

# Atypical Femur Fractures: A Case - Control Study



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## Background

Atypical Femur Fractures (AFF) have been associated with antiresorptive therapies for osteoporosis. Studies evaluating AFF have varied in methodology and AFF definition. The ASBMR Task Force on Atypical Femur Fractures published revised criteria for AFF definitions in 2014. We conducted a retrospective case-control study, evaluating femur subtrochanteric/ diaphyseal fractures for features of AFF using ASBMR 2014 criteria.

## Methods

**Inclusion criteria:** Women and men age 30 and over with low trauma femur shaft fracture from January 1, 2005 to June 30, 2014, and assessable plain radiographs.

**Exclusion criteria:** Evidence of major trauma; periprosthetic fracture; Pagets, or other bone lesions in the femur.

**Design:** Retrospective case-control study using electronic health records from a multi-institution health information database. The earliest occurrence of the above criteria was the index date.

### Fracture evaluation (see Figure 1):

- Radiographs were identified using ICD9 codes for femur shaft fractures (821.XX and 733.97). CT scans or other imaging modalities were not utilized.
- Pre-screening was completed by a radiology physician assistant for exclusion criteria.
- Two musculoskeletal radiologists blinded to treatment status then reviewed and scored each radiograph using the ASBMR 2014 AFF feature definitions. Any radiographs with exclusion criteria missed on pre-screening were removed by the radiologists. All discrepancies on individual AFF features were jointly adjudicated.
- AFF features were summed to determine whether a fracture was an AFF or a non-AFF femur shaft fracture.
- Radiologists also measured shaft diameter, lateral and medial cortical thickness 5 cm below the lesser trochanter.

Figure 1. Flowchart of radiograph evaluation.

2779	• Fractures identified by ICD9 code; applied ICD9 exclusions
1479	• Images available prescreened by radiology physician assistant for exclusion criteria: location, trauma, bone lesion
427	• Radiographs evaluated by two blinded senior musculoskeletal radiologists
345	• Verified as non-traumatic
327	• Radiographs interpretable for AFF criteria
203	• Non-periprosthetic fracture
98	• Fracture location confirmed to be from below the lesser trochanter to just proximal to the supracondylar flare
57	• Atypical femur fractures (ASBMR 2014 criteria)

### Case-control study:

- Patients with AFF were matched for race and sex to two patients with low-trauma “control” femur fractures, from radiographs evaluated during radiologist review, including shaft, hip/intertrochanteric or distal femur fractures; excluding periprosthetic fractures or bone lesions.
- Chart review was performed for structured (coded) and unstructured (text) data in the health record. Comorbidities were obtained via ICD9 codes. Mechanism of injury was confirmed as low-trauma by review of text notes surrounding the fracture event.
- Medication use (osteoporosis medications, glucocorticoids, proton pump inhibitors, etc.) was determined primarily from dispensing records and augmented by chart review.

## Results

- 98 patients had low-trauma fracture in the correct location for possible AFF. Table 1 describes AFF features.
- 57 patients had AFF: 53 (93%) white; 49 (86%) female.
- 54 AFF cases matched to 108 non-AFF fracture controls (see Table 2).
- Control fractures (19 proximal; 29 shaft; 56 distal) could be outside AFF location due to low number of controls in shaft.
- Clinical variables were similar between control fractures in the femoral shaft (n=29) and non-shaft regions (n=79).
- Age, cortical thickness, prior fracture, other medical conditions and proton pump inhibitors were not associated with AFF.

Feature	N (%)
<b>Mandatory feature</b>	
Fracture location along the femoral diaphysis from just below the lesser trochanter to just proximal to the supracondylar flare*	98 (100%)
<b>Major features (4 of 5 required for AFF)</b>	
1. Low-trauma fracture (confirmed from chart review)*	98 (100%)
2A. Fracture line originates*:	
Medially	0 (0%)
*Laterally	14 (14%)
*Indeterminant	84 (86%)
2B. Fracture line is substantially transverse (≤ 20 degrees)*	63 (64%)
<b>Intersection of 2A and 2B</b>	63 (64%)
3. Complete/incomplete fracture:	
*Complete fracture	88 (90%)
*Lateral incomplete fracture	8 (8%)
Anterior incomplete fracture	2 (2%)
<b>Meeting criteria</b>	96 (98%)
4. Fracture comminution*	
Comminuted	28 (29%)
*Minimally comminuted	6 (6%)
*Noncomminuted	64 (65%)
<b>Meeting criteria</b>	70 (71%)
5. Localized periosteal/endosteal reaction of the lateral cortex*	48 (49%)
<b>Number of major features</b>	
Exact number	Minimum no. features
1	0 (0%)
2	17 (17%)
3	24 (24%)
*4	16 (16%)
*5	41 (42%)
<b>Atypical femur fractures (ASBMR 2014 criteria)</b>	<b>57 (58%)</b>
<b>Initial radiologist major feature score agreement for AFF: 93% (kappa 0.85)</b>	
<b>Atypical femur fractures (ASBMR 2010 criteria)</b>	<b>46 (47%)</b>

### Regarding minor features:

- We were unable to assess delayed fracture healing.
- Generalized increased cortical thickness occurred in 13/98 (13%).
- Bilateral femoral shaft fractures (not necessarily simultaneously) occurred in 11 patients, each with AFF; 10 with bilateral AFF.
- Prodromal symptoms assessed during case-control chart review.

Cases (N=54)	Controls (N=108)	OR (95% CI)	p-value	
Age (SD) years	73.0 (11.2)	74.0 (16.5)	1.00 (0.97-1.02)	0.67
BMI	27.8 (3.8)	28.2 (8.4)	0.99 (0.92, 1.06)	0.70
Charlson Comorbidity Index	1.7 (2.8)	2.2 (2.6)	0.93 (0.81, 1.06)	0.28
Alkaline Phosphatase (U/L)	64.2 (22.3)	89.4 (42.5)	0.97 (0.94, 0.99)	<0.01
Creatinine (mg/dl)	1.0 (0.4)	1.1 (0.9)	0.74 (0.41, 1.31)	0.29
CKD stages 3-5	18 (33%)	48 (44%)	0.62 (0.31, 1.24)	0.18
Lateral cortical thickness/diameter*	0.26 (0.04)	0.25 (0.24)	1.55 (0.19, 12.84)	0.69
Prodromal pain	21 (39%)	5 (5%)	13.04 (3.87, 43.88)	<0.0001
Osteoporotic Fracture within 5 years pre-index	8 (15%)	29 (27%)	0.47 (0.20, 1.14)	0.09
Osteoporosis ICD9 within 5 years pre-index	26 (48%)	23 (21%)	3.47 (1.67, 7.21)	<0.001
Osteoporosis or Osteopenia ICD9 within 5 years pre-index	32 (59%)	28 (26%)	4.00 (1.96, 8.16)	<0.001
<b>Drugs in 5 years preceding fracture</b>				
Bisphosphonates	31 (57%)	9 (8%)	13.69 (4.81-38.99)	<0.0001
Calcitonin	1 (2%)	3 (3%)	0.67 (0.07, 6.41)	0.73
Raloxifene	3 (6%)	1 (1%)	6.00 (0.62, 57.68)	0.12
Proton pump inhibitors	9 (17%)	27 (25%)	0.61 (0.26, 1.40)	0.24
Oral glucocorticoids at time of fracture	9 (17%)	3 (3%)	6.00 (1.62-22.16)	<0.01
<b>*5 cm below the lesser trochanter</b>				

## Conclusion

Over half of the low-energy trauma femoral shaft fractures met the ASBMR 2014 AFF criteria. Notably almost half of the AFFs occurred without bisphosphonate exposure. AFFs were associated with multiple risk factors. AFFs were associated with osteoporosis diagnosis, bisphosphonates within 5 years, glucocorticoid use at fracture occurrence, prodromal pain and lower alkaline phosphatase.