

# Prevalence and risk factors for atypical femoral fracture among Lebanese patients with hip and shaft fractures

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## Abstract

This retrospective study investigates the prevalence of atypical femoral fractures (AFFs) among patients admitted with hip and shaft fractures at a tertiary referral center in Beirut, Lebanon. We analyzed electronic medical records and radiology studies of patients aged above 40 admitted with hip and shaft fractures between January 2006 and December 2019. Fractures were confirmed by ICD9 or ICD10 codes. All cases were reviewed by radiologists, and AFFs were identified according to the 2013 revised ASBMR criteria. We identified 1366 hip and shaft fracture patients, of which 14 female patients had 19 AFFs. This represents a prevalence of 1.0% among all hip and shaft fractures patients and 1.7% among all female hip and shaft fracture patients. Bilateral AFFs were found in 5 of the 14 patients. Patients with AFF tended to be younger, with a mean age of 74.3 ( $\pm 8.6$ ) yr compared to 78.0 ( $\pm 10.6$ ) for patients with non-AFF fractures. A total of 36% of AFF patients had a prior history of non-traumatic fracture at first admission. A high percentage of patients with AFFs reported intake of proton pump inhibitors (42.9%) and glucocorticoids (21.4%). Bisphosphonate exposure was noted in 64.3% of AFF patients. None of the AFF patients were active smokers or consumed alcohol regularly. BMD assessments were available for 7 AFF patients, indicating osteoporosis in 4 and osteopenia in 3 cases. Hip axis length measurements showed no significant difference between AFF patients ( $N = 7$ ) and sex and age-matched controls ( $N = 21$ ). The study underlines the prevalence and characteristics of AFFs in Lebanon, which is consistent with the numbers reported in the literature (0.32%–5%). A larger prospective study that includes hospitals across the nation is needed to gain a more comprehensive view of the prevalence of AFFs in the Lebanese population.

**Keywords:** bisphosphonates (BP), atypical femoral fractures (AFF), hip fractures, osteoporosis, risk factors, epidemiology

## Lay Summary

This study investigated the prevalence of atypical femoral fractures (AFFs) in Lebanon, which are rare fractures of the thigh bone associated with the use of bisphosphonate (BP), medications that are used to strengthen bones. We evaluated medical records of patients from the American University of Beirut Medical Center between 2006 and 2019. Out of 1440 hip and shaft fractures that were identified among 1366 patients, 19 were AFFs occurring in 14 patients. All patients with AFFs were women, and they were younger on average than the other hip and shaft fracture patients. These women did not smoke or drink alcohol. Many had a history of breaking bones before and were taking medications like BP and medications for heartburn. The findings of this study are aligned with other reports worldwide. They help us understand these rare fractures better, especially in Lebanon. It shows that more research is needed to better understand why these fractures happen and how to prevent them.

## Introduction

Food Drug Administration (FDA) approval for the first bisphosphonate (BP) for osteoporosis treatment was in 1995<sup>1</sup>. There was a subsequent steady rise in the prevalence of BP use among women older than 55 yr of age from 2.7% in 1996 to 15.1% in 2005.<sup>2</sup> The description of atypical femoral fractures (AFFs) at the metaphyseal-diaphyseal bone junction with minimal trauma post long-term BP use began to emerge in the literature in 2000.<sup>3</sup> This led to a substantial decline in BP prescriptions by 2012, thus contributing to an increase in the care gap in osteoporosis management.<sup>2</sup>

In 2010, the ASBMR convened a multidisciplinary and international task force to develop a case definition of AFF and harmonize data obtained from subsequent studies reporting on the condition.<sup>4</sup> It concluded that although the incidence of AFF was much lower than that of classical osteoporotic fractures, it raised concerns regarding the effect of long-term therapy on estimates collected then. Four years later, the ASBMR re-convened the task force and updated its review on the topic, including epidemiology, pathogenesis, and management. It still reported a low risk of AFF ranging between 3–50/100000 person-years, a risk that can, however, be as high as 100/100000 with a long duration of BP use, but declines

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**Table 1.** Number and proportions of hip fracture patients admitted by year, sex, and type of hip fracture.

Year of Admission	Female		Total patient count	Male	Total patient count
	No AFF	AFF		total patient count	
	Count (% of female fracture patients)	Count (% of female fracture patients)	Count (% of all fractures patients)	count (% all fracture patients)	
2006	39 (95.1%)	2 (4.9%)	41 (61.2%)	26 (38.8%)	67
2007	54 (96.4%)	2 (3.6%)	56 (62.2%)	34 (37.8%)	90
2008	51 (98.1%)	1 (1.9%)	52 (56.5%)	40 (43.5%)	92
2009	57 (100.0%)	0 (0.0%)	57 (57.0%)	43 (43.0%)	100
2010	68 (98.6%)	1 (1.4%)	69 (67.0%)	34 (33.0%)	103
2011	49 (100.0%)	0 (0.0%)	49 (66.2%)	25 (33.8%)	74
2012	43 (100.0%)	0 (0.0%)	43 (61.4%)	27 (38.6%)	70
2013	47 (100.0%)	0 (0.0%)	47 (65.3%)	25 (34.7%)	72
2014	52 (96.3%)	2 (3.7%)	54 (63.5%)	31 (36.5%)	85
2015	53 (98.1%)	1 (1.9%)	54 (62.1%)	33 (37.9%)	87
2016	86 (97.7%)	2 (2.3%)	88 (57.9%)	64 (42.1%)	152
2017	77 (97.5%)	2 (2.5%)	79 (61.2%)	50 (38.8%)	129
2018	72 (100.0%)	0 (0.0%)	72 (60.0%)	48 (40.0%)	120
2019	71 (98.6%)	1 (1.4%)	72 (57.6%)	53 (42.4%)	125
<b>Grand Total</b>	<b>819 (98.3%)</b>	<b>14 (1.7%)</b>	<b>833 (61.0%)</b>	<b>533 (39.0%)</b>	<b>1366</b>

Abbreviation: AFF, atypical femoral fracture

when the drugs are discontinued. The task force also provided a revised definition of AFFs in 2013, based on major criteria describing its unique radiographic features,<sup>5</sup> as summarized in Table 1 in the Supplemental Data section.

The task force noted that Asian ethnicity and lower limb geometry are risk factors for AFF.<sup>5</sup> Other risk factors include low serum vitamin D level, simultaneous use of multiple antiresorptive bone medications, concurrent glucocorticoid use, rheumatoid arthritis, younger age at initiation of BP treatment, prolonged BP use without drug holiday, hypophosphatasia, and osteogenesis imperfecta.<sup>6-8</sup> We are unaware of any studies characterizing the epidemiology of AFF in the Middle Eastern region. The objective of this study is to describe the prevalence of AFFs in a population of subjects admitted with hip and shaft fractures to a tertiary referral center, in Lebanon.

## Materials and methods

### Settings and subjects

This is a retrospective study involving the review of the electronic medical records, including available radiology studies, of all patients admitted to the American University of Beirut Medical Center (AUBMC), with hip and shaft fractures, from January 2006 until December 2019. AUBMC is a tertiary referral center affiliated with the American University of Beirut Medical School. AUBMC serves the greater Beirut area and beyond. Inclusion criteria include any adult patient aged 40 yr and above with a diagnosis of FN, trochanteric, intertrochanteric, subtrochanteric (ST), and femoral shaft (FS) fractures by International Classification of Diseases (ICD) codes. The epidemiology of osteoporotic fractures is characterized by an increase in Colle's fractures starting at the age of 40, with an increase in spine and hip fracture to follow.<sup>9</sup> We therefore started the screening at age 40, taking into account this epidemiology.

### Data collection

We extracted clinical data and imaging findings for patients diagnosed with femoral fractures. ICD-9CM was used from

January 2006 till October 2018, and ICD-10CM was used from November 2018 onward. The ICD codes were for FN fractures (ICD-9-CM 820.XX and ICD-10-CM S72.009), trochanteric fractures (ICD-9-CM 820.XX and ICD-10-CM S72.109), sub-trochanteric fractures (ICD-9-CM 820.XX and ICD-10-CM S72.102), and FS fractures (ICD-9-CM 821.01-821.11 and ICD-10-CM S72.309). ICD codes assigned to each fracture event are based on discharge diagnosis and validated by medical coders.

The Operations Research Principal Analyst at AUBMC (H.M) retrieved 1627 hospital admissions related to hip and shaft fractures, identified by the specified ICD codes. The information provided includes date of birth, age, sex, and date (year month) of fracture by year. Duplicate admissions were screened (same case number, same classification, and same year) and removed, leaving 1465 admissions. If the same case number appeared several times but admissions were during different years with different fracture classifications or sites, then the case number was screened to differentiate between a true duplicate and an independent second fracture in the same patient. After screening, 1437 admissions remained. Additionally, 3 patients had 2 AFFs each discovered during the same admission, and hence the final number of distinct fractures was 1440.

### Characterization of atypical femoral fractures

All 1440 cases were re-read by one musculoskeletal radiologist with more than 20 yr of experience (N.J.K.) and 2 Radiology senior residents (C.Z., V.R.) to identify AFFs based on the 2013 revised ASBMR criteria (Table S1). To fulfill the definition of AFF, the fracture should be low trauma or non-traumatic and located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, it should satisfy 3 out of 4 major radiological criteria as defined by the ASBMR AFF Task Force revised criteria in 2013 (see Table S1).

We reviewed all imaging studies including those of hips and femora performed at the time of the index hip and shaft fracture, as well as those performed before and after the actual

event, as available in our radiology electronic records. We examined radiographs, CT scans, and MRIs of hips to identify any associated or underlying AFF in both the affected and contralateral limbs.

### Chart review

We conducted a review of medical records of patients identified as having AFFs by radiologists. We collected information on pre-specified clinical and biochemical characteristics such as age and date at the time of AFF, sex, height, weight, BMI, history of previous fractures, diagnosis of diabetes mellitus, diagnosis of rheumatoid arthritis, vitamin D level, alkaline phosphatase level, alcohol use, smoking history, glucocorticoid use, proton pump inhibitor (PPI) use, BP use and duration, denosumab (Dmab) use and duration, BMD, and Fracture Risk Assessment Tool (FRAX) score without BMD. We obtained data for risk factors from electronic health records relevant to the timing before the occurrence of AFF, except for BMD. We reported the available BMD closest to AFF, whether pre or post-AFF.

### Hip axis length

We identified hip axis length (HAL) in 6 AFF patients who underwent a DXA scan at AUBMC. One patient had experienced AFFs on 2 separate occasions, 4 yr apart, contributing to 2 HAL measurements. This resulted in a total of 7 HAL measurements in our AFF patient group. To compare these measurements with a control group, we selected 21 age- and gender-matched control subjects from the dataset of non-AFF hip and shaft fractures in a 3:1 ratio.

### Literature review

We conducted a literature review to compare our findings with those of similar studies. We searched MEDLINE and PubMed databases without language restrictions from August 9, 2014 until August 9, 2024. We used Medical Subject Headings terms and keywords such as “atypical femoral fractures,” “osteoporotic fractures,” “diphosphonates,” “femoral fractures,” and “hip fractures.” We extracted information from relevant publications on the study population, the country where the study was conducted, the total number of participants, the total number of AFFs identified, the prevalence percentage of AFF patients among hip and shaft fractures, sex distribution of AFF patients, study duration, and patient characteristics including inclusion criteria as presented in the original publication.

### Statistical methods

We compared the means of continuous variables between patient subgroups (male vs female, female AFF patients vs female non-AFF patients) using independent T-test, and frequency distributions of dichotomous variables using Chi-Square.

The aforementioned statistical analysis tests were done using SPSS software, version 27.0 (SPSS, Chicago, IL). Results were expressed as Means  $\pm$  Standard Deviation and statistical significance was set at  $p < .05$ ;  $p$ -values were unadjusted for multiple testing.

## Results

### Characteristics of patients with hip and shaft fractures

Between 2006 and 2019, AUBMC had an average of 67–152 patients admitted per year for hip and shaft fractures. The mean age of patients at the time of admission was 78.0 ( $\pm 11.0$ ) yr. Of the 1366 patients admitted for a total of 1440 hip and shaft fractures, 833 (61.0%) were female patients, with an average age of 78.0 ( $\pm 10.6$ ) yr, while 533 (39.0%) were male patients with an average age of 78.1 ( $\pm 11.5$ ) yr. There was no difference in the mean age at the time of admission between male and female patients admitted with hip and shaft fractures ( $p = .79$ ).

### Characteristics of patients with AFF

Nineteen hip and shaft fractures in 14 patients met the 2013 ASBMR criteria of AFF. All of these occurred in female patients. X-rays detected all 19 fractures, and 3 of them were also detected by accompanying MRIs, which showed the presence of AFFs.

Between January 2006 and December 2019, the prevalence of AFFs was 1.0% among all hip and shaft fracture patients and 1.7% among all female hip and shaft fracture patients admitted to AUBMC (Table 1). Notably, there were no cases of AFF among hip and shaft fracture admissions recorded in 2009, 2011, 2012, 2013, and 2018. Out of the 14 patients identified with AFF in the 14-yr span, 35.7% ( $N=5$ ) had bilateral AFFs. Of the patients with bilateral fractures, 3 patients presented with simultaneous bilateral fractures during a single admission, while the remaining 2 had their fractures recognized in separate encounters, 1 yr and 4 yr apart. Of the 19 identified fractures, 8 occurred in the right femur, whereas 11 occurred in the left femur (Table 2). FS fractures were identified in 12 out of the 19 AFFs, and ST fractures were identified in 7 (Table 2). All AFFs were associated with minimal or no trauma, were non/minimally comminuted, and 18 of the 19 AFFs had localized thickening of the lateral cortex at the fracture site. Out of the 19 AFFs, only 3 fulfilled the ASBMR minor criteria.

The average age at the time of admission for patients with AFF was 74.3 ( $\pm 8.6$ ), which is lower than that of female patients with non-AFF hip and shaft fracture ( $78.0 \pm 10.6$ ,  $p = .20$ ). In terms of age distribution, 71.4% of patients with AFF were below the mean age of female patients with non-AFF hip and shaft fracture at the time of admission of 78.0 ( $p = .032$ ). Dividing the age groups of female patients with non-AFF hip and shaft fracture into quartiles, 42.9% of AFF patients belonged to the lower quartile of age at the time of admission ( $p = .054$ ) (Figure 1).

Of all identified patients with AFF, 1 patient was an ex-smoker, 9 patients were non-smokers, 4 did not have smoking status available in their charts, none were active smokers at the time of fracture. In addition, 10 patients were not alcohol consumers and 4 patients did not have alcohol use stated in their chart. At the time of first admission with an AFF, 5 out of the 14 (36%) patients had a history of prior non-traumatic fracture (Table 3).

Four of the 14 AFF patients (28.6%) were previously diagnosed with type 2 diabetes mellitus, 2 did not have the data available in their charts, and 8 were non-diabetic. Two (14.3%) patients were known to have rheumatoid arthritis, 4 had no mention of rheumatoid arthritis in their charts, and

**Table 2.** Frequency and distribution of major and minor criteria AFF ASBMR 2013 fulfillment in 19 atypical femoral fractures.

Fracture ID	Patient ID	AFF location	Laterality	AFF ASBMR 2013 Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	1	FS	R	Associated with minimal or no trauma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	1	FS	L	Originates at the lateral cortex and is substantially transverse in its orientation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
				Complete fractures extend through both cortices and may be associated with a medial spike OR incomplete fractures involve only the lateral cortex	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
				Non-comminuted or minimally comminuted	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
				Localized periosteal or endosteal thickening of the lateral cortex at the fracture site	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
				Minor criteria <sup>a</sup>	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

<sup>a</sup>Minor criteria features: generalized increase in cortical thickness of the femoral diaphysis, unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh, bilateral incomplete or complete femoral diaphysis fractures, delayed fracture healing. Abbreviations: FS, femoral shaft; L, left; R, right; ST, subtrochanteric.

8 patients did not have rheumatoid arthritis. Six of 14 AFF patients (42.9%) were confirmed to be taking PPIs, one had an unknown PPI status and 7 were not on PPIs. Three patients (21.4%) were actively taking (2 patients) or discontinued glucocorticoids within 1 yr of fracture (1 patient), 8 were not recently exposed to glucocorticoids, and the remaining 3 had no data on glucocorticoid exposure in their chart. Nine of the 14 AFF patients (64.3%) were either current users (7 patients) or were previously exposed (2 patients) to BP at the time of fracture detection. Ten AFF patients were not exposed to Dmab and 4 had no data on dmab exposure. The average vitamin D level of all 8 patients with records was 31.2 ng/dL ( $\pm 8.9$ ), and the average of all 10 recorded alkaline phosphatase levels was 83.6 IU/L ( $\pm 31.7$ ), both values fall within the normal range. The average of 8 recorded BMIs within 1 yr before the fracture event for AFF patients was 28.6 kg/m<sup>2</sup> ( $\pm 3.7$ ), falling in the “overweight” range.

The results of DXA scans for a total of 7 of the 14 AFF patients were accessible. For the LS, T scores ranged from  $-4.2$  to  $-1.4$ , with the risk of Major Osteoporotic Fracture varying between 6.4% and 30%. At the hip, T scores were between  $-2.4$  and  $-0.7$ , with a hip fracture risk ranging from 1.5% to 15%. Finally, for the FN, T scores spanned from  $-3.3$  to  $-0.4$ . Over half ( $N = 4$ , 57.1%) of the 7 patients had a BMD scan diagnostic of osteoporosis, whereas the other 3 (42.9%) had a BMD scan diagnostic of osteopenia. The interval between the fracture and DXA scan varied between 5.7 yr before the fracture event to 0.8 yr after the fracture event. On average, the DXA scans were conducted 0.6 yr ( $\pm 0.9$  yr) before the fracture events.

### Patients with bilateral AFFs

In 4 out of the 5 patients with bilateral AFFs, the fracture was either ST on both sides or in the FS on both sides (Table 2). Patients with 2 AFFs had an average age of 68.8 ( $\pm 7.5$ ), which is 8.2 yr younger than those with only one AFF who had an average age of 77.0 ( $\pm 8.1$ ,  $p = .09$ ). It is worth noting that patients who had 2 separate occurrences of AFF were assessed based on their age at the time of their first AFF. Out of the 5 patients who had two AFFs, 4 (80%) were previously exposed to BP, which is a slightly higher proportion than those who had only had one AFF. Only 5 out of 9 (56%) with a single AFF had ever been exposed to BP ( $p = .58$ ).

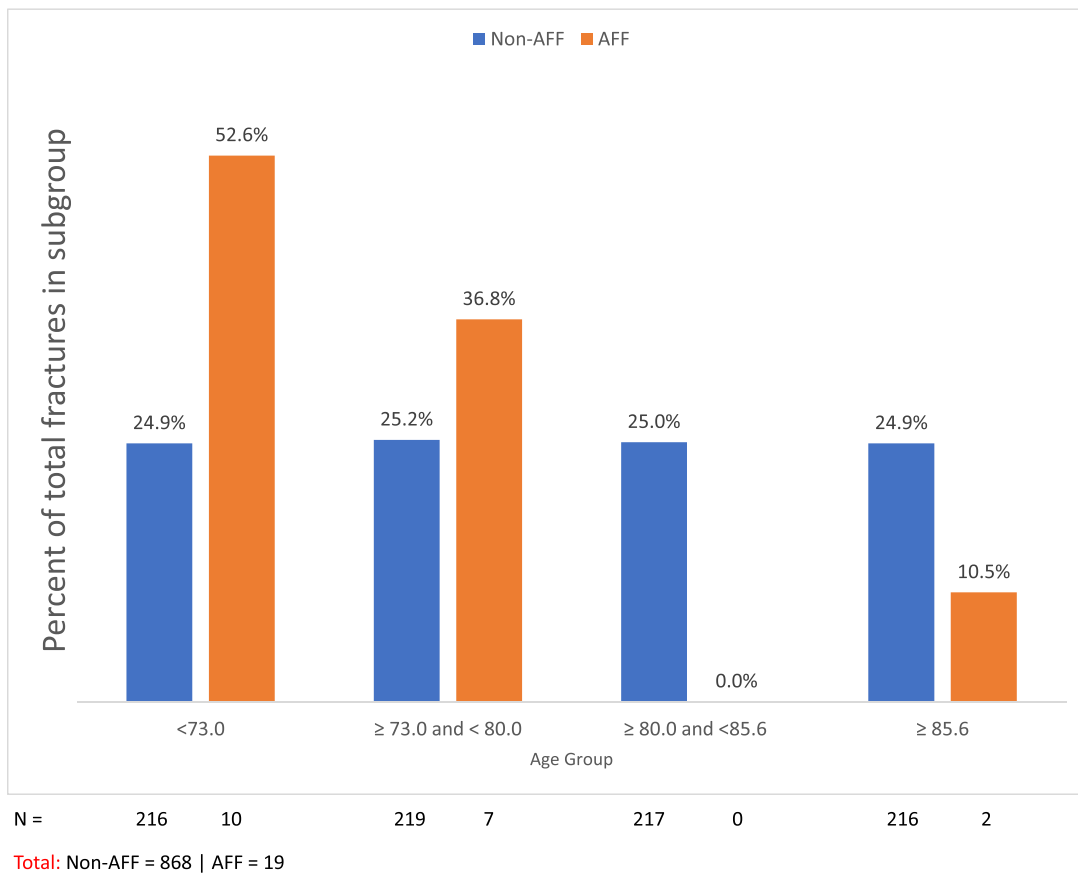
### Hip axis length

There was no significant difference in the average HAL between the 7 patients with AFF (101.29 mm  $\pm$  2.63) and their 21 age- and sex-matched control counterparts (101.33 mm  $\pm$  6.28) ( $p = .98$ ).

### Discussion

To the best of our knowledge, this is the first study exploring the prevalence of AFFs in Lebanon and the Middle East and North Africa region.

Among 1336 patients with hip and shaft fractures identified in a 14-yr period, 19 fractures, all of which occurred in 14 female patients, met the 2013 ASBMR AFF criteria. Approximately a third of the patients had bilateral AFFs. AFF patients tended to be younger than their female non-AFF hip and shaft fracture counterparts, and had comparable HALs. Five out of 14 patients (35.7%) had a history of prior fracture at their



**Figure 1.** Age distribution of female patients with non-AFF hip fractures and AFF hip fractures as percent of non-AFF and Total of AFF hip fractures, respectively.

**Table 3.** Characteristics and risk factors for 14 patients with 19 AFFs.

Fracture ID	Patient ID	Age at time of AFF	Hx of previous fracture	BP Use	FRAX without BMD
1, 2 <sup>a</sup>	1	70	No	Current use, > 5 yr	MOF: 6.4 Hip: 1.9
3	2	71	No	No	N/A
4	3	73	N/A	Current use	N/A
5	4	77	Yes, One	N/A	N/A
6, 7 <sup>a</sup>	5	57	Yes, One	No	N/A
8	6	64	N/A	Current use	MOF: 7 Hip: 1.7
9	7	78	N/A	No	N/A
10	8	70	N/A	Ever used	MOF: 12 Hip: 3.8
11	8	74	Yes, One	Ever used	MOF: 26 Hip: 13
12	9	75	Yes, One	Ever used	N/A
13	10	91	Yes, Multiple	N/A	N/A
14	11	77	Yes, One	Current use, > 5 yr	MOF: 19 Hip: 7
15	12	87	Yes, One	Current use, > 5 yr	MOF: 26 Hip: 14
16	13	78	No	Current use, > 5 yr	MOF: 10 Hip: 3.6
17	13	79	Yes, One	Current use, > 5 yr	MOF: 10 Hip: 3.6
18, 19 <sup>a</sup>	14	69	Yes, Multiple	Current use, > 5 yr	N/A

<sup>a</sup>Patient had experienced bilateral fractures detected during the same admission . Abbreviations: AFF, atypical femoral fracture; BP, bisphosphonate; FRAX, Fracture Risk Assessment Tool; Hx , history; MOF, major osteoporotic fracture; N/A , not available.

**Table 4.** Prevalence of atypical femoral fractures in various populations.

Author/Year/Reference	Country	Population characteristics/inclusion criteria	Study period	Prevalence, n (%)	F/M Ratio of AFF
Pedrazzoni et al./ Journal of Bone and Mineral Metabolism (2017) <sup>10</sup>	Italy	Patients aged 40 and older admitted to Parma University Hospital for a femoral fracture	7 yr (2007–2013)	22/4003 (0.6%)	19/2
Schilcher et al./ <i>Acta Orthopaedica</i> (2014) <sup>16</sup>	Sweden	All patients aged 55 and older admitted to any hospital in Sweden for a femoral fracture according to the Swedish National Patient Register	2 yr (2008–2010)	172/5342 (3.2%)	160/12
Eisenstein et al./ BMC Musculoskeletal Disorders (2017) <sup>17</sup>	United Kingdom	All patients admitted to a specific major trauma center for a femoral fracture	5 yr (2009–2014)	10/3150 (0.32%)	9/1
Kim et al./Rheumatology International (2016) <sup>18</sup>	South Korea	Females aged 45 and older with low energy femoral fractures hospitalized at a single university hospital	10 yr (2003–2013)	30/607 (4.9%)	30/0
Lee et al./ Osteoporosis International (2017) <sup>14</sup>	South Korea	Community dwelling ambulatory patients aged 50 and older hospitalized with low energy femoral fractures from 16 tertiary hospitals	2 yr (2014–2016)	17/1361 (1.2%)	15/2
Clout et al./Journal of Orthopaedic Surgery (2016) <sup>13</sup>	Australia	Patients aged 50 and older admitted with femoral shaft fracture <sup>a</sup> were identified from a trauma database	5 yr (2009–2014)	66/1574 (5%)	63/3
	Lebanon	Patients aged 40 and older admitted to AUBMC, a tertiary referral center, for a femoral fracture	14 yr (2006–2019)	14/1366 (1.0%)	14/0

<sup>a</sup>Patients with periprosthetic fracture, fracture through metastasis, and shaft fracture extending above the lesser trochanter or distal to the supracondylar flare were excluded. Abbreviation: AFF, atypical femoral fracture

first admission. Almost two-third of AFF patients (64.3%) were either currently using or had recently discontinued BP therapy at the time of fracture.

The prevalence of AFFs among all hip and shaft fractures patients (1.0%) in our population falls within the range of values reported in other studies (0.32%–5%) (Table 4). The prevalence of AFFs in our study is nearly double that seen in Italy (0.6%), the only identified Mediterranean country where AFF prevalence was studied.<sup>10</sup> Methodologies between the 2 studies were similar, both had a similar population of adults aged 40 and above admitted for a hip and shaft fracture at a single center. The difference in the prevalence of AFF could be accounted for by different baseline risk factors between ethnic groups and other risk factors such as a higher prevalence of vitamin D deficiency in the Lebanese population.<sup>11,12</sup> The prevalence in our population was found to be much lower than the prevalence of AFFs seen in the Australian (5%) population.<sup>13</sup> However, it is similar to that seen in one South Korean study (1.2%), an unexpected finding considering that Asian populations are at higher risk for AFFs.<sup>14,15</sup> This may partially be explained by the relatively shorter study period in the Korean study of 2 yr compared to a 14-yr span in ours. Studies from Northern European countries show a variation in the prevalence of AFF among all hip and shaft fractures ranging from 0.32% in the UK to 10 times more in Sweden (3.2%).<sup>16,17</sup> The study performed in the UK was from a single major trauma center, while the other was based on a nationwide registry and thus more representative of the rate of AFFs in Sweden.<sup>16,17</sup>

The prevalence of AFFs among female hip and shaft fracture patients (1.7%) in our study is less than half of the one reported in the South Korean study (4.9%).<sup>18</sup> These differences could be explained by the higher prevalence of AFF in Asian populations.<sup>5</sup> However, differences could also be explained by different methodologies in the various studies, including age cutoffs and other selection criteria to identify

hip and shaft fractures. For example, we could not properly exclude non-osteoporotic fractures from our population, which could have diluted our prevalence estimates, compared to others.<sup>18</sup> However, the age cutoff we selected should have narrowed the pathology to osteoporotic hip and shaft fractures. Other studies used different age cutoff points to select their populations, similarly affecting prevalence estimates derived.<sup>13</sup>

Although our study found AFF exclusively in female patients, others have reported AFF cases in both sexes, albeit with a consistent predominance of female subjects (Table 4, Table S2). It may be possible that we did not capture any male AFF patients because our study population was small, and only collected from a single center.

Our AFF patients tended to be younger (74.3 yr) than their non-AFF counterparts (78.0 yr); however, the difference was not significant, likely due to our small sample size. This is still in accordance with other studies, where AFF patients are significantly younger than their non-AFF counterpart.<sup>10,13,14,17,18</sup> However, studies based in South Korea showed a slightly lower mean age of AFF patients, ranging between 71.1 and 71.4 yr, when compared to other studies, including ours (72 to 74 yr), potentially underlining the higher risk of AFFs in Asian populations.

In our study, over one-third (35.7%) of AFF cases were bilateral, with the majority occurring in the same anatomical location of the femur on both sides. Rates of bilateral AFFs have varied significantly in the literature, ranging from 6.1% in Australia and 10.8% in the Japanese population to 62.9% of patients in one Canadian study. Many studies note that the AFF occurred at the same anatomical location of the femur bilaterally, similar to our observations.<sup>13,19,20</sup> The literature also suggests that AFF patients have a high risk of radiological abnormality (pre-AFF) or contralateral fracture and that these patients may benefit from contralateral imaging.<sup>5,17</sup> Interestingly, one of our patients with AFF initially

presented with chronic left hip pain in an outpatient setting. The patient subsequently presented with an intertrochanteric fracture (Figure S2). Initial MRI and X-rays were re-reviewed (Figure S1) as part of this study and in retrospect confirmed AFF. This underscores the importance of rigorous scrutiny of patients' complaints of groin pain when on long-term BPs or Dmab, coupled with a careful assessment of bone films.

We did not find any difference in HAL in the subset of 7 patients with AFF and their sex and age-matched controls. Although it is true that the literature has suggested a potential link between shorter HAL and AFFs, other characteristics related to hip geometry that correlate with AFF risk, such as femoral offset, proximal femoral neck angle in varus, and proximal cortical thickness—variables that were not measured in our study.<sup>21</sup> Our findings may be explained by a small sample size.

In our study, 42.9% of AFF patients were taking PPIs, which is higher than that seen in Swedish (37.8%), Danish (35%), British (30%), and South Korean (13.3%) studies.<sup>16-18,22</sup> There are limited studies, to our knowledge, investigating PPI use in Lebanon or other countries in the MENA region. The literature from Lebanon is mainly focused on patients who were prescribed PPIs, and reports overuse in the outpatient setting.<sup>23</sup> The lower prevalence of PPI use among South Korean AFF patients when compared to Northern European populations may be explained by a higher baseline risk for AFFs among Asian patients.<sup>15</sup> However, the same inference may not necessarily be made for our Lebanese cohort given the aforementioned PPI overuse in our population, which may act as a confounding variable.

A little over one-third (35.7%) of our patients had a history of previous fracture at their first admission, compared to 20%–35% in studies from South Korea, and 44.2% in studies from Sweden.<sup>14,16,18</sup> Interestingly, a study conducted in Denmark found that although a prior fracture increases the risk of future hip and shaft fracture, it does not affect AFF risk.<sup>22</sup> It is therefore unclear as to whether or not the history of fracture acts as a risk factor for AFFs.

Two of our 14 AFF patients (14.3%) were actively taking glucocorticoids at the time of fracture. This is in concordance with the literature, where glucocorticoid use ranged between 10% in a UK study and 20% in another South Korean study.<sup>17,18</sup> However, this rate increases to 21.4% in our study when also taking into account cases where glucocorticoids were discontinued within less than a year of the fracture. Although the correlation between cumulative exposure to glucocorticoids and AFFs has been explored in the past,<sup>24</sup> there have been no studies, to our knowledge, about the risk of AFFs in cases where patients were exposed to steroids in the recent or distant past.

The link between BP use and AFFs is clear (Table S2). In our study, 9 out of the 14 (64.3%) AFF patients had evidence of previous BP exposure. This is similar to a study conducted in Italy, where 62% of AFF patients were previously exposed to BP.<sup>10</sup> Interestingly, exposure to BP in the AFF population was smaller when compared with 3 other large US and European population-based studies in which 90.5%, 78%, and 69% of AFF patients had evidence of previous BP or Dmab use and a smaller UK study where 70% of AFF patients were previously exposed to BP.<sup>16,17,22,24</sup> However, 3 smaller studies in South Korea and Thailand found a smaller proportion of AFF patients, ranging from 35.3% to 44.4%, with previous exposure to BPs.<sup>14,18,25</sup> This could be explained by different populations having different baseline risks for AFF, with more

at-risk populations having AFFs with less exposure to BP. This may suggest that Lebanese patients may have a higher baseline risk for AFFs than Northern European patients, but a lower risk when compared to Asian populations. It is important to note that none of the AFF patients in our cohort were exposed to Dmab. This may be because Dmab was not introduced to the Lebanese market until November 2016 (GEHF personal communication with the exclusive distributor of Dmab in Lebanon, Mersaco). Many studies investigating the risk of AFFs among BP users have found that the use of BP for longer periods significantly increases the risk of AFFs.<sup>22,24</sup> This may explain why 3 out of the 5 patients (60%) with bilateral AFFs were long-term users of BP, whereas only 2 of the nine patients (22%) with only one AFF were exposed to BP for over 5 yr.

Although BP use, specifically prolonged exposure, increases the risk of AFF, the beneficial effects of BP therapy in adults more than 50 dramatically outweigh this increased risk where the ratio of reduced hip fracture to increased AFF risk favors BP treatment in a Danish study.<sup>22</sup> Similar to our study, almost one-third of those with AFF had no BP exposure and other risk factors may be the cause.<sup>22</sup> In addition, discontinuation of BPs leads to a decrease in AFF risk.<sup>22</sup> Therefore, the physician prescribing BPs to patients with osteoporosis should highlight that AFFs are infrequent, as was also seen in our study, and the benefits of BPs to reduce osteoporotic fractures outweigh the risks.

This study has several strengths. Our study collected data over a longer period of time (14 yr) when compared to similar studies identified in the literature (between 2 and 10 yr) (Table 4), ensuring a comprehensive dataset capable of identifying temporal variations and trends. Moreover, our study was not limited to plain radiographs but also included several imaging modalities such as CT scans and MRIs reviewed for all 1440 identified hip and shaft fractures by expert musculoskeletal radiologists, allowing a thorough evaluation of each case identified.

This study has few limitations. First, because this was a retrospective chart review, some of the relevant clinical information was missing, especially on non-AFF hip and shaft fractures, and we were unable to directly interview patients of interest. This also limited our ability to control for potential confounding variables that were not recorded in patient charts. It was a single-center study, limiting the generalizability to the population around the greater Beirut area. This limitation could also explain why we did not identify any AFF cases in 2009, 2011, 2012, 2013, and 2018. Furthermore, the patient population at AUBMC tends to come from a relatively higher socioeconomic status, a factor that may affect hip fracture incidence.<sup>26,27</sup>

To conclude, the prevalence of AFFs among all hip and shaft fractures and the correlation with various known risk factors at our institution are mostly aligned with the findings in the literature. A large multicentric prospective study is necessary to draw robust conclusions regarding the prevalence and risk factors for AFF in the Lebanese population.

## Author contributions

Abir Bou Khalil (Writing—Original Draft Preparation; Writing—Review & Editing; Investigation; Formal Analysis[equal]), Ryan Yammine (Investigation; Writing—Review & Editing; Visualization; Formal Analysis [equal]), Vanessa Rameh (Formal analysis, manuscript editing, and approval of final version), Catherina Zadeh (Writing—Review & Editing; investigation), Randa Saad (Investigation; Writing—Review & Editing; Methodology), Hasan Mallah

(Writing—Review & Editing; Data Curation), Nabil J. Khoury (Investigation; Writing—Review & Editing), and Ghada El-Hajj Fuleihan (Conceptualization; Methodology; Supervision; Writing—Original Draft Preparation; Writing—Review & Editing)

## Supplementary material

Supplementary material is available at *JBMR Plus* online.

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## Conflicts of interest

All authors declare having no conflict of interest with regard to the submitted work.

## Data availability

The data underlying this article are available on reasonable request to the corresponding author.

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