Fracture Risk Following an Atypical Femoral Fracture

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ABSTRACT

Atypical femoral fractures (AFFs) occurring during the course of osteoporosis treatment usually lead to discontinuation of anti-resorptive (AR) drugs. However, the risk of fracture after an AFF is unknown. We conducted a follow-up study of patients with AFF matched 1:3 for age and gender with patients with a peripheral major osteoporotic fracture (pMOF), in the setting of a fracture liaison service, to investigate the incidence of subsequent low-trauma fractures. Fifty-five patients with AFF (95% women, age [mean ± standard deviation] 75 ± 10 years, 89% exposed to AR drugs), followed for 6.2 ± 3.7 years, were compared to 165 matched controls with a pMOF (hip 85%) followed for 4.3 ± 2.6 years. During the follow-up, 38% of patients in the AFF group and 16% in the pMOF group received AR therapies. Continuation of AR drugs after an AFF was associated with contralateral AFF in 27% of subjects. The risks of new low-trauma, major osteoporotic and imminent (within 2 years) fractures, were similar between the two groups: incidence rate ratio (95% confidence interval [CI]) of subsequent fracture following AFF relative to pMOF, 1.30 (95% CI, 0.82–2.04), 1.28 (95% CI, 0.74–2.15), and 1.11 (95% CI, 0.54–2.15), respectively. Moreover, the risk of sustaining multiple fractures per participant was significantly increased among patients with AFF compared to pMOF (hazard ratio 1.48 [95% CI, 1.00–2.19]; p = 0.049). When taking mortality into account, the risk of subsequent fractures tended to be higher in the AFF group (sub-hazard ratio 1.42 [95% CI, 0.95–2.12]). In conclusion, patients who sustained an AFF are at high risk of subsequent fragility fractures, at least equal or even greater to the risk observed after a pMOF. However, continuation of AR drugs increases the risk of contralateral AFF. Therefore, optimal modalities for secondary fracture prevention after AFF require further evaluation. © 2021 The Authors. Journal of Bone and Mineral Research published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: ANTiresorptives; THERAPEUTICS; FRACTURE RISK ASSESSMENT; OSTEOPOROSIS; DISEASES AND DISORDERS OF/RELATED TO BONE

Introduction

A

typical femoral fractures (AFFs) are rare insufficiency fractures of the subtrochanteric or diaphyseal region of the femur, which occur in a number of metabolic bone disorders but are mainly recognized as a long-term complication in subjects with long-term anti-resorptive (AR) therapies. Atypical femoral fractures (AFFs) have been associated with the duration of treatment with AR therapies; ie, incidence increasing from three to more than 50 cases per 100,000 person-years between 1 and 10 years of exposure. However, the benefit of AR drugs on fracture prevention in patients with established osteoporosis or at high risk of fractures largely exceeds the risk of AFF, with about 1200 fractures prevented for one AFF associated with 3 years of bisphophonate therapy. Even in the context of bone fragility, clinical management of patients who sustained an AFF generally includes cessation of AR treatments, which decreases the risk of AFF by 70% after 1 year, despite the long-term remnant effect of bisphosphonates in bones. Low-quality evidence is available concerning medical management of patients with AFF, whereby the possibility of a second AFF is balanced with the need to prevent future fragility fractures in high-risk patients.
The current attitude is case-specific, but a consensus-based strategy includes surgical fixation depending on the pattern of the fracture (intramedullary nailing in majority of cases), discontinuation of AR treatments, adequate calcium and vitamin D supplementation, and consideration of teriparatide for patients with delayed healing.\(^{[6,10]}\)

Poor postoperative outcomes (required revision surgery, implant failure, and delayed radiological union) have been reported after AFF\(^{[11-13]}\) whereas no excess risk of mortality was established in AFF patients when compared to the general population\(^{[14]}\). It is noteworthy that data are lacking on the incidence of subsequent fragility fractures after an AFF. In particular, it remains unknown whether AFF should be considered as a predictor of imminent fracture risk, similarly to a recent osteoporotic fracture.\(^{[15,16]}\)

In this follow-up study, we compared the incidence of new fragility fractures following an AFF to the one following an osteoporotic fracture.

**Patients and Methods**

**Study design and population**

We conducted an observational follow-up study at Geneva University Hospitals, Switzerland between August 2000 and March 2020. Cases of AFF were identified based on radiographic assessment of all incident femoral fractures admitted to the orthopedic ward and enrolled in our fracture liaison service (FLS) in addition to patients referred to our bone diseases clinic.\(^{[17,18]}\) All patients aged 18 years and older with an AFF corresponding to the 2013 American Society of Bone and Mineral Research Task Force criteria\(^{[10]}\) were considered, including also rare cases of atypical periprosthetic femoral fractures, as reported.\(^{[19-22]}\) Exclusion criteria were as follows: osteogenesis imperfecta,\(^{[23]}\) no follow-up or follow-up limited to less than 12 months, and absence of available matched-control. AFF were classified as complete or incomplete, subtrochanteric or diaphyseal, and X-rays were screened to identify contralateral incomplete AFF at baseline. Each case of AFF was matched for age (±2 years) and gender with three control patients, randomly identified within our FLS or within the Geneva Retirees Cohort (GERICO; http://www.isrcn.com/ISRCTN11865958), a community-dwelling cohort of elderly healthy subjects, whose characteristics were previously described.\(^{[24]}\) Control patients had sustained a low-trauma peripheral major osteoporotic fracture (pMOF), mostly hip fractures, and some proximal humerus or forearm fractures for the few younger controls (hip fracture being very rare at this age, matching with hip fracture was not possible in these cases). The study was approved by the Ethics committee, University of Geneva, Geneva, Switzerland.

**Data collection**

Baseline characteristics of patients were recorded, including age, gender, body mass index (BMI), prior low-trauma fractures, as well as characteristics of AR treatment (type of drugs, duration before baseline, and continuation during follow-up). All comorbidities at the time of the index fracture were collected to calculate the Charlson’s comorbidity index adjusted for age. Areal bone mineral density (aBMD) of the lumbar spine, femoral neck, and total hip was measured by dual-energy X-ray absorptiometry (DXA) at the closest time to AFF or pMOF, for cases and controls, respectively. Osteoporotic status was defined as a T-score ≤ −2.5 SD at least at one site among lumbar spine, femoral neck, and total hip.\(^{[25]}\)

Data about subsequent vertebral and peripheral low-trauma fractures, as well as new atypical femoral fractures and mortality, were obtained retrospectively from the electronic medical records, until March 2020. Outcomes of patients in the GERICO cohort were recorded prospectively during the follow-up visits planned at 3-year intervals. In both groups, the use of any anti-osteoporosis drugs was also recorded, using all electronic medical reports available over the follow-up. All incident fractures were confirmed by X-rays or medical reports. Low-trauma fractures were defined as occurring without any fall/impact or from a fall from a standing height or less. Traumatic and pathological fractures were not recorded. New moderate or severe morphometric vertebral fractures according to Genant semiquantitative classification were also included when vertebral fracture assessment or any spine films were available.\(^{[26]}\) We defined vertebral, hip, forearm, and proximal humerus fractures as incident major osteoporotic fractures (MOF), and the first 2 years following the index fracture as the period to assess imminent fracture risk.\(^{[10]}\) New contralateral AFFs were also recorded and analyzed specifically, and not included as subsequent low-trauma fractures.

**Statistical analysis**

Baseline characteristics were compared between groups with chi-square test for categorical variables and a Mann-Whitney test for continuous variables. For these variables, mean imputation was used if less than 5% of data were not available. Time to first subsequent fracture was calculated as the time between the index AFF or pMOF, and the subsequent fracture. Second AFFs were analyzed separately. Multiple fractures that occurred on the same day for an individual subject were treated as a single event. The Andersen-Gill model was used to estimate time to multiple subsequent fractures occurring at several time points. For those who did not sustain a subsequent fracture, follow-up time was calculated as time to either death or the last follow-up record. Person-time incidence rates (per 1000 patient-years) were used to represent the incidence rate of subsequent fragility fractures and compare incidence rate ratio between groups. As a sensitivity analysis, Fine and Gray regression for survival analyses were secondly fitted to account for competing mortality risk and estimate sub-hazard ratio (SHR) with 95% confidence interval (CI) on the association between the index fracture type and subsequent fracture occurrence.\(^{[27]}\) Additional univariate Cox proportional hazard models were applied to investigate the predictors of fractures among baseline characteristics, in each group. A p value of <0.05 was considered statistically significant.

Analyses were conducted with STATA version 14.0 (StataCorp LP, College Station, TX, USA).

**Results**

Among 82 AFFs identified between August 2000 and July 2018, 55 were included in our study. The main reason for exclusion was loss of follow-up or follow-up less than one year (Fig. 1). The AFF group included 51 (93%) complete AFFs, all surgically treated, and four (7%) incomplete AFFs. Among these incomplete AFFs, two of them were treated with prophylactic nailing and one received teriparatide. Twelve (22%) AFFs occurred at the subtrochanteric region of the femur and 43 (78%) at the femoral diaphysis. Two of them were sub-prosthetic AFFs (both exposed to AR and discontinued after AFF, one treated with
Patients were mostly women (94%), and mean age was 75 years (range, 56–90 years) (Table 1). Forty-nine patients (89%) were treated or had been treated with AR drugs at the time of AFF (43 bisphosphonates, one denosumab, five bisphosphonate followed by denosumab), whereas six patients (11%) had no current or previous exposure to these drugs. Mean duration of AR treatment in treated patients was 7.5 ± 4.6 years (range, 3 months to 20 years). AR therapies were given mainly for osteoporosis and prevention of fragility fractures, except in one patient with metastatic breast cancer.

Table 1. Baseline Characteristics and Follow-Up of Patients With AFF and With pMOFs

| Characteristic | AFF (n = 55) | pMOF (n = 165) | p   |
|---------------|-------------|----------------|-----|
| Gender (women), (%) | 95          | 95             | 1.000 |
| Age (years), mean ± SD | 75 ± 10     | 75 ± 10        | 0.896 |
| Weight (kg), mean ± SD | 66 ± 13     | 65 ± 15        | 0.951 |
| Height (cm), mean ± SD | 158 ± 8     | 161 ± 9        | 0.005 |
| Body mass index (kg/m²), mean ± SD | 26.3 ± 5.1  | 25.0 ± 5.4     | 0.063 |
| Charlson Comorbidity Index, mean ± SD | 3.9 ± 1.6   | 4.6 ± 2.1      | 0.013 |
| Prior clinical fracture (excluding index AFF or pMOF) (%) | 67          | 33             | <0.001 |
| Lumbar spine T-score, mean ± SDa | −1.4 ± 1.7  | −1.3 ± 1.6     | 0.799 |
| Total hip T-score, mean ± SDa | −1.3 ± 1.3  | −1.7 ± 1.0     | 0.216 |
| Femoral neck T-score, mean ± SDa | −1.9 ± 0.9  | −2.0 ± 1.0     | 0.626 |
| Osteoporotic status on DXAa | 0.980       |                |      |
| Normal BMD, (%) | 14          | 13             |     |
| Osteopenia, (%) | 40          | 40             |     |
| Osteoporosis, (%) | 46          | 47             |     |
| Prior AR therapy, (%)b | 89          | 12             | <0.001 |
| AR therapy during follow-up, (%)c | 38          | 16             | <0.001 |
| Follow-up duration (years), mean ± SD | 6.2 ± 3.7   | 4.3 ± 2.6      |     |

Bold values are significant at p < 0.05.

AFF = atypical femoral fracture; AR = anti-resorptive; BMD = bone mineral density; DXA = dual energy X-ray absorptiometry; pMOF = peripheral major osteoporotic fracture; SD = standard deviation.

aOsteoporosis defined as at least one T-score ≤ −2.5 SD and osteopenia as at least one T-score between −1 and −2.5 SD with none ≤ −2.5 SD at the lumbar spine, total hip, or femoral neck. Data available for a subgroup of patients (spine n = 148, total hip n = 131, femoral neck n = 136).
bBefore index fracture.
cContinued or started after index fracture or during the follow-up.

Curved plate, the other with hip prosthesis). Patients were mostly women (94%), and mean age was 75 years (range, 56–90 years) (Table 1). Forty-nine patients (89%) were treated or had been treated with AR drugs at the time of AFF (43 bisphosphonates, one denosumab, five bisphosphonate followed by denosumab), whereas six patients (11%) had no current or previous exposure to these drugs. Mean duration of AR treatment in treated patients was 7.5 ± 4.6 years (range, 3 months to 20 years). AR therapies were given mainly for osteoporosis and prevention of fragility fractures, except in one patient with metastatic breast cancer.

Fig. 1. Study flowchart. AFF = atypical femoral fracture; FLS = Fracture Liaison Service; GERICO = Geneva Retirees Cohort.
cancer. Delayed fracture healing or non-union was observed in 11 patients (20%) after surgical management, including five who continued AR therapies after the AFF.

The index fracture in the matched control group (pMOF group) were hip (n = 140, 85%), forearm (n = 16, 10%), and proximal humerus (n = 9, 5%) fractures. The baseline characteristics and follow-up of patients in the AFF group and control group are reported in Table 1. As compared with the control group, patients in the AFF group had more prevalent fractures (67% versus 33%; p < 0.001, excluding the index one) and were more often on AR drugs before (89% versus 12%; p < 0.001) and after (38% versus 16%; p < 0.001) the index fracture. Furthermore, the AFF group had lower Charlson comorbidity index adjusted for age (p = 0.013), and longer follow-up duration (p < 0.001). Weight and body mass index were comparable between both groups, but height was slightly lower in the AFF group. Osteoporosis on DXA was detected in 46% and 47% of patients in the AFF and pMOF groups, respectively.

In the AFF group, a contralateral AFF was observed in 19 patients (35%). At time of first AFF, contralateral AFF was observed in 14 patients (25%) (13 contralateral incomplete AFFs and one complete AFF). Five patients (9%) developed a contralateral AFF later during the follow-up (two incomplete AFFs, time ranges 1.5 to 4.7 years after index AFF). The characteristics of patients with a concomitant contralateral AFF were not different from those without contralateral AFF (Supplemental Table S1). Among 15 incomplete contralateral AFFs, eight of them were treated with prophylactic nailing and one received teriparatide. Patients who developed a contralateral subsequent AFF over the follow-up had lower BMI (p = 0.026). Continuation of AR drugs after an AFF was associated with subsequent contralateral AFF in 27% of subjects (versus 4% in those who discontinued AR drugs, p = 0.031).

A total number of 66 incident fractures occurred in 31 patients in the AFF group (56%), and 74 fractures in 61 patients of the pMOF group (37%) over the course of follow-up. Fracture sites are detailed in Supplemental Tables S2 and S3, and their distribution was different between the groups, the most frequent ones being vertebral, pelvis, and humerus in the AFF group, and hip, vertebrae, and humerus in the pMOF group. The incidence of new low-trauma fractures was 142 (95% CI, 100–202) per 1000 patient-years in the AFF group, and 109 (95% CI, 85–140) per 1000 patient-years in the pMOF group. The incidence rate ratios (IRRs) and 95% CIs of subsequent fracture following AFF relative to pMOF were 1.30 (95% CI, 0.74–2.04), p = 0.117 for all low-trauma fractures, and 1.28 (95% CI, 0.74–2.15), p = 0.171 for incident MOF (Table 2). In Cox-regression analyses, hazard ratio for all low-trauma fractures following AFF relative to pMOF was HR 1.22 (95% CI, 0.79–1.90), p = 0.369. In multivariate Cox-regression including height, Charlson comorbidity score, fracture prior to the index one, and use of AR drugs after the index fracture, as potential confounders, adjusted HR for subsequent fracture was 1.15 (95% CI, 0.71–1.89), p = 0.568. We did not include in this model the use of AR drugs before the index fracture because of its high collinearity with the exposure (AFF).

The incidences of new low trauma fractures were 109 (95% CI 60, 197) per 1000 patient-years in the AFF group without osteoporosis and 186 (95% CI 108, 320) per 1000 patient-years in the AFF group with osteoporosis (IRR 1.70 [95% CI, 0.70–4.19], p = 0.100).

When restricting the follow-up period to 2 years after the index fracture, the imminent fracture risk was also similar between the two groups (IRR 1.11 [95% CI, 0.54–2.15], p = 0.364 for all incident low-trauma fractures; IRR 0.86 [95% CI, 0.36–1.86], p = 0.359 for incident pMOF). Similar results were reported in Table 2. As compared with the control group, patients in the AFF group had more prevalent fractures (67% versus 33%; p < 0.001, excluding the index one) and were more often on AR drugs before (89% versus 12%; p < 0.001) and after (38% versus 16%; p < 0.001) the index fracture.
obtained in subgroups analyses considering only AFF matched
with controls with hip fractures (Supplemental Table S4) or con-
sidering only AFF with prior exposure to AR drugs (Supplemental
Table S5).

Multiple fracture events occurred in 12 (22%) patients in the
AFF group and nine (5%) in the pMOF group. Using an
Andersen-Gill model allowing for analysis of multiple fractures
per participant, the risk of new low-trauma fractures was signi-
ficantly increased in patients with AFF compared to those with
pMOF (HR 1.48 [95% CI, 1.00–2.19], \( p = 0.049 \)). In univariate ana-
lyses in the AFF group, using the same model considering the
possibility of multiple fractures events per participant, we identi-
fied that the only and strongest predictor of new fractures was
osteoporosis on DXA at the time of the index AFF (all subsequent
fractures, HR 1.99 [95% CI, 1.12–3.56], \( p = 0.020 \); subsequent
MOF, HR 2.52 [95% CI, 1.15–5.52], \( p = 0.021 \)). Gender, prior frac-
ture to the index one, use of AR therapies before the index frac-
ture, and discontinuation of AR drugs during the follow-up, were
not associated with subsequent fractures.

Mortality was significantly lower in the AFF group (15 per 1000
patient-years) compared to the pMOF group (50 per 1000
patient-years), with an IRR of 0.29 (95% CI, 0.09–0.75), \( p = 0.002 \)
(Table 2). In models taking into account competing mortality risk
in fracture risk estimates, the risk of new low-trauma fractures
tended to be higher in the AFF group compared to the pMOF
group (sub-hazard ratio 1.42 [95% CI, 0.95–2.12], \( p = 0.087 \) for
all incident low-trauma fractures; 1.40 [95% CI, 0.88–2.23],
\( p = 0.152 \) for incident pMOF) (Fig. 2).

Discussion

To our knowledge, this is the first study that provides longitudi-
nal data regarding the risk of subsequent low-trauma fractures
in subjects who have experienced an AFF. Patients in the AFF
group had more frequently sustained a prior clinical fracture and
subsequently used AR drugs, which is not surprising
because long-term AR drugs use is a major risk factor for
AFF.\(^{(10)}\) Despite a higher proportion of prior and subsequent
use of anti-osteoporotic drugs in the AFF group, the
incidence of new fragility fractures following an AFF was at least
as high as following a pMOF, itself a well-recognized risk factor
of subsequent fracture. Both groups were at very high risk of
fractures, with similar proportion of patients with osteoporosis
on DXA at start of the follow-up. The incidence of secondary
fractures was particularly high in the two study groups
(142 and 109 fractures per 1000 patient-years, respectively). In
comparison, the incidence of fracture in the general Swiss pop-
ulation is 20 to 30 fractures per 1000 patients-years between
the age of 70 and 79 years.\(^{(28)}\) The incidence of subsequent
fractures after a low-trauma fracture reported in the Dubbo
Osteoporosis Epidemiology Study in Australia was 63 subse-
quently fractures per 1000 patient-years in women between the
age of 70 and 79 years.\(^{(15)}\) In our study, the risk of imminent
fracture was also high (24%–22%) and not different between
the two groups (IRR 1.11 [95% CI, 0.54–2.15]). These results were
obtained with a follow-up censored at 2 years for all patients,
excluding a potential bias induced by the difference in follow-
up duration between groups. Furthermore, the only and stron-
gest predictive factor of subsequent fracture in AFF patients
was the osteoporotic status on DXA. Taken together, these data
indicate a particularly high incidence of fractures in patients
who sustained an AFF, particularly in osteoporotic ones, sup-
porting the concept of persistent bone fragility in these
patients despite previous long-term AR therapies. Fracture sites
description reveals that two-thirds of new fractures were major
osteoporotic fractures (vertebral fractures, hip, humeral, or
forearm fractures).

Fig. 2. Estimated cumulative risk of new low-trauma fractures* (A) and pMOF (B) taking into account mortality risk, after an index AFF or pMOF. * Contralateral AFF were not recorded as new low-trauma fractures. AFF = atypical femoral fracture; pMOF = major osteoporotic fracture; sHR = sub-hazard ratio (95% confidence interval).
Mortality was more important in the pMOF group compared to the AFF group (22% versus 9%; \(p = 0.036\)), which is consistent with higher Charlson comorbidity index at baseline and the increased mortality risk observed after hip fractures, which account for 85% of pMOF in our study. \(^{29-31}\) Furthermore, previous studies did not report excess mortality associated with AFF when compared to non-AFF and general population. \(^{14,32}\) In a sensitivity analysis comparing the risk of new fracture between the AFF and pMOF groups, and integrating competing mortality, a nonsignificant trend of 40% increase in fracture risk was observed in the AFF group compared to the pMOF group (Fig. 2). In addition, the risk of multiple fractures was significantly higher in the AFF group compared to the pMOF group. Taken together, these data support the need to consider prevention of subsequent fractures in patients with AFF.

Thirty-five percent of patients with AFF developed a contralateral AFF, the majority concomitantly, as previously reported (22% to 63% according to studies). \(^{8,9}\) Subsequent contralateral AFFs were associated with the continuation of AR drugs after the index AFF. This is consistent with the risk of AFF increasing with longer duration of bisphosphonate use and greater adherence. \(^{48,34}\) A recent study showed that the radiographic progression of incomplete AFF contralateral to a complete AFF was associated with a higher frequency of postoperative bisphosphonates use (61% in progression group versus 25% in non-progression group). \(^{35}\) In a retrospective cohort of 126 patients with AFF, the risk of contralateral AFF was 54% in patients who continued bisphosphonates for more than 3 years after the first AFF compared to 19% if bisphosphonates were stopped in the first few months following the event. \(^{56,37}\) These data suggest the relevance of AR drugs discontinuation after AFF. Furthermore, in patients receiving bisphosphonates, their discontinuation is associated with a rapid and significant decrease in the risk of AFF. \(^{56,39}\)

The issue raised by these data is how to prevent subsequent fractures after AFF. These patients are at very high risk of major osteoporotic fracture, but continuation of AR therapies after the index AFF increases the risk of contralateral subsequent AFF, without being associated with a lower incidence of subsequent fracture in this observational study. Considering these data, discontinuation of AR drugs, as proposed currently in order to prevent contralateral AFF, appears to be an insufficient strategy, despite the promotion of classical general measures such as optimizing nutritional intakes, adequate calcium, and vitamin D intake or supplements, and prevention of falls. \(^{6,10,38}\) In this context, prophylactic intramedullary nailing should also be considered in patients with intractable pain, non-union or active incomplete fractures. \(^{39}\) After healing of bilateral, surgically managed AFFs, AR drugs might be continued in patients at high risk of subsequent fragility fractures. \(^{38}\) In addition, anabolic agents, such as teriparatide, abaloparatide, or romosozumab, might be of potential interest, particularly in osteoporotic patients. This is reinforced by the particular high incidence of new vertebral fractures observed in patients who sustained an AFF (42%), suggesting teriparatide and other anabolics as potential treatments of choice in these patients. Whether these drugs might also improve AFF healing in this context is less established in observational studies. \(^{40-43}\) The results of the first randomized placebo-controlled trial testing teriparatide for the healing of incomplete AFF (TAFF trial), were recently reported. In this 2-year study, teriparatide failed to demonstrate benefits on clinical and radiographic healing outcomes in incomplete AFFs. \(^{44}\) In addition, data are lacking on the effect of teriparatide on BMD, bone turnover markers, and fracture prevention in the specific population of patients with AFF, and usually with long prior exposure to AR drugs. It also remains unknown how to maintain the benefit of teriparatide and manage bone fragility after 18 to 24 months of teriparatide, a period after which bisphosphonates or denosumab are proposed in the general osteoporotic population. Concerning romosozumab, which also has AR properties, its association with the risk of AFF is questionable and there is currently no data on its use after an AFF. \(^{38}\)

We recognize this study has some limitations. AFF being a rare complication, the sample size is limited, even with nearly 20 years of recruitment in our center with approximately 450 osteoporotic hip fractures per year. \(^{45}\) Therefore, the risk equivalency or risk increase of fractures in the AFF group compared to the pMOF group, which are discussed in this work, are based on analyses with notorious power limitations. The identification of our cases of AFF was mainly through our FLS, and therefore most of them were complete AFF. Also, as any retrospective study and medical record-based data collection, there was no systematic follow-up and possibility of missing data or underestimation of the proportion of patients receiving AR drugs in the control group. Despite matching for age and gender, some factors such as follow-up duration, Charlson’s comorbidity index, and bisphosphonate exposure were not well balanced between AFF and pMOF groups and could have impact our results to some extent. These data illustrate on one side the high exposure to AR therapies in AFF patients and on the other side the treatment gap of osteoporosis after an MOF (16% receiving AR therapies). \(^{36}\) Furthermore, 27 (16%) of the 165 pMOF patients were from a community-dwelling database, whereas all AFF patients were identified in an hospital setting (Fig. 1). Nevertheless, our study is the first follow-up study that addresses fracture risk after AFF. Our finding of a particularly high risk of fracture following an AFF needs to be replicated in prospective studies to definitely confirm that AFF requires secondary fracture prevention.

In conclusion, this study shows that patients who sustained an AFF are at very high risk of subsequent fractures, at least equal or even greater if considering multiple fractures risk, to the risk of fracture observed after a pMOF. In parallel, the risk of a subsequent AFF was increased in patients with an index AFF who did not discontinue AR therapies. Hence there is an urgent need to design randomized controlled trials (RCTs) to evaluate the risks and benefits of osteoporosis therapies in patients with AFF.

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**Disclosures**

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Peer Review

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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