

RESEARCH ARTICLE

Subsequent Fracture after Proximal Humerus Fragility Fracture in Patients Included in a Fracture Liaison Service in Spain

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Abstract

Introduction: The objective of this study was to determine the incidence of subsequent fracture following a proximal humerus fracture (PHF) on the basis of an analysis of patients included in a fracture liaison service (FLS) and to identify risk factors for subsequent fracture in these patients.

Methods: This was a retrospective study of patients aged 50 years or older who sustained a low-energy PHF included in an FLS with a minimum follow-up of 2 years. The real incidence of subsequent fractures was calculated as the total number of fractures that occurred during the study period after the index PHF divided by the total number of patients in the study. Descriptive statistics were used to summarise the data. Regression analyses were used to evaluate risk factors for subsequent fracture.

Results: A total of 442 patients were recruited, with a mean age of 75.1 years. (87.33% women and 12.67% men). The incidence of subsequent fracture was 10.18% (n=45) at 2 years. Only 30.32% of patients with PHF had previously received antiosteoporotic drugs. Significant risk factors in the univariable analyses for subsequent fracture were female gender, age >75 years and patients at very high-risk of fracture.

Conclusion: The incidence of subsequent fracture in patients included into an FLS after an index PHF was 10.18% at 2 years. Variables such as female gender, age>75 years and very high-risk patients were significantly associated with subsequent fracture after index PHF. Identifying risk factors for subsequent fracture after a PHF may increase awareness among both patients and healthcare professionals.

Keywords: Proximal Humerus, Fragility Fractures, Subsequent Fracture, Fracture Liaison Service.

1. Introduction

Fragility fractures (FFs) have become a serious health problem for patients, clinicians and healthcare systems. Fragility fractures increase morbidity and mortality and are important risk factors for future fractures [1-5]. Much attention has been given to hip and vertebral fractures because of their high impact on subsequent fracture, morbidity and mortality, as well as the enormous burden they impose on

healthcare systems. In contrast, relatively few similar findings have been reported for proximal humerus fractures (PHFs), despite being the third most commonly observed FF in elderly patients and the second most common upper extremity [6-11]. PHF accounts for 6–8% of all adult fractures, and incidence rates of approximately 66–83/100,000 persons/year worldwide have been reported, with the incidence increasing with age [12,13]. The 1-year

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mortality rate after sustaining a PHF can range from 7.8% to 16% for patients requiring hospital admission [14,15]. PHF is a risk factor for sustaining subsequent fractures; it increases morbidity and causes higher rates of mortality [1,13,16–18]. Trends in the last three decades of the past century show that the incidence of PHF is expected to triple within the next 30 years [10,15,18–20].

Fracture liaison services (FLSs) have been established to address the care gap found in clinical practice since the majority of patients who have sustained fragility fractures are not further investigated and remain untreated after this event. There are different models of FLS intervention [21], but they usually include the four major osteoporotic fractures (hip, vertebral, wrist and proximal humerus). FLS units identify, evaluate and initiate treatment to reduce the intervention gap seen in patients who have sustained a fragility fracture outside FLS settings [21].

The purpose of this study was to determine the incidence of subsequent fracture following a proximal humerus fracture on the basis of an analysis of patients included in an FLS and to identify potential risk factors for subsequent fracture in these patients.

2. Methods

This was a retrospective study of patients aged 50 years or older who sustained a low-energy proximal humerus fracture and were included in an FLS for investigation, fracture risk assessment, treatment initiation and subsequent follow-up. All patients that attended the emergency department between January 2017 and December 2022 were identified using ICD-9MC diagnostic codes for PHF (812.0, 812.00, 812.01, 812.02, 812.09, 812.1 and 812.10) and included into our FLS. The exclusion criteria were pathological and high-energy fractures. The protocol after inclusion in our FLS unit involves attending the FLS initial visit for clinical assessment, laboratory, radiological and dual-energy X-ray absorptiometry (DXA) evaluations and interventions (lifestyle, falls, exercise, pharmacological) [23,24]. Standard follow-up of at least 2 years was carried out by review at 6 months, 1 year and 2 years after inclusion. Some patients were followed up for over two years due to several clinical reasons (such as inadequate adherence, treatment change due to adverse events, sequential treatment, subsequent fractures). The data obtained included patient demographics, previous fractures and falls, comorbidities, fracture risk assessment via the FRAX[®] tool, history of previous anti-osteoporotic treatment, DXA measurements, estimated daily

calcium intake and vitamin D blood levels. All data were determined at the time of inclusion into the FLS. Follow-up data on treatment persistence and adherence, adverse drug effects, falls and new fractures were available for all the subjects. Data from all patients were included in our FLS purpose-built database, which works as a management tool for data storage, production of treatment plan communication reports and scheduling agendas for follow-up visits. We considered very high-risk patients when FRAX for major osteoporotic fracture (MOF) was >30% and/or FRAX[®] for hip fracture was >4.5% [22]. Adherence to antiosteoporotic treatment (AOT) and calcium/vitamin D supplements was defined as high when patients had taken >80% of their medicines as prescribed, intermediate (between 50–80%) and low (<50%). Emergency reports and/or radiographs available on the hospital platform were checked to identify index and subsequent fractures and mortality. To avoid duplication in subsequent fracture counts, PHFs occurring at the same skeletal site were only considered subsequent fractures when they were diagnosed at least 6 months after the index PHF.

2.1 Statistical Methods

Descriptive statistics were used to summarise the data. Categorical variables were expressed in terms of counts with percentages, while continuous variables were presented as averages with standard deviations and ranges. Age, BMI and vitamin D levels were considered a categorical variable and were divided into groups using previously defined thresholds. Differences in parameters between patients with versus without subsequent fractures were assessed with the chi-square test or Fisher's exact test for categorical variables, and with the Student's t test or the Snedecor F test from the ANOVA model for normally-distributed continuous variables, as well as the Kruskal–Wallis or Mann–Whitney test for non-normally-distributed continuous variables. The real incidence of subsequent fractures was calculated as the total number of fractures that occurred during the study period after the index PHF (more than one fracture possible per patient) divided by the total number of patients in the study. The location of refracture was analysed for the full cohort, as well as per age group. Time to subsequent fracture was defined as the number of months from the index PHF to the first subsequent fracture. Univariable logistic regression analyses were performed to determine associations of the categorical outcome of subsequent fracture with explanatory variables (age, gender, seasonality, falls within the last year, mobility prior

to index PHF, lumbar T-score, femoral neck T-score, FRAX hip, FRAX MOF, estimated calcium intake, vitamin D levels, AOT prior to index PHF, AOT following index PHF, calcium supplements following index PHF, and vitamin D supplements following index PHF). Associations were presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI) and p values. Multivariable logistic regression analyses were performed for the same outcome, after selecting explanatory variables using a stepwise model, including variables with $p < 0.15$ in the univariable analysis. Statistical analysis of the data was performed via SAS© v9.4 software (SAS Institute, Cary, NC, USA), and p-values < 0.05 were considered statistically significant.

3. Results

A total of 442 patients who had sustained a PHF were available for analysis, with a mean follow-up of 29.4 (SD 5.4, range 24–47). The mean age was 75.1 (SD 10.0, range 50–99). In our series, 386 (87.33%) patients were women, and 56 (12.67%) were men; the mean body mass index (BMI) was 33.2 (SD 5.8, range 18.4–44.9, $n=442$), and 36.9% of the patients had a BMI ≥ 30 . More than one-third of patients (36.20%) had suffered a previous fracture prior

to the index PHF (mainly at the wrist or vertebra). The demographic data of the entire series, including those of the subsequent fractured and no subsequent fractured groups, are shown in Table 1. Statistically significant differences between both were observed with regard to femoral neck T-score, FRAX (MOF and hip fracture), previous AOT and previous calcium/vitamin D supplements.

With respect to the seasonality of the index PHF fracture, 29.41% of PHFs occurred in autumn, 25.57% in summer, 22.62% in winter and 22.40% in spring, with no statistically significant difference ($p=0.93$). Mobility prior to the index PHF was unassisted in 85.68% of patients, 9.39% were using a cane or similar cane, 3.52% used a walker and 1.41% were in a wheelchair most of the time.

The mean estimated calcium intake for the group was 664.3 mg/dL (250–1600), with a difference ($p=0.052$) between women (672.2 mg/dL) and men (607.1 mg/dL). The mean value for the vitamin D blood level was 28.1 ng/mL, with significantly lower values found in men (mean value 19.89 mg/dL) than in women (21.61 ng/mL), $p < 0.05$. More than half of the patients had vitamin D levels below normal values, and nearly 10% had severe deficiency (< 10 ng/mL).

Table 1. Demographic data for all patients, patients with subsequent fractures and patients with no subsequent fractures.

	All patients (n=442)		Subsequent fracture (n=45)		No subsequent fracture (n=397)		p value
Age	n	%	n	%	n	%	p=0.42
50-59	31	7.02	2	4.44	29	7.30	
60-69	99	22.40	7	15.56	92	23.17	
70-79	146	33.03	13	28.89	133	33.50	
≥ 80	166	37.55	23	51.11	143	36.02	
Gender	n	%	n	%	n	%	p=0.16
Female	386	87.33	343	86.40	43	95.56	
Male	56	12.67	54	13.60	2	4.44	
Previous fracture	n	%	n	%	n	%	p=0.58
Yes	160	36.20	18	40.00	142	35.77	
No	282	63.80	27	60.00	255	64.23	
Seasonality	n	%	n	%	n	%	p=0.97
Autumn	130	29.41	13	28.89	117	29.47	
Winter	100	22.62	11	24.44	89	22.42	
Spring	99	22.40	9	20.00	90	22.67	
Summer	113	25.57	12	26.67	101	25.44	
Mobility prior to index PHF	n	%	n	%	n	%	p=0.87
unassisted	365	85.68	36	81.82	329	86.13	
cane	40	9.39	5	11.36	35	9.16	
walker	15	3.52	2	4.55	13	3.40	
wheelchair	6	1.41	1	2.27	5	1.31	
BMI	n	%	n	%	n	%	p=0.5

<25	103	24.24	13	29.55	90	23.62	
25-29	165	38.82	18	40.91	147	38.58	
≥30	157	36.94	13	29.55	144	37.80	
DXA T score	mean	SD	mean	SD	mean	SD	
Lumbar	-1.45	1.44	-1.67	1.12	-1.42	1.47	p=0.25
Femoral neck	-1.65	0.96	-2.14	0.91	-1.59	0.95	p=0.001
FRAX®	mean	SD	mean	SD	mean	SD	
MOF	15.2%	9%	19%	11%	15%	9%	p=0.02
Hip	7.3%	7%	10%	9%	6%	6%	p=0.005
	mean	SD	mean	SD	mean	SD	
Estimated Ca intake (mg/dl)	664.3	222.3	687.0	231.3	661.7	221.4	p=0.49
Vitamin D blood levels	n	%	n	%	n	%	p=0.33
<10 ng/mL	24	9.92	2	5.88	22	10.58	
10-20 ng/mL	58	23.97	6	17.65	52	25.00	
21-30 ng/mL	52	21.49	6	17.65	46	22.12	
>30 ng/mL	108	44.63	20	58.82	88	42.31	
Previous AOT	n	%	n	%	n	%	p=0.0001
No	308	69.68	16	35.56	292	73.55	
Yes	134	30.32	29	64.44	105	26.45	
Previous Ca/vit D supplements	n	%	n	%	n	%	p=0.008
No	249	56.33	17	37.78	232	58.44	
Yes	193	43.67	28	62.22	165	41.56	

BMI: body mass index. AOT: antiosteoporotic treatment. P values are shown to indicate significant differences between subsequent and no subsequent fracture groups.

3.1 Antiosteoporotic Treatment and Adherence

Only 30.32% of patients with PHF had previously received antiosteoporotic drugs. Bisphosphonates (60.45%) were most commonly received prior to PHF, followed by denosumab (19.40%), teriparatide (17.91%) and others (2.24%). With regard to new treatment initiated after PHF, 344 patients (77.8%) received anti-osteoporotic drugs. New treatments

included bisphosphonates in 54.94% of patients, followed by denosumab (35.57%), teriparatide (7.95%), romozosumab (1.45%) and others (0.03%). With regard to calcium and/or vitamin D supplements, 43.67% had received previous supplements, and 375 patients (84.8%) initiated calcium/vitamin D supplements after the index PHF. Better adherence to AOT was found in women (p=0.02) compared to men. For more details on adherence, see Table 2.

Table 2. Adherence to antiosteoporotic treatment (AOT) and calcium/vitamin D supplements during follow-up, shown as a percentage of patients at each time point

		High	Intermediate	Low	Not applicable*
Adherence to AOT	6 months	85.05%	0.52%	8.76%	5.67%
	12 months	87.69%	1.15%	8.08%	3.08%
	24 months	84.83%	1.56%	9.84%	3.77%
		High	Intermediate	Low	Not applicable*
Adherence to supplements	6 months	87.63%	4.12%	6.19%	2.06%
	12 months	89.23%	1.92%	6.92%	1.92%
	24 months	89.95%	2.23%	6.17%	1.65%

*Not applicable include data from patients not available at each time point or when treatment was not indicated at that time

3.2 Subsequent Fracture

The incidence of subsequent fracture was 10.18% (n=45) at 2 years. When analysing the time to subsequent fracture, we found that 13.3% of subsequent FFs were sustained within the first 6 months, 15.6%

between 6 and 12 months and 71.1% between 12 and 24 months after the index PHF. Subsequent fractures occurred at the wrist (25.93%), hip (16.67%), proximal humerus (16.67%), vertebral (11.11%), pelvic rami (7.41%) and other sites (22.22%). A total of 43 patients

who sustained a subsequent fracture were women (95.6%), with a mean age of 80.2 years (range 65-91). When analysed by anatomical fracture site and age group, the most common subsequent fracture site was the wrist in the 60-70 years age group (55.56%) and in the 70-80 years age group (26.67%), whereas the hip (28.57%), followed by the proximal humerus (21.43%), was the most common subsequent fracture site in the >80 years age group.

3.3 Risk Factors For Subsequent Fracture (Table 3)

Univariable analyses revealed that variables such as

Table 3. Significant risk factors for subsequent fracture after PHF (OR: odds ratio, CI: confidence interval)

SUBSEQUENT FRACTURE	Univariate logistic model		Multivariate logistic model	
	p value	OR (CI 95%)	p value	OR (CI 95%)
Female gender	0.08	3.4 (0.8-14.3)	0.49	1.6 (0.1-2.5)
Age >75 years	0.02	2.1 (1.1-4.1)	0.03	2.1 (1.1-4.3)
FRAX MOF >30%	0.08	1.9 (0.7-5.5)	0.11	1.7 (0.2-1.5)
FRAX hip >4.5%	0.01	2.2 (1.1-4.4)	0.03	1.8 (0.3-1.0)

4. Discussion

The present study shows that the incidence of subsequent fracture in patients who sustained a PHF was 10.18% at 2 years. Variables such as female gender, age>75 years and very high-risk patients for hip fracture (FRAX[®] hip fracture >4.5%) were significantly associated with subsequent fracture after index PHF.

Compared with other fragility fractures, proximal humerus fragility fractures are common events and tend to be underestimated. Patients who suffer from PHF have not gained much attention, even though PHF is recognized as an indicator of fragility and is likely the precursor of hip fracture [17, 19, 27]. The inclusion of patients with PHF in an FLS secondary prevention protocol increases the percentage of patients initiating anti-osteoporotic drugs after fracture and improves adherence to treatment and calcium-vitamin D supplements, reducing the risk and incidence of subsequent fracture compared with standard care outside an FLS setting [11,23,24]. The mean estimated cumulative incidence of subsequent fracture reported in other series varied between 10.9% and 13.4% in an FLS setting [23,24], although higher and lower rates were also observed in these meta-analysis reports; these differences could be explained by variability in patient selection, particularly related to age (older patients suffering more subsequent fractures), different anatomical fracture sites reported and duration of follow-up.

As shown by previous authors [9,16,25,26], in our series, PHFs were also more common in women

female gender (p=0.08, OR=3.4, 95%CI=0.8-14.3), age>75 years (p=0.02, OR=2.1, 95%CI=1.1-4.1), and very high-risk patients for hip fracture with FRAX[®] hip fracture >4.5% (p=0.01, OR=2.2, 95%CI=1.1-4.4) were significantly associated with subsequent fracture after index PHF. Multivariable analysis revealed that only age >75 years (p=0.03, OR=2.1, 95%CI=1.1-4.3) and FRAX[®] hip fracture >4.5% (p=0.03, OR=1.8, 95%CI=0.3-1.0) were significantly associated with subsequent fracture. For more detailed uni and multivariable analyses, see supplementary material available.

than in men, with only 12.6% of men suffering such an injury, which is well in line with other fragility fracture sites. The mean age of our patients was low (75.1 years, with almost two-thirds of the PHFs sustained by patients <80 years old) compared with hip fractures, which tend to be sustained by older patients. As with other fragility fractures, PHF patients sustain a previous fracture in 36% of cases, which reinforces the fact that patients above 50 years of age tend to suffer recurrent fragility fractures [1-3].

Our results show a reduction in subsequent fractures compared with an incidence of 18% reported by Balasubramanian et al and slightly higher than the incidence of 9.61% reported by Jung et al at 2 years [2,16]. Nevertheless, a significant number of new fractures were suffered by our patients, even though they were on pharmacological drugs after the index PHF, so secondary prevention cannot be overemphasized.

We did not find a statistically significant difference in the seasonality of the PHF, but it may be clinically relevant to note that almost 30% of the fractures occurred during the autumn, though no information was available about whether the fall took place indoors or outdoors; therefore, the influence of weather conditions on the frequency of fractures could not be determined. Similar findings on PHF seasonality have been presented in other studies [25,26].

Mobility prior to PHF was unassisted in most of our patients (as would be expected in these “younger patients”), and in fact, the use of any kind of walking

aid was found to be a significant risk factor for mortality. This would be expected, as limited mobility is commonly associated with comorbidities and older age and, therefore, an increased risk of mortality. However, mobility was not found to be a risk factor for subsequent fractures.

Assessing fracture risk is a key element in evaluating subsequent fracture risk, and we found that the FRAX[®] calculation was a useful tool for identifying very high-risk patients. Higher values of FRAX[®] for hip fracture (>4.5%) were a significant risk factor for subsequent fracture in our series, probably because FRAX[®] can be used to evaluate actual clinical risk factors. Conversely, dual-energy X-ray absorptiometry (DXA) scans were not found to be good predictors for subsequent fracture, which enhances the concept of fragility fracture beyond bone density alone and being closely related to bone quality and microarchitecture [1]. The influence of adherence to treatment on subsequent fracture could not be reliably evaluated since data on adherence were retrieved from patients' own information.

Despite living in a Mediterranean country, below-normal values of serum vitamin D were present in more than half of our group, with significantly lower levels found in men than in women. Previous vitamin D supplements were more commonly taken by women. No significant difference could be detected in terms of vitamin D blood levels or subsequent fracture. Again, we cannot draw any conclusions regarding calcium intake, as the values recorded were purely estimations obtained from patients.

As previously published [23,28,29], including patients in an FLS setting, improved adherence to treatment, and we also found a high level of adherence in our group. Data on adherence to treatment were retrieved by asking patients and/or by checking that drug prescriptions were being collected by patients.

Among the skeletal sites of subsequent fractures, the wrist was the most common skeletal site for subsequent fracture in our series, which reveals wrist fractures not only as a common sentinel fracture but also as a significant event as a subsequent fracture, especially in the younger age group (55% of wrist fractures in the 60–70 years old). As expected, subsequent hip fracture was more common in the group aged >80 years, closely followed by a second humeral fracture.

There are some limitations in our study. First, there is no comparative control group (non-FLS patients)

within the same institution, which limits the strength of the conclusions regarding the effectiveness of FLS in this setting. Second, the average follow-up period was 2 years, and more subsequent fractures are expected to occur after 2 years. Third, data on treatment adherence were obtained through patient self-reported information, which may be subject to recall bias.

5. Conclusion

The incidence of subsequent fracture in patients who sustained an index PHF included for secondary prevention into an FLS was 10.18% at 2 years. Variables such as female gender, age>75 years and very high-risk patients for hip fracture (FRAX[®] hip fracture >4.5%) were significantly associated with subsequent fracture after index PHF. A better understanding of the risk factors that increase the incidence of subsequent fracture after a proximal humerus fragility fracture may improve patient counselling and increase awareness among both patients and healthcare professionals.

List of Abbreviations

- AOT: anti-osteoporotic treatment
- BMI: body mass index
- DXA: dual-energy X-ray absorptiometry
- FF: fragility fracture
- FLS: fracture liaison service
- MOF: major osteoporotic fracture
- PHF: proximal humerus fracture

Ethics Approval

This study was approved by the Aragon Scientific Research Ethics Committee (CEICA) of the Government of Aragon. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients included in our database signed an informed consent form as part of the protocol. The study used secondary data collected as part of routine care and was maintained in a deidentified manner.

Conflicts of Interest

Rafael Izquierdo-Avino, David García-Aguilera, Jara Badiola-Vargas and Vicente Canales-Cortés declare that they have no potential conflicts of interest that could influence the work reported in this paper.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author upon request.

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