolute (n) and relative (%) frequencies were used, and for continuous variables, mean (X) and standard deviation (SD), or median (M) and interquartile range (IQR), as appropriate. To compare the categorical variables, the X^2 test or Fisher's exact test was used, as appropriate.

As predictors of mortality, the values of calcium, phosphorus, PTH, FGF 23, Fetuin-A, Kauppila score and Adragao score were evaluated. The area under the curve (AUC) of the ROC (receiver operating characteristic) curve analysis and its 95% confidence interval (95% CI) was used. The calculation of the AUC was performed using the method of Hanley and Mac Neil. ROC curves were plotted. Of the predictive variables with statistical significance, the best cut-off point was established using the Youden Index J criterion[20]. In turn, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive value were evaluated. The risk of cardiovascular mortality from the best cut-off point was quantified using the relative risk (RR) with its 95% CI.

The association between all the variables included in the database and the best predictive tool for cardiovascular mortality were analyzed. To evaluate the association between continuous variables, Pearson's correlation (r) was used and for the dichotomous variables the odd ratio (OR) with its 95% CI. Both the best predictive tool for cardiovascular mortality, and its associated variables, were included in the multivariate logistic regression analysis. To this analysis the variables were added: months of permanence in dialysis at the beginning of the study and months of follow-up at the end of the study, at the discretion of the researcher, regardless of the previous association analysis.

All tests were two-tailed and a value of p less than 0.05 was considered statistically significant.

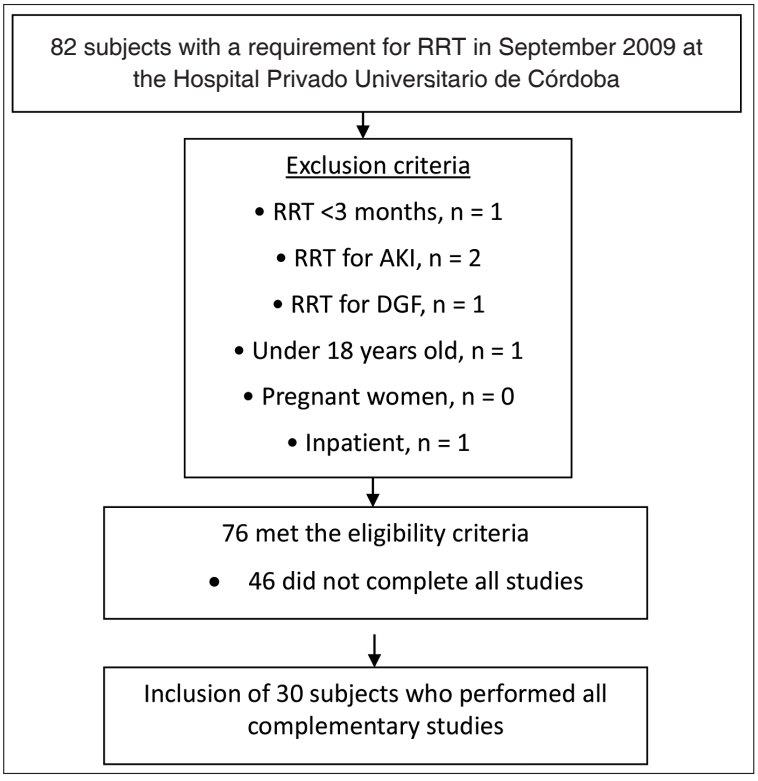
Statistical analysis was performed with the Stata 14 program (StataCorp. LP. College Station, TX) and Medcalc 15.11.4 (MedCalc Software, Ostend, Belgium).

The study was approved by the Research Committee of the Private University Hospital of Córdoba (number 2018_53).

Results

Of the 82 patients undergoing renal replacement therapy at our institution in September 2009, six met some exclusion criteria (One had started renal replacement therapy less than 3 months before, two with acute renal failure, one with delayed function of the graft, one under 18 years old and one hospitalized patient). Of the 76 that met the eligibility criteria, 30 subjects complied with all necessary complementary studies. All of them agreed to participate in the study (Fig. 1). Baseline characteristics, pathological

Fig. 1.– Flow chart of the inclusion of the subjects in the study



RRT: renal replacement therapy; AKI: acute kidney injury; DGF: delayed graft function

personal history, specific dialysis characteristics, blood tests in general and specific bone mineral metabolism, and calcification scores of the subjects are summarized in Table 1.

At the end of the follow-up, of the 30 patients, 11 (36.7%) had received a kidney transplant, 2 (6.7%) continued on chronic dialysis, 17 (56.7%) had died, and of these 7 (41.2%) were due to cardiovascular causes. The average follow-up time was 44.1 ± 30.4 months (range = 1.4-112 months).

In the ROC analysis, although calcium (AUC = 0.69; p = 0.082), phosphorus (AUC = 0.61; p = 0.465), PTH (AUC = 0.65; p = 0.175), FGF 23 (AUC = 0.68; p = 0.175), Fetuin-A (AUC = 0.61; p = 0.433) and the Kauppila score (AUC = 0.61; p = 0.461) had high AUC values, the same they did not reach statistical significance to predict long-term cardiovascular death. The only predictive variable in the ROC analysis for cardiovascular death was the Adragao score (AUC = 0.82; 95% CI = 0.64-0.94; p < 0.001) (Table 2). Figure 2 shows the ROC curves of the different variables in predicting cardiovascular mortality.

According to the Youden Index J analysis, the best cut-off point for the Adragao score to predict cardiovascular mortality was 5 points or more, with a sensitivity of 85.7%, specificity of 78.3%, positive likelihood ratio of 3.94, negative likelihood ratio of 0.18, a positive predictive value of 54.5% and a negative predictive value of 94.7%.

The incidence of cardiovascular death in the group of patients with an Adragao score below 5 points was 5.3% (1/19) and in the group with a score of 5 points or more, it was 54.6% (6/11), there being a significant difference between both groups (p = 0.002). Subjects with an Adragao score of 5 points or more have a 10-fold higher risk of cardiovascular mortality than those with a score lower than 5 (RR = 10.36; 95% CI = 1.4-75.2; p = 0.002).

Of all the variables included in our database, the only ones associated with an increase in the Adragao score were: age (r = 0.43; p = 0.018), Kauppila score (r = 0.39; p = 0.034), the history of diabetes mellitus (OR = 10.2; p = 0.008) and coronary heart disease (OR = 7.1; p = 0.029). In multivariate analysis, Adragao score was a predictive tool for cardiovascular death regardless of the variables mentioned above, and also adjusted for the time spent on dialysis at the beginning of inclusion in the study and follow-up time during the study (Adjusted OR = 1.77; 95% CI = 1.06-2.96; p = 0.028) (Table 3).

TABLE 1.– *Baseline demographic and laboratory data of the population studied*

Baseline characteristics	All (n:30)
Age (years), X ± SD	56.3 ± 15.2
Male sex, n (%)	20 (66.7)
Body mass index (Kg/m2), X ± SD	25.8 ± 4.9
Obesity, n (%)	5 (16.7)
Smoking, n (%)	5 (16.7)
Hypertension, n (%)	22 (73.3)
Diabetes, n (%)	8 (26.7)
Coronary disease, n (%)	7 (23.3)
Peripheral vascular disease, n (%)	9 (30)
Stroke, n (%)	3 (10)
Etiology of chronic kidney disease	
- Diabetes	8 (26.7)
- Nephroangiosclerosis	8 (26.7)
- Glomerulonephritis	3 (10)
- Renal polycystosis	2 (6.7)
- Others	9 (30)
Peritoneal dialysis, n (%)	2 (6.7)
Hemodialysis, n (%)	28 (93.3)
Time in renal replacement therapy (months), X ± SD	52.7 ± 72.9
Hemodialysis catheter, n (%)	5 (16.7)
Hemoglobin (g/dl), X ± SD	10.7 ± 1.7
Albumin (g/dl), X ± SD	3.8 ± 0.4
Calcium (mg/dl), X ± SD	8.4 ± 0.7
Phosphorus (mg/dl), X ± SD	5.2 ± 1.8
Parathyroid hormone (pg/ml), X ± SD	445.9 ± 472
FGF 23 (pg/ml), X ± SD	178.2 ± 212
Fetuin A (g/l), X ± SD	0.50 ± 0.29
Adragao score, X ± SD	3.97 ± 2.93
Kauppila score, X ± SD	5.47± 6.46

X: mean; SD: standard deviation; FGF 23: fibroblast growth factor 23

Discussion

Cardiovascular disease is the leading cause of death in patients with CKD on dialysis[1-4] and alterations in BMM and VCs play an important role in its development.

TABLE 2.– *Ability to predict cardiovascular mortality of the different methods according to the area under the ROC curve*

Predictor variables	AUC (95% CI)	p
Calcium (mg/dl)	0.69 (0.49-0.84)	0.082
Phosphorus (mg/dl)	0.61 (0.42-0.78)	0.465
PTH (pg/ml)	0.65 (0.45-0.81)	0.175
FGF 23 (pg/ml)	0.68 (0.48-0.83)	0.175
Fetuin A (g/l)	0.61 (0.41-0.78)	0.433
Adragao score	0.82 (0.64-0.94)	< 0.001
Kauppila score	0.61 (0.41-0.78)	0.461

AUC: area under the curve; 95% CI: 95% confidence interval; PTH: parathyroid hormone; FGF 23: fibroblast growth factor 23

Fig. 2.– ROC curves to predict cardiovascular mortality of: A: Calcium. B: Phosphorus. C: FGF 23. D: Fetuin A. E: PTH. F: Kauppila score. G: Adragao score.

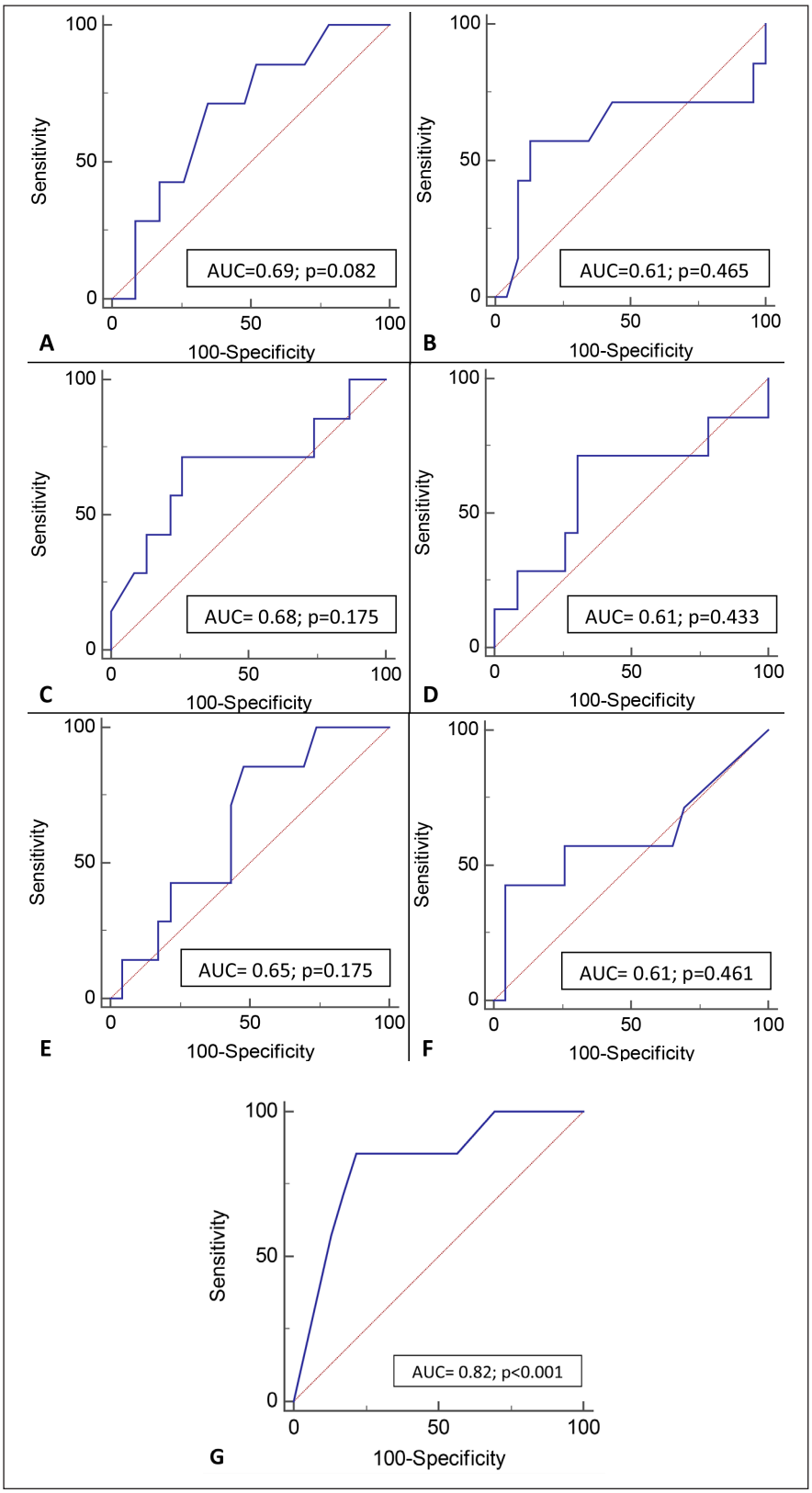


TABLE 3.– *Association between the Adragao score and cardiovascular mortality, adjusted for the possible confusing variables. Multivariate logistic regression analysis*

Cardiovascular mortality	aOR (95% CI)	p
Adragao score	1.88 (1.07-3.32)	0.029
Age (years)	0.94 (0.83-1.07)	0.385
Diabetes	1.46 (0.09-23.4)	0,789
Coronary heart disease	1.16 (0.07-20.3)	0.918
Kauppila score	1.08 (0.85-1.38)	0.531
Months on dialysis at the start of the study	0.98 (0.95-1.01)	0.238
Follow-up months	0.97 (0.92-1.03)	0.327

aOR: adjusted Odds Ratio; 95% CI: 95% confidence interval

Over time, new molecules involved in MOM and in the physio pathogenesis of VCs such as FGF 23 and Fetuin A have been discovered. According to recent studies, both high FGF 23 values and decreased Fetuin A values increase the risk of cardiovascular events[21-23] and death[14-16] in patients with CKD. Currently, serum determination of these markers is expensive and there is little availability for use in clinical practice. In our study, neither of the two determinations was useful to predict cardiovascular mortality over time in patients with terminal CKD in different dialysis modalities.

In Argentina, there is a high prevalence of VCs in subjects with CKD on dialysis detected by plain radiography[24]. A recent meta-analysis shows that the Kauppila score is a significant predictor of all-cause mortality and cardiovascular events in dialysis patients[25]. However, this score does not appear to be higher than the Adragao score to predict mortality [26], as our study also shows. Adragao et al.[18] showed that patients with CKD in hemodialysis who have an Agragao score greater than 3 have almost four times greater risk of cardiovascular mortality than those with a lower score. This paper also evaluates the role of the phospho-calcium product and PTH in cardiovascular mortality, but not of FGF 23 and fetuin A, since at the time of that study, these molecules were still poorly understood. In our trial, the cut-off point of the Adragao score with the best predictive capacity for cardiovascular death was somewhat higher than 3 points (5 points or more), with a risk of cardiovascular death increased 10 times in these patients. This tool was superior in predictive capacity not only of the traditional MOM analytical determinations such as calcium, phosphorus and PTH, but also of the new biomarkers such as FGF 23 and Fetuin A, and that the Kauppila score.

It is important to keep in mind that while BMM biomarkers reflect the risk to which an individual is exposed at the time of measurement[27], VCs images quantified from the scores represent the cumulative result of prolonged exposure to multiple factors of risk over time[28].

The increase in the Adragao score was associated with traditional clinical variables such as age, history of diabetes mellitus and coronary heart disease, and also calcifications in other territories such as the aorta (Kauppila score). Like the time spent on dialysis at the beginning of each patient's study and the follow-up time at the end of the study, these variables mentioned above could also be risk factors for cardiovascular death and therefore could function as confounding factors for predictive ability of the Adragao score on cardiovascular death. To avoid this bias and evaluate the true role of the score, the adjusted multivariate analysis was performed taking into account all these variables and thus demonstrating their true utility.

Both the recommendations of the Spanish Society of Nephrology in 2011[29], the Argentine Society of Nephrology in 2017[30], the KDIGO guides in 2017[31], and other authors[28, 32] consider reasonable the use of VCs information to guide the management of BMM alterations.

The main strengths of our study are the evaluation of new biochemical markers of BMM such as FGF 23 and fetuin A, as there are few publications evaluating these measurements in dialysis patients as predictors of cardiovascular mortality, and prospective follow-up with prediction of long-term hard events.

In conclusion, vascular calcifications quantified from the Adragao score were the only independent predictor of long-term cardiovascular mortality. The best cut-off point for the Adragao score was 5, with a high predictive value. This score represents a simple, low cost, useful, accurate and superior tool to the new BMM biomarkers.

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Conflict of interest: None to declare

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