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ORIGINAL ARTICLES

Predictive factors of fragility fractures and associated mortality: assessment of patients observed at emergency department

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ABSTRACT

Aim: To assess the predictive factors for a subsequent fragility fracture (FF) and mortality.

Methods: Retrospective monocentric study including patients observed at the emergency department (ED) of a referral hospital with a FF, between 1st January 2017 and 31st December 2018. Fractures events were identified through discharge codes using the 9th International Classification of Diseases codes and FF were adjudicated after revision of the clinical files. We identified 1673 patients with FF. After calculating a representative sample (95% confidence interval), 172 hip, 173 wrists and 112 vertebral fractures were included in the analysis. Their clinical files were reviewed until 31st December 2020. A multivariable analysis was performed in order to identify predictive factors for FF.

Results: Overall, during the follow-up period 76 patients (16.6%) had a new FF and 120 patients (26.3%) died. Multivariable analysis showed that previous visits to the ED due to falls (p=0.002) and malignancy (p=0.026) were independent risk factors for a new FF. The main predictors of mortality were age, hip fracture, oral corticosteroid treatment, normal or low BMI and cardiac, neurologic or chronic kidney disease.

Conclusions: FF are a very prevalent public health problem that can lead to significant morbidity and death. Certain comorbidities seem to be associated with new FF and increased mortality. There might be a substantial missed opportunity for intervention in these patients, namely in ED visits.

Keywords: Bone; Quality of health care; Outcome measures; Osteoporosis.

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone density and deterioration of bone microarchitecture that compromises bone strength[1]. This greatly increases the bone fragility and the consequent risk to the development of fracture, even after a minor fall, the so-called fragility fractures (FF). These fractures are known as 'low energy' trauma, that result from mechanical forces that would not ordinarily lead to fracture, such as a fall from a standing height or less[2, 3].

FF represent the main clinical consequence of osteoporosis and are one of the main causes of morbidity and impairment in the elderly[3].

Common sites for osteoporotic fracture include vertebral, proximal femur (hip), and distal forearm (wrist), although patients with osteoporosis are prone to all types of fractures.

Osteoporosis is a global problem accounting for 1.75% of the total disability-adjusted life-years (DALYs) associated with noncommunicable diseases in Europe[4]. It is estimated that one in three women and one in five men will experience a FF in their lifetime. Moreover, the prevalence of osteoporosis is increasing worldwide, resulting in rising burden to society[5].

For those who survive, most do not recover their pre-injury level of function and 30% experience loss of autonomy, whereas if the FF is recognized and adequate anti osteoporotic treatment is started, the risk of a subsequent fracture is reduced by approximately 50%[1, 4, 6].

Furthermore, many studies have shown that mortality increases after an osteoporotic fracture. For example, a woman's risk of dying from a hip fracture is high, exceeding the lifetime risk of death from breast, uterine and ovarian cancer combined, and this mortality risk is even higher for a man. Some studies have shown that mortality also increases after a vertebral fracture[1, 7].

For these reasons, early diagnosis and treatment of osteoporosis is essential to help prevent FF and its consequences.

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Although the hallmark of osteoporosis is the decrease of bone mass, defined in terms of bone mineral density (BMD) and measured by dual-energy X-ray absorptiometry (DXA), there are several other factors that are associated with an increased risk of fracture. As osteoporosis has no obvious symptoms, most people are unaware of the disease until they suffer the FF and so, the timely comprehension of those risk factors could help predict fractures in high-risk patients[6].

Some factors are well-recognized and include lifestyle factors, such as smoking or alcohol intake, certain medical conditions and drugs, that increase risk fracture directly or indirectly, by affecting bone remodeling[3, 8].

Systemic glucocorticoid, thyroid hormones, anticonvulsants or anticoagulants are examples of drugs than may affect bone density. Secondary osteoporosis can also be a result from various diseases, such as endocrinological (hypogonadism, hypocortisolism, hyperparathyroidism), hematological (thalassemia, multiple myeloma, systemic mastocytosis), gastrointestinal (malabsorption, celiac disease), kidney and rheumatic inflammatory diseases[4].

The risk of a FF is also increased in patients who have had a previous FF. The risk of refracture is especially higher immediately after the initial fracture, which suggests that patients should be treated as soon as possible after the occurrence of a first fracture[6].

The assessment of risk of fracture should then be based on the measurement of bone density and by assessing the potential clinical risk factors, since some of them contribute significantly to fracture risk beyond what is provided by BMD. Age, glucocorticoid exposure and rheumatoid arthritis are examples of risk factors that may contribute for risk of FF, independently of BMD.

There are algorithms that integrate the influence of clinical factors on fracture risk, with or without BMD data input; the most widely used is FRAX. Nevertheless, these tools are limited since they do not include all risk factors and may lack relevant details to risk assessment. For this reason, even these algorithms are likely to provide an underestimated fracture risk[3, 5, 6].

The goal of the current study was to determine the predictive factors for a new fracture after a FF, helping identifying those patients with a greatest risk, in whom medical intervention would benefit more. In addition to this, the present study also aimed to investigate predictive factors of mortality associated to FF, since the available studies evaluating the global risk of mortality are scarce.

METHODS

Study design: We performed a retrospective monocentric study including patients with FF observed at the emergency department (ED) in a referral hospital between 1st January 2017 and 31st December 2018. Patients eligible for inclusion were adult patients with FF of the wrist, hip and vertebrae.

Fractures were identified through research of discharge code analysis, using the 9th International Classification of Diseases codes and then a revision of their medical files was made. We identified 3659 admissions to the ED for fractures between these dates, of which 2250 corresponded to low impact fractures and so, were adjudicated as FF.

Patients with relevant missing data to the study were excluded, as well as patients with peri-prosthetic fractures and osteometabolic diseases other than osteoporosis (i.e., Paget's disease) as these fractures may have occurred due to bone fragility not related to osteoporosis. We also excluded totally dependent patients or those in palliative care in whom the use of anti-osteoporotic treatment might be controversial.

One thousand six hundred and seventy-three FF were identified, namely 720 hip fractures, 733 wrist fractures and 220 vertebral fractures. The patient selection flowchart is shown in Figure 1. After calculating a representative sample (90% confidence interval), 172 hip, 173 wrist and 112 vertebral fractures were randomly included.

Variables

Baseline variables: In addition to the demographic data, potential risk factors for FF and mortality were collected from the patient's computerized medical files. Thus, the following variables were recorded: existence of previous fractures and their location, previous visits to ED due to falls, lifestyle variables such as smoking and alcohol intake, visual impairment, body mass index (BMI), comorbidities (rheumatic inflammatory diseases, diabetes, hypertension, neurologic, pulmonary, renal, hematological and malignant disease), daily medication (namely anticonvulsants, oral corticosteroid, anti-osteoporotic drugs), need for hospitalization at the time of the fracture; and BMD measures. Corticosteroids were considered if the patient is or has been exposed to a dose of prednisolone of equal or higher than 5mg, or equivalent doses of other glucocorticoids, for more than 3 months.

Follow-up variables: The occurrence of a new FF, its location and time-to new FF were recorded until 31st December 2020, which corresponds to a median follow-up time of 3 years after FF in study (range 2 to 4 years). It shall be noted that regarding vertebral fractures, both clinical and radiographically detected fractures were considered. We also recorded all-cause mortality during this period and when the death occurred after the fracture.

Statistical analysis: Categorical variables are pre-

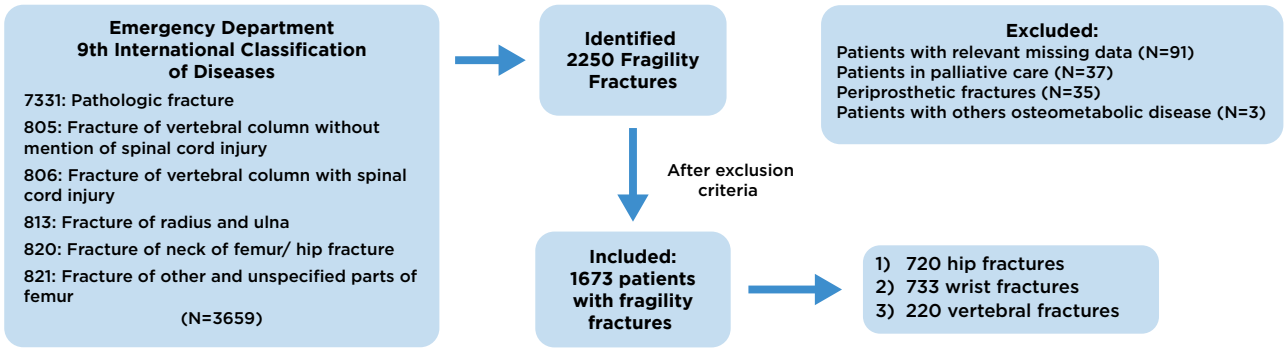

Figure 1. Patient selection flowchart

sented as frequencies and percentages, and continuous variables as means and standard deviation (SD) for variables with normal distribution, and medians and interquartile range (IQR) for variables with skewed distributions. Multivariable logistic regression models, enter method, were performed to identify the predictors of FF. Variables with significant association in univariate analysis and clinical relevance or descripted in literature with significant association to FF were added to the models.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS)® v.24. and significance level was defined as 2-sided $p<0.05$.

RESULTS

Study population

Among the 457 patients included in the study, the majority (79.9%) were females with a mean age of 77.6 (SD=10.3) years old at the time of the fracture, ranging from 50 to 100 years old. Patients were taking a median of 5 (IQR=4) different daily medications and had a median of 4 (IQR=2) comorbidities. A previous FF was observed in 30.6% of patients. Sixteen percent of patients had a previous BMD test.

A history of neoplasia was noted in 45 patients, including 21 of the reproductive organs, 7 of the gastrointestinal tract, 7 skin melanoma, 5 of the respiratory tract, 3 of the lymphohematopoietic system and 2 of the urinary tract.

Sociodemographic and clinical characteristics of the study population at baseline are shown in Table I.

Overall, 7.4% patients (n=34) have been treated with anti-osteoporotic agents (AOA) and 8.1% (n=37) of patients did a DEXA during the follow-up period.

Of the 34 patients who were on AOA after refracture, 12 patients were previously on bisphosphonate, for at least one year, and maintained this treatment; 4 were on bisphosphonate and changed therapeutic class; and 18 started *de novo* AOA, mostly antiresorptive drugs. Among treated patients 88.2% were females with a mean of 75.7 years-old. Patients with a vertebral fracture received an AOA more frequently than those with a wrist or hip fracture, 13.4%, 9.3% and 1.7%, respectively.

Interestingly, 18 of the patients who were on AOA before the fracture, stopped this treatment at the time of refracture and have not been restarted during the follow-up period.

Predictive factors of subsequent clinical fracture following a fragility fracture

Overall, 76 patients (16.6%) had a new FF during the follow-up period, with most occurring in the hip (30.3%) and wrist (15.8%). Among these, 46.1%, 42.1% and 11.8% refractured within 1, 2 and 3 years, respectively.

Of those with a new FF, 19.7% had more than one subsequent fracture during the follow up time. Patients who had a new fracture were older than the ones who did not (80.8 [SD=10.5] *vs* 77.4 [SD=10.3] years old, respectively). The risk of a new FF was numerically higher, especially after a vertebral fracture (20.5%), than hip (16.3%) and wrist (14.5%) fractures, although, without reaching statistical differences.

In the univariate analysis, the occurrence of a subsequent FF was positively associated with older age ($p=0.025$), previous visits to the ED due to falls ($p<0.001$), number of comorbidities ($p=0.006$), previous diagnosis of chronic pulmonary disease ($p=0.002$), hematologic disease ($p=0.005$) or malignancy ($p=0.024$), and previous diagnosis of osteoporosis based on BMD test ($p=0.036$).

No associations were found between the number or type of daily medication, previous fractures and their localization nor the presence of other specific comorbidities other than those mentioned above.

Multivariable analysis showed that previous visits to the ED due to falls ($p=0.002$) and malignancy

Table I. Sociodemographic and clinical characteristics of the study population at baseline.

Age at the time of the fracture, years (mean (SD))		77.6 (10.3)
Female gender, % (n/N)		79.9% (365/457)
Previous fragility fracture, % (n/N)		30.6% (140/457)
Dyslipidaemia, % (n/N)		60.4% (276/457)
Arterial Hypertension, % (n/N)		70.7% (323/457)
Diabetes Mellitus, % (n/N)		24.9% (114/457)
Other comorbidities, % (n/N)	Inflammatory Rheumatologic disease	1.8% (8/457)
	Hematologic disease	6.6% (30/457)
	Pulmonary disease	15.3% (70/457)
	Neurological disease	33.0% (151/457)
	Cardiac disease	32.4% (148/457)
	Gastrointestinal disease	5.9% (27/457)
	Psychiatric disease	36.8% (168/457)
	Malignancy	9.8% (45/457)
	Chronic kidney disease	7.9% (36/457)
	Stage 1	25% (9/36)
	Stage 2	11.1% (4/36)
	Stage 3	44.4% (16/36)
	Stage 4	13.9% (5/36)
	Stage 5	5.6% (2/36)
History of use of oral corticosteroids, % (n/N)		2.2% (10/457)
Need for hospitalization, % (n/N)		38.7% (177/457)
Previous DXA scan, % (n/N)		16.0% (73/457)
Normal bone density		26.0% (19/73)
Osteopenia		23.3% (17/73)
Osteoporosis		50.7% (37/73)
Anti-osteoporotic treatment, % (n/N)		7.4% (34/457)

SD: standard deviation; DXA: dual-energy X-ray absorptiometry; NS: non-significant association

Table II. Multivariable analysis: linear multiple regression for predictive factors of new fragility fracture.

Determinants	Unstandardized Coefficients	Standardized Coefficients	95.0% CI	p-value
Age	0.014	1.014	0.978-1,051	NS
Gender (male)	-0.069	0.933	0.362-4.407	NS
Number of comorbidities	0.116	1.123	0.893-1.412	NS
Previous visits to the emergency department due to falls	1.480	4.395	1.749-11.040	0.002
Pulmonary disease	0.731	2.076	0.936-4.605	NS
Hematologic disease	0.655	1.924	0.650-5.701	NS
Malignancy	1.040	2.829	1.133-7.064	0.026
Previous diagnosis of osteoporosis by a DXA scan	0.788	2.200	0.916-5.280	NS
Oral corticosteroids	-20.287	0	0	NS
Current smoking	0.302	1.294	0.273-6.701	NS
Excess alcohol intake	-0.572	0.563	0.162-1.969	NS

DXA: dual-energy X-ray absorptiometry; NS: non-significant association; CI: confidence interval

(p=0.026) remained associated with the occurrence of new FF after the adjustment for comorbidities, smoking, alcoholism and corticosteroid therapy (Table II).

Predictive factors of death following a fragility fracture

One hundred and twenty patients (26.3%) died during the follow-up period; 35.9% of the men and 23.8% of women included in this study. Of these patients 75% and 24.2% had at least one hip and vertebral fracture during their lifetime, respectively, and 46.7% had more than one FF.

Overall, 30.8% of the deaths occurred in the first year and 10% in the first month post-fracture. Concerning the mortality rate in the hip and vertebral fractures group, the 1st month -mortality rate was even higher, with 11.3% and 13% rate, respectively. On the contrary, there were no deaths recorded in the 6-month periods post fracture in the wrist fracture group.

Also, the mortality rate was higher in the patients who had a refracture (29.3%) than those with a single FF (24.1%), however, without statistical significance.

We found a positive association between mortality and male gender (p=0.024), older age, hip fracture (p<0.001), more daily medication (p<0.001) and comorbidities (p=0.001), daily oral corticosteroid treatment (p=0.024), normal or low body index mass (BMI) (p<0.001), previous visits to the ED due to falls (p=0.022), type 2 diabetes (p=0.022), cardiac disease (p<0.001), neurologic disease (p<0.001), chronic kidney disease (p<0.001). Oppositely, a negative association was found with anti-osteoporosis treatment started after the FF (p=0.007).

No associations were found between mortality and previous fractures before the fracture included in this study, anxiolytic or antiepileptic treatment, arterial hypertension, dyslipidaemia, endocrinopathies, psychiatric disease, hematologic disease, chronic pulmonary disease, other comorbidities or cancer diagnosis not in palliative care.

After adjustment for gender, daily medication, comorbidities, anti-osteoporotic treatment, previous visits to the ED due to falls and type 2 diabetes, the main predictors of mortality were age, hip fracture, daily corticosteroid treatment, normal or low BMI, and cardiac, neurologic or chronic kidney disease (Table III).

DISCUSSION

In this retrospective monocentric study, 76 of the total of 457 patients included had a new FF during the 2-year median follow-up time.

Certain comorbidities seem to be associated with new FF. Previous visits to the ED due to falls and a current or previous diagnosis of malignancy were the most important predictors of new fracture, after adjustment for potential confounders.

Age is a well-known predictor for FFs, either initial or subsequent. The aging process of bone includes de-

Table III. Multivariable analyses: linear multiple regression for predictive factors of mortality after a fragility fracture.

Determinants	Unstandardized Coefficients	Standardized Coefficients	95.0% CI	p-value
Age at fracture time	0.10	1.11	1.07 – 1.15	<0.001
Gender (male)	0.64	1.89	0.98 – 3.66	NS
Number of comorbidities	-0.04	0.97	0.73 – 1.29	NS
Oral corticosteroids	2.30	9.94	1.75 – 56.3	0.009
Previous visits to the emergency department due to falls	0.06	1.06	0.56 – 2.03	NS
Hip fracture	0.83	2.29	1.31 – 4.02	0.004
Normal or low body mass index	1.60	4.95	2.22 – 11.0	<0.001
Type 2 diabetes	0.54	1.72	0.89 – 3.320	NS
Cardiac disease	0.61	1.83	1.03 – 3.27	0.041
Neurologic disease	0.57	1.78	1.00 – 3.12	0.049
Chronic kidney disease	1.87	6.49	2.43 – 17.3	<0.001
Number of daily medication	-0.01	0.99	0.83 – 1.13	NS
Anti-osteoporotic treatment after fragility fracture	1.07	2.92	0.58 – 14.7	NS

NS: non-significant association; CI: confidence interval

teriorations in its composition and structure that, in combination with extrinsic factors such as degeneration of the musculoskeletal system or some medications, predispose elderly people to falls and fall-related injuries including FF[9].

Our study shows that previous falls were one of the strongest predictive factors for FF as previously described in the literature[2, 3, 10, 11].

Another risk factor for FF described in the literature is malignancy. Cancer negatively affects bone health, directly, through inflammatory reactions, and indirectly, due to drugs used in the cancer treatment, for example. Thus, prevention of osteoporosis and consequent fractures is mandatory for cancer survivors of any age[12].

In our study the risk of subsequent fracture decreased over time, 88.2% refractured in the first two years in contrast to the 11.8% that refractured in the third year of follow up. This is consistent with other studies that have shown that the risk is highest immediately after the initial fracture, although it persists for up to 10 years[13, 14].

Despite what is reported in the literature[10, 11], we found no evidence strong enough to prove the association between new FF and the number or type of medication taken daily (including oral corticosteroids), previous fractures, and their localization, nor the presence of other specific comorbidities other than the diagnosis of malignancy. One possible explanation is the small sample size of patients which may have hindered the detection of a significant difference.

Regarding mortality, 120 patients (26.3%) died during the study period, 75% of these patients had a hip fracture in their lifetime and 24.2% a vertebral fracture. 30.8% of deaths occurred in the first year of follow up. The main predictors of mortality were age, hip fracture, oral corticosteroid treatment, normal or low BMI and cardiac, neurologic or chronic kidney disease, which is consistent with other published studies[15-19].

Low BMI, older age, cardiovascular and neurologic disease have already been reported as risk factors for mortality[11, 17, 20]. In contrast, corticosteroid treatment and chronic kidney disease, to our knowledge, had not previously been reported to be associated with mortality after FF.

Our work did not confirm the association between mortality and previous fractures, anxiolytic or antiepileptic treatment, arterial hypertension, dyslipidaemia, endocrinopathies, psychiatric disease, hematologic disease, chronic pulmonary disease or other comorbidities than those mentioned above[16].

There are, however, potential limitations. This is a retrospective study, therefore depending on accurate clinical recordkeeping which may expose the recall to biases. Moreover, the identification of the fragility fracture was based on ICD-9 fracture diagnosis codes. So, vertebral fractures, which are typically silent, may have been underestimated in this cohort. Although patients with relevant missing data were excluded, we found that the data regarding smoking status, alcohol intake or body mass index were sometimes inconsistent, which could have led to lack of accurate information about this data. Similarly, cause of death was unavailable, which may influence the interpretation of the results regarding mortality. Finally, data were collected in a referral hospital, reflecting a small portuguese population, and so results may not generalize to other races and specific ethnic groups.

In conclusion, FF are a very prevalent public health problem that can lead to disability and death. We need to make a multifaceted risk-factor assessment to recognize the risk factors for osteoporosis and its complications. The active search for osteoporosis in the high-risk patients might improve the management of osteoporosis and prevent FF.

Non-pharmacologic approaches to limit falls, particularly in elderly patients, are also important adjunctive measures, since most osteoporotic fractures occur during a fall.

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