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## Risk of fracture according to FRAX<sup>®</sup>, hypovitaminosis D, and quality of life in a population with osteoporotic fracture cared for in primary care: baseline description of the VERFOECAP cohort

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### Summary

**Background:** the patient with an osteoporotic fracture cared for in primary care has seldom been studied. The VERFOECAP study has dual objectives: to estimate if the risk of fracture (FRAX<sup>®</sup>) in fractured patients is different in patients with or without a re-fracture; and to study the prevalence of hypovitaminosis D and the impact of the fracture on quality of life. We present a baseline description.

**Material and method:** design and ambit: multicentred prospective cohort study in primary care (12 centres in Catalonia). Population: random sample of patients with a history of principal osteoporotic fracture between 2006 and 2008 cared for in primary care. Information gathering: at initial inclusion meetings clinical information was gathered, quality of life questionnaires ECOS16 (specific) and EuroQol-5D (generic) completed, spinal X-ray carried out, and levels of vitamin D in the blood measured. Subjects were followed up for two years. Analysis: comparison between two groups using T-test or chi-squared test. Prevalence of hypovitaminosis D and confidence interval using binomial test.

**Results:** 194 patients were included. The average risk (standard deviation) of fracture of the hip, according to FRAX<sup>®</sup> was calculated as: 6.9% (6.4), and of principal osteoporotic fractures: 14.8% (8.6). EuroQol-5D showed frequent limitations to walking (47.6%) and to daily activities (45.5%); 55.0% reported moderate pain, and 41.0% anxiety/depression. The ECOS-16 score was higher in patients with a history of vertebral fracture ( $p < 0.001$ ). The prevalence of hypovitaminosis D was 61.4% (CI 95%: 53.6%-68.9%).

**Conclusions:** the VERFOECAP cohort includes patients with osteoporotic fractures cared for in primary care at high risk of re-fracture with significant deterioration in quality of life. In these patients vitamin D deficiency is highly prevalent.

**Key words:** osteoporosis, primary care, vitamin D, osteoporotic fractures, risk factors, FRAX<sup>®</sup>, therapeutic compliance.

## Introduction

Osteoporosis is a chronic process characterised by low bone mass and alterations in microarchitecture which result in bone fragility and, therefore, a high probability of suffering fractures<sup>1</sup>. It is a silent pathology until the moment a fracture occurs, which means that the evaluation of individual risk of osteoporosis is important for the prevention of their occurrence. It is, in addition, a common disease which mainly affects people in developed countries such as in North America, in Europe and Japan; in general terms it is estimated that 33% of women over 50 years of age will suffer from osteoporosis during their lifetimes<sup>2</sup>. The prevalence of osteoporosis increases with age. In Spain the global prevalence of osteoporosis in the femoral neck is 4.3%, and in the lumbar spine, 11.3%. In the population of Spanish women over 50 years of age, the prevalence of femoral osteoporosis would be around 9% and in the lumbar region, it would exceed 23%<sup>3</sup>.

The measurement of bone mineral density by means of densitometry with DXA (dual source X-ray absorptiometry) was previously considered by the WHO<sup>4</sup> as a valid method of diagnosis, capable of predicting the risk of fracture. However, certain limitations have been found, such as the fact that different populational cohorts<sup>5,6</sup> show that 50% of women with fractures are classified, according to the WHO, as normal or osteopenic, which means that the BMD used as the single determinant does not identify well the risk of suffering a fracture<sup>7</sup>. In addition, it is not a method which is available in all geographic areas. In the year 2007, the WHO published a new document<sup>4</sup> in which it recognised the need to include clinical risk factors in the assessment of risk of fracture, with those considered to be the main ones being age, previous personal or family history of fractures, the use of corticoids over long periods, sedentary life-style and active smoking<sup>8</sup>.

After the publication in 2008 of the FRAX<sup>®</sup> scale<sup>9</sup>, this has become a good tool for identifying the absolute risk at 10 years of suffering both a fracture of the hip, as well as other principal fractures (clinical vertebral, humerus and forearm fractures). This is based on the aforementioned risk factors, and may include the DXA value, if available. One of the current needs is to confirm the usefulness of this scale in each of the different populations before introducing it into routine practice in primary care.

Hence, the VERFOECAP (Evaluation of the FRAX<sup>®</sup> risk scale in established osteoporosis in primary care in Catalonia) cohort study was designed with the main aim of confirming if there were differences in FRAX<sup>®</sup> risk between patients who suffered fractures during the follow up and those who did not. In addition, secondary objectives were set, which were to determine the prevalence of hypovitaminosis D in the population of those with fragility fractures seen in primary care, and to assess the impact of osteoporotic fractures on quality of life. We present here the baseline description of this cohort.

## Patients and methods

**Design:** prospective, multi-centred cohort study: VERFOECAP cohort. We present the baseline description of the patients recruited.

**Ambit:** carried out in twelve urban primary care centres in Catalonia.

**Sample size:** accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, and assuming an annual incidence of fracture of 2% (20% at 10 years on average according to the FRAX<sup>®</sup> estimate) 190 subjects were required to detect a difference equal to or greater than a standard deviation between groups (patients with incident fractures versus those who did not suffer fracture during the follow up period) in the variable "absolute risk of fracture estimated according to the FRAX<sup>®</sup> tool". A forecast rate of loss during the follow up period of 15% has been taken into account. With respect to one of the secondary objectives, accepting an alpha risk of 0.95, in a bilateral contrast for the prevalence of vitamin D insufficiency estimated at 7%, according to the literature<sup>10</sup>, a randomised sample of 81 subjects would be sufficient to ensure a precision of 10% in our estimate.

**Participants:** using each centre's computerised clinical history records system (eCAP program), lists of patients were obtained of both sexes, and aged between 40 and 90 years of age, of Spanish nationality, and who had had a principal fragility fracture between January 2006 and December 2008 in the humerus, distal radius, vertebrae, hip or pelvis (see the list of CIE-10 codes used in Appendix 1).

The participant population was selected using simple randomised sampling. Patients whose telephone contact details were not available, those with dementia or serious psychiatric illness, those who were suffering from terminal illness or who were being cared for at home, those who had had in the last year a weight loss of more than 10% or who had a history of any disease which might cause secondary osteoporosis (except for corticotherapy and rheumatoid arthritis, both included in the FRAX<sup>®</sup> tool) were excluded.

Each patient was contacted by telephone to confirm that the fracture was a fragility fracture, that the location of the fracture was correct, that it had occurred in the period indicated and that they complied with the inclusion criteria. The affirmative cases were invited for an interview with a researcher at which the objectives of the study were explained, and in cases where the subject was interested in participating they were asked to give their informed consent. This study was presented to and approved by the clinical research ethics committee (CEIC) of the Jordi Gol IDIAP.

## Information gathering:

By means of a clinical interview, information was gathered on the location of fragility fractures, record of personal history of osteoporosis and previous densitometry, use of anti-osteoporosis treatment or calcium and vitamin D supplements and

compliance with the former (using the Morinsky-Green and Haynes-Sackett tests), number of falls in the last year, and variables necessary for the calculation of the FRAX® risk of fracture (age, sex, weight in kilograms and height in centimetres measured at the inclusion visit, active smoking, consumption of alcohol above 3 standard units a day, paternal/maternal family history of hip fracture, presence of rheumatoid arthritis or corticotherapy above 5 mg/day of prednisone or equivalent for more than 3 months). The probability of having a hip fracture or principal osteoporotic fracture at 10 years was calculated according to the on-line FRAX® tool for the Spanish population [<http://www.sheffield.ac.uk/FRAX/tool.jsp?lang=spl>]. The impact of the fractures on quality of life was also measured using generic (EuroQol-5D) and specific (ECOS-16) questionnaires<sup>11,12</sup>. The intake of calcium in the diet was assessed using the validated survey INDI-CAD<sup>13</sup>. Finally, lateral X-rays of dorsal and lumbar spine in lateral projection were requested to discount earlier silent fractures, and an analysis was carried out to discount secondary causes of osteoporosis, measuring the following parameters: 25-hydroxyvitamin D-25(OH)D-, calcium, phosphorus, albumin, alkaline phosphatase, creatinine, glomerular filtration rate estimated by MDRD-4, velocity of sedimentation and thyroid function. In case where a secondary cause appeared the patient was excluded but offered the same follow up as those included.

### Statistical analysis:

The characteristics of the population studied are described by means of univariate descriptive analysis, calculating mean and standard deviation for the continuous variables, and absolute frequency and percentage for the variable categories. To find the distribution of risk factors associated with suffering a fracture, bivariate comparisons were made using the chi squared test between categorical variables and the student's T test between continuous and categorical variables. All the statistical tests were carried out with a confidence of 95% and assuming a bilateral contrast. The SPSS statistical software package was used.

### Results

194 patients were included, recruited in twelve primary care centres in Catalonia. The baseline

Table 1. Baseline characteristics of the VERFOECAP cohort

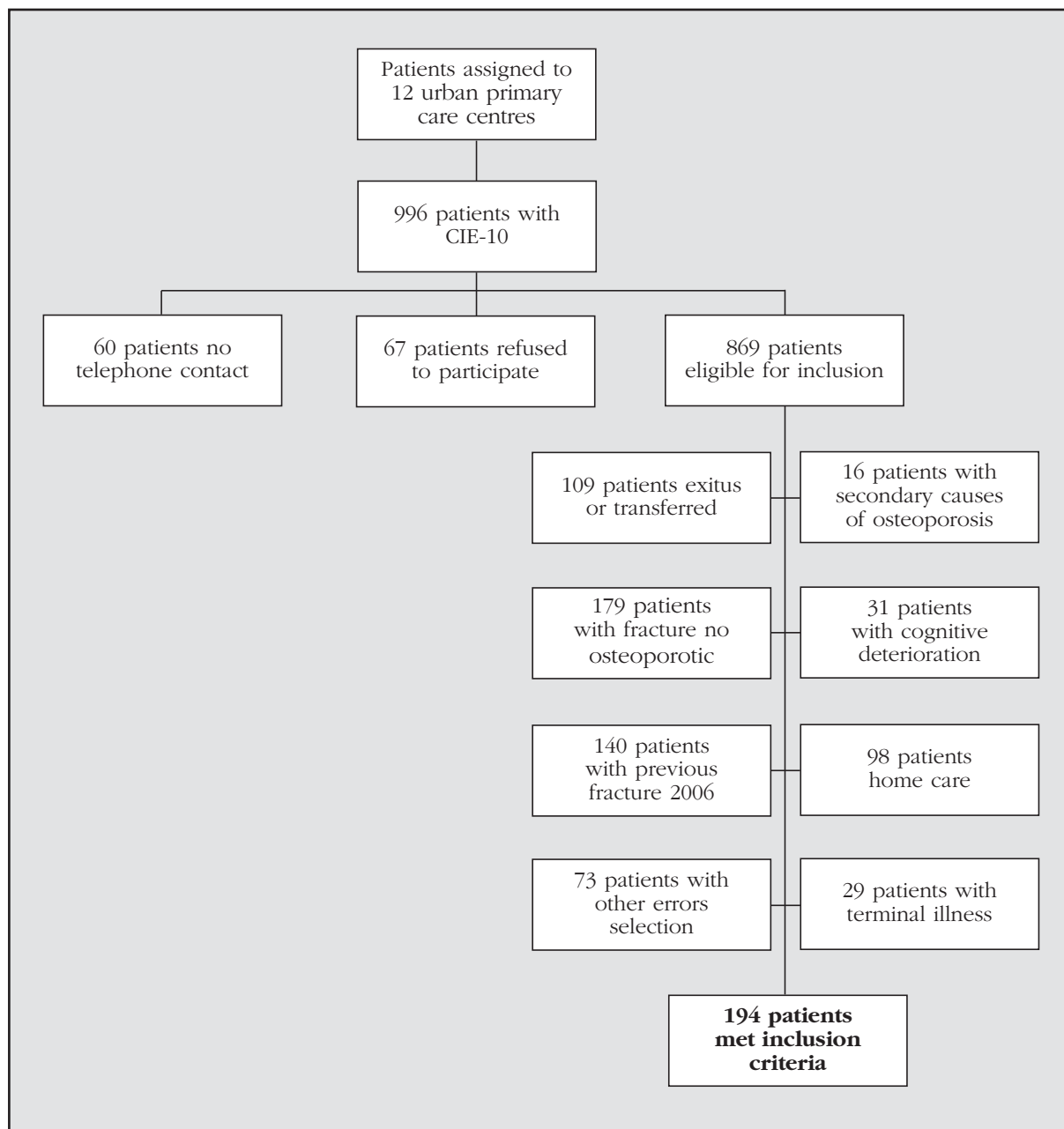
<b>Age (years): mean, SD</b>	74	9.1
<b>Male gender: n, %</b>	26	13.4
<b>Height (m): mean, SD</b>	1.54	0.08
<b>Weight (kg): mean, SD</b>	68	12.4
<b>BMI (kg/m<sup>2</sup>): mean, SD</b>	28.6	4.8
<b>Low weight (BMI&lt;19 kg/m<sup>2</sup>): n, %</b>	4	2.1
<b>Normal weight: n, %</b>	37	19.0
<b>Overweight: n, %</b>	88	45.4
<b>Obesity I: n, %</b>	46	23.7
<b>Obesity ≥II: n, %</b>	19	9.8
<b>Patients on antiosteoporotic drugs: n, %</b>	129	66.5
<b>Oral bisphosphonates</b>	104	80.6
<b>Iv bisphosphonates</b>	4	3.1
<b>Strontium ranelate</b>	15	11.6
<b>PTH</b>	4	3.1
<b>Calcitonin</b>	2	1.6
<b>Years of treatment: mean, SD</b>	2.4	2.8
<b>Calcium supplements: n, %</b>	127	65.5
<b>Vitamin D supplements: n, %</b>	124	63.9

characteristics of the population included are shown in Table 1. The flow diagram of the population included can be seen in Figure 1.

In 143 cases (74.9%) densitometry had been requested, and in 80 (41.2%) the results of the test had been recorded. Only 7 (8.8%) patients had normal BMD, 48 (59.9%) had osteopenia, and the remaining 25 (31.3%) showed values compatible with osteoporosis (Figure 2).

On analysing the risk factors for fracture included in the FRAX® calculation, 157 patients (80.9%) were over the age of 65, 168 (86.6%) were women, 35 (20.8%) had early menopause, 45 (23.2%) had paternal history of hip fracture, 15 (7.7%) were active smokers, 9 (4.6%) consumed more than 3 standard units/day of alcohol, 7 had received corticotherapy, 4 (2.1%) had a BMI ≤ 19 kg/m<sup>2</sup> and 4 (2.1%) had a history of rheumatoid arthritis. Out of all the cases, 113 (61.4%), 39 (21.2%), 5 (2.7%) and 3 (1.6%) cases had 3, 4, 5

Figure 1. Scheme of the study. Population flow



and 6 accumulated risk factors, respectively. The mean (standard deviation) of the absolute risks of fracture estimated at 10 years according to FRAX<sup>®</sup> was 6.9% (6.4) and 14.8 (8.6) for hip and principal fracture, respectively. Table 2 shows the median and interquartile range of FRAX<sup>®</sup> risk in the total population, according to number of prevailing fractures, and by age groups, and the number and percentage of patients with risk higher than the therapeutic threshold proposed by the British NOGG (National Osteoporosis Guidelines Group) guide, and the European guide to osteoporosis. 89.7% of the participants had an estimated risk of fracture of the hip which exceeded the therapeutic

threshold proposed in these guides. In addition, of the 194 patients included, all with previous fracture, 59 (20.1%) had two fractures, and 23 (11.9%) three or more fractures. The most prevalent fractures were vertebral, followed by those of the humerus (Table 3). After reviewing the dorso-lumbar spinal X-ray from the baseline visit, it was observed that 18.8% of the cases with vertebral fracture had more than one vertebra affected. The absolute risk of fracture estimated according to FRAX<sup>®</sup> was not significantly different between those patients with one or more fractures ( $p=0.39$  for FRAX<sup>®</sup> for the hip and  $p=0.43$  for FRAX<sup>®</sup> for the principal fracture) (Table 2).

The impact on quality of life in relation to health (ICVRS) of the fractures in our patients measured using the EuroQol-5D questionnaire showed limitations in walking in 47.6%, in personal care in 20.4% and in daily activities in 45.5%; 55.0% reported moderate pain or discomfort, and 13.6% heavy pain or discomfort; 41% reported anxiety or depression.

The mean (standard deviation) of the ECOS-16 score was 2.03 (0.96). In those patients with previous vertebral fracture, the ECOS-16 score was significantly higher than in those patients with fractures in other places ( $p < 0.001$ , with an average difference of 0.62 [CI 95%: 0.39-0.85]).

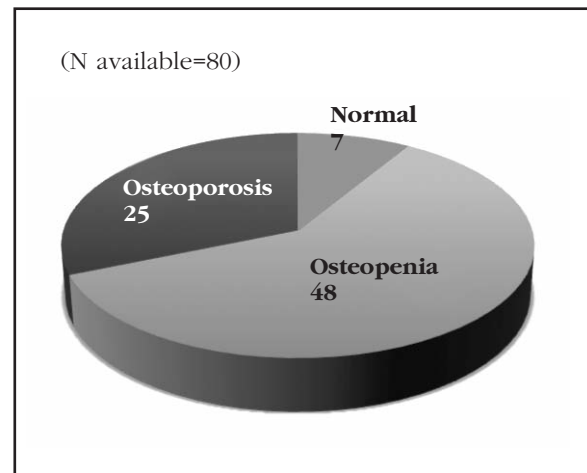
In those patients who were already receiving a drug for the treatment of osteoporosis, the declared compliance level was 63.4% with the Morinsky-Green test, and 77.8% with the Haynes-Sackett test (Kappa index 0.54;  $p < 0.001$ ).

Of the 166 patients in whom the levels of 25(OH)D had been determined, the mean value (standard deviation) was 31.3 (23.3) ng/ml. 102 patients (61.4% [CI 95%: 53.6%-68.9%]) had levels compatible with vitamin D insufficiency, in 47 (28.3%) with a deficit (below 20 ng/ml) and in 14 (8.4%) with a severe deficit (below 10 ng/ml). The levels of 25(OH)D were significantly higher in the 106 patients who took calcium and vitamin D supplements (51 patients -48%- took 800 units/day, and 55 patients -52%- took 400), than in those 60 patients who did not take them ( $p < 0.001$  with an average difference of 13.5 ng/ml [CI 95%: 6.2 - 20.9]). No significant differences were found in levels of blood vitamin D between those patients with a single fracture and those with two or more ( $p = 0.91$ ) (Figure 3), or between the different places in which the fractures had occurred ( $p = 0.16$ ).

## Discussion

This study shows the clinical characteristics, the risk factors and the impact on the quality of life of osteoporotic fractures in primary health care and in the Spanish population. This consists of patients with a high risk profile for future fractures: 75% had osteoporosis, more than 80% were over 65 years of age and female, and nearly a quarter had paternal/maternal history of hip fracture. In terms of future risk of new fractures estimated by the FRAX® tool, the majority (more than 65%) had at least three of those risk factors included in the tool, and the absolute risk of re-fracture at 10 years, estimated according to the same formula, was around 7% and 15% on average for hip and principal fractures, respectively. Although there are no established risk thresholds for FRAX® in this country, some authors work with the thresholds proposed for the United Kingdom<sup>14</sup>. Almost 90% of patients included had an average risk above that of the treatment threshold according to FRAX® of the hip proposed in the last European guide to osteoporosis<sup>15</sup>, and in the British NOGG guide<sup>16</sup>. It is remarkable that despite consisting of patients at high risk and existing fractures, a third of the population recruited did not take any treatment to

Figure 2. Bone mineral density in the VERFOECAP cohort according to WHO criteria



prevent fractures occurring. In addition, of those patients which did take them, nearly 40% were not compliant (with a moderate agreement between the two tests used).

With respect to the prevalence of fractures in these patients, almost a third of them had at least two fractures. Those patients with two or more fractures did not have a higher FRAX® risk than those with only one fracture, which suggests that this tool does not discriminate well with high risk patients, in addition to the fact that it does not take into account the number of fractures, rather the history of fracture (yes or no) as a risk factor. This has been criticised as one of the limitations of FRAX®<sup>17</sup>, since, as the literature shows, the number and severity of existing fractures are related to the risk of future fractures<sup>18</sup>.

We also found that there were few patients (scarcely 2%) with low weight, and in contrast, a high proportion (more than a third) of obese patients with fractures in this cohort. This is consistent in the work recently published by Premaor et al.<sup>19</sup> which highlights the possibility that the association between the body mass index and fracture is complex, and that obese patients also have a high a risk of fracture, in particular in some specific locations, such as in the upper extremities.

With regard to the prevalence of hypovitaminosis D, we showed that in the VERFOECAP cohort this is higher than 60%, a datum consistent with other studies which analysed levels of vitamin D in the blood in a population with fractures treated in hospital for hip fracture in the same region<sup>10</sup>.

Also significant is the high impact observed in this population in terms of quality of life: almost half the patients recruited had limitations in walking and daily activities, pain or discomfort, and anxiety or depression. This has been shown in different studies which included populations treated in hospital<sup>20</sup>, and, recently, in a populational study carried out in Valencia<sup>21</sup>.

Table 2. Absolute risk of fracture at 10 years according to the FRAX® tool in the population of the VERFOECAP cohort

		Risk FRAX® of principal fracture		Risk FRAX® of hip fracture	
		Median (range inter-quartile)	N (%) nogg above threshold	Median (range inter-quartile)	N (%) nogg above threshold
<b>Total population (N=194)</b>		14.0 (7.9-20.0)	22 (11.3)	5.2 (2.4-9.4)	174 (89.7)
<b>By background fracture (No. of fractures)</b>	1	13.0 (7.1-20.3)	13 (9.8)	4.9 (2.1-9.2)	118 (89.4)
	2	14.0 (8.9-20.0)	4 (10.3)	5.2 (2.7-10)	36 (92.3)
	≥3	19.0 (8.6-22.0)	5 (21.7)	7.4 (2.9-9.3)	20 (87.0)
<b>By age (years)</b>	≥50 a <55	7.0 (4.0-10.0)	1 (50.0)	2.5 (0.7-4.3)	2 (100)
	≥55 a <60	8.2 (6.5-9.4)	2 (22.2)	1.2 (0.8-2.6)	9 (100)
	≥60 a <65	5.3 (3.6-6.6)	21 (100)	1.3 (0.8-1.6)	20 (95.2)
	≥65 a <70	8.1 (6.4-11.0)	2 (10.5)	2.3 (1.7-4.2)	18 (94.7)
	≥70 a <75	12.0 (8.8-16.8)	5 (13.9)	4.7 (3.1-7.7)	35 (97.2)
	≥75 a <80	15.5 (11.0-20.0)	3 (7.1)	6.5 (4.4-9.8)	37 (88.1)
	≥80	21.5 (18.8-25.0)	9 (15.0)	9.4 (7.4-13)	53 (88.3)

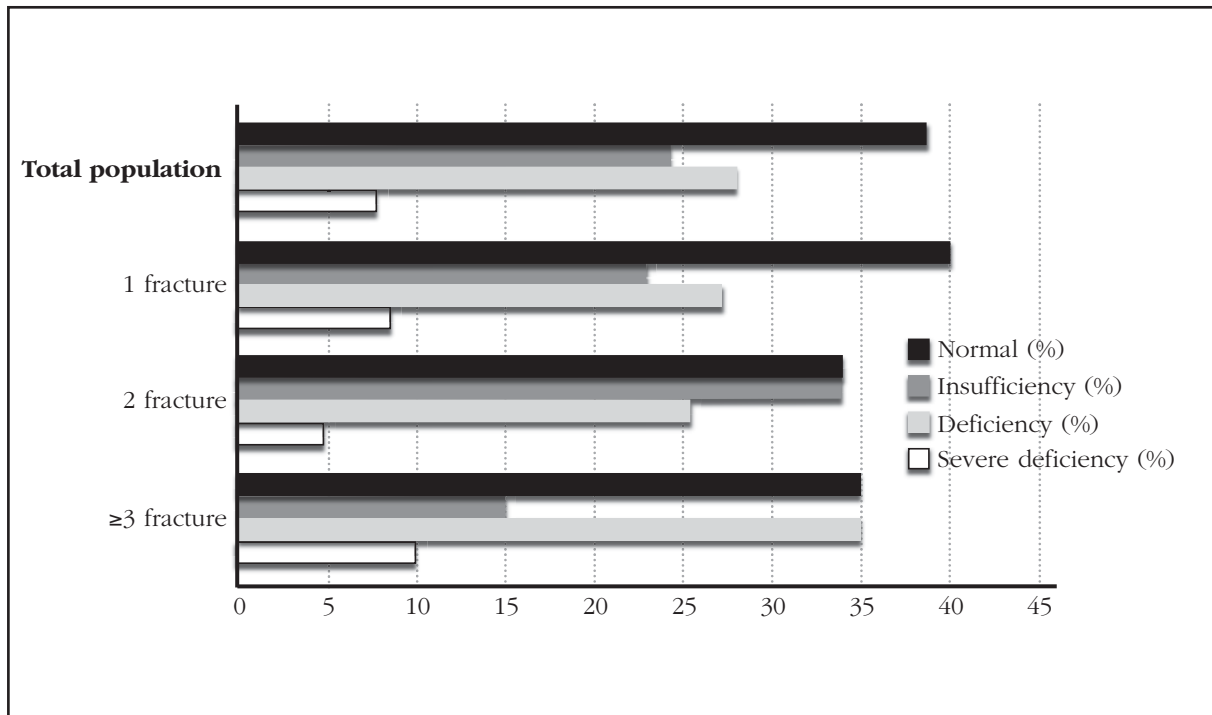
In spite of the fact that the FRAX® tool was designed for application in patients not treated with drugs for osteoporosis, our study includes patients treated at the time of inclusion. Although this is a limitation, the non-treatment of patients with established osteoporosis, the patients recruited to the VERFOECAP cohort, is of dubious justification, both ethically and clinically. It will be interesting to see the predictive capacity for new fractures in these patients with previous treatment. The limitations and after effects of the fracture in this type of patient has made their inclusion in this study enormously difficult, since many of the patients with recent history of fracture of the hip were either institutionalised or being cared for at home during the period of recruitment. This may limit the external validity of our results, which will only be valid for those patients with previous fracture who have maintained their autonomy and live in their normal home after having the fracture.

## Conclusions

The VERFOECAP cohort consists of a population of patients with fragility fractures seen in primary care, who have a high absolute risk of future fracture, and show a high degree of deterioration of quality of life in relation to health. In these patients, the vitamin D deficit is high. Currently, the cohort continues with prospective visits, and a follow up is planned for at least two years. This will give us information regarding the usefulness of the FRAX® formula in the prediction of risk in these patients within our ambit on the impact of vitamin D deficit on the risk of fracture and on the impact of the incident fracture on the quality of life of those patients who have already suffered a previous fracture.

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Figure 3. Levels of vitamin D and number of fractures



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Table 3. Number and locations of existing fractures in the VERFOECAP cohort

		N	%
<b>Number of fractures</b>	1	132	68.0
	2	39	20.1
	≥3	23	11.9
<b>Location</b>	Vertebral	85	43.8
	Humerus	77	39.4
	Colles	27	13.9
	Hip	36	18.6
	Pelvis	7	3.6

**Appendix 1:** List of diagnoses

M80	Osteoporosis with pathological fracture.
M80.0	Postmenopausal osteoporosis, with pathological fracture.
M80.1	Postoforectomal osteoporosis, with pathological fracture.
M80.2	Osteoporosis due to disuse, with pathological fracture.
M80.3	Osteoporosis due to postsurgical malabsorption, with pathological fracture.
M80.4	Drug-induced osteoporosis, with pathological fracture.
M80.5	Idiopathic osteoporosis, with pathological fracture.
M80.8	Other types of osteoporosis, with pathological fracture.
M80.9	Non-specified osteoporosis, with pathological fracture.
S22	Fracture of ribs, sternum and thoracic spine (dorsal).
S22.0	Fracture of thoracic vertebra.
S22.1	Multiple fractures of thoracic spine.
S32	Fracture of lumbar spine and pelvis.
S32.0	Fracture of lumbar vertebra.
S32.1	Fracture of sacrum.
S32.2	Fracture of coccyx.
S32.3	Fracture of iliac bone.
S32.4	Fracture of acetabulum.
S32.5	Fracture of pubis.
S32.7	Multiple fractures of the lumbar spine and pelvis.
S32.8	Fracture of other parts and unspecified in the lumbar spine and pelvis.
S52	Fracture of forearm.
S52.0	Fracture of the upper epiphysis of the ulna.
S52.1	Fracture of the upper radial epiphysis.
S52.2	Fracture of the diaphysis of the ulna.
S52.3	Fracture of the radial diaphysis.
S52.4	Fracture of the diaphysis of the ulna and radius.
S52.5	Fracture of the lower radial epiphysis.
S52.6	Fracture of the lower epiphysis of the ulna and radius.
S52.7	Multiple forearm fracture.
S52.8	Fractures in other parts of the forearm.
S52.9	Fracture of forearm, unspecified part.
S62	Fracture of the wrist and the hand.
S62.1	Fracture of other carpal bone(s).
S62.8	Fracture of other parts, and those unspecified, of the wrist and hand.
S72	Fracture of the femur.
S72.0	Fracture of the femoral neck.
S72.1	Pertrochanteric fracture.
S72.2	Subtrochanteric fracture.
S72.3	Fracture of the femoral diaphysis.
S72.4	Fracture of the lower femoral epiphysis.
S72.7	Multiple femoral fractures.
S72.8	Fracture of other parts of the femur.
S72.9	Fracture of the femur, unspecified part.
T08	Fracture of the spinal column, section unspecified.

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