Osteoporosis and Sarcopenia 11 (2025) 111–120

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: www.elsevier.com/locate/afos

Review article

Asian Federation of Osteoporosis Societies 2025 consensus on atypical femoral fractures in patients with osteoporosis

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ARTICLE INFO

Keywords:
Atypical femoral fractures (AFFs)
Osteoporosis
Anti-resorptive therapy
Anabolic therapy
Asian consensus
Regional guidelines

ABSTRACT

Atypical femoral fractures (AFFs) are a rare but serious complication of prolonged anti-resorptive therapy for osteoporosis. This study aimed to develop consensus-based recommendations for the clinical management of AFFs across the Asian Federation of Osteoporosis Societies (AFOS), for harmonizing practice and improving patient outcomes.

A structured questionnaire covering ten key domains related to AFFs was distributed to expert representatives from the 10 AFOS member countries or regions. Responses were analyzed to identify areas of consensus and variation in regional practice. A concurrent narrative review of the literature was conducted to inform evidence-based recommendations.

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https://doi.org/10.1016/j.afos.2025.11.001
Received 7 September 2025; Received in revised form 25 October 2025; Accepted 1 November 2025
Available online 24 November 2025

Survey responses were obtained from 8 of 10 participating AFOS member nations or regions. Among these, Thailand, Malaysia, South Korea, and Hong Kong reported established national guidelines or position statements on AFFs. Contributing risk factors include extended anti-resorptive therapy, femoral geometry, comorbidities, and specific pharmacologic exposures. Diagnosis depends on clinical suspicion and multimodal imaging, with high concordance in diagnostic criteria across regions. Screening emphasizes full-length femoral imaging in high-risk individuals. Incomplete AFFs are managed conservatively or with prophylactic fixation, while complete AFFs typically require intramedullary nailing, tailored to anatomic variations such as femoral bowing. Post-fracture care involves discontinuation of anti-resorptives, assessment for secondary osteoporosis, and potential initiation of anabolic therapy, including teriparatide, abaloparatide, and romosozumab.

This AFOS-led initiative highlights the importance for early detection, individualized management, and region-specific strategies. A multidisciplinary, patient-centered approach—encompassing risk assessment, imaging surveillance, surgical intervention, and tailored pharmacologic treatment—is crucial to reduce AFFs impact and improve skeletal health outcomes across Asia.

1. Introduction

Atypical femoral fractures (AFFs) are defined as low-energy fractures of the femoral shaft, typically occurring between the distal aspect of the lesser trochanter and the proximal supracondylar flare. According to the revised 2013 criteria established by the American Society for Bone and Mineral Research (ASBMR), AFFs are characterized by a transverse or short oblique fracture line initiating from the lateral femoral cortex, with minimal or no comminution and often associated with cortical thickening at the fracture site [1,2].

These fractures are distinct from typical osteoporotic fragility fractures and are most commonly linked to prolonged use of anti-resorptive agents, particularly bisphosphonates and, more recently, denosumab. A registry-based analysis in Switzerland involving 9,956 patients reported AFFs incidence rates of 7.1 per 10,000 person-years in denosumab-treated individuals, compared with 0.9 per 10,000 person-years in those receiving bisphosphonates. Although the hazard ratio (HR 7.07; 95% CI, 0.74–68.01; P = 0.090) did not reach statistical significance, it suggests a possible trend toward increased risk with denosumab [3,4].

The long-term FREEDOM Extension study further emphasized the rarity of AFFs, identifying only two cases per treatment arm over a decade of follow-up [5]. Nevertheless, accumulating reports of bilateral and recurrent AFFs in patients receiving denosumab have raised concerns and prompted reconsideration of ongoing therapy following an AFF event [4]. Post-marketing surveillance indicates that the number needed to harm (NNH) for denosumab-related AFF is approximately 1 in 10,000, underscoring the importance of individualized risk-benefit analysis in long-term treatment planning [6].

The absolute risk of AFFs associated with bisphosphonate therapy remains low, with incidence estimates ranging from 3.2 to 50 per 100,000 person-years [1,2]. However, a well-documented relationship has been established, showing that the risk increases significantly with longer durations of exposure. Hazard ratios increase from 8.86 (95% CI, 2.79–28.20) after 3 to 5 years of treatment to 43.51 (95% CI, 13.70–138.15) after 8 or more years of use [7].

Although AFFs may superficially resemble typical fragility fractures, their distinct radiographic characteristics and underlying mechanisms indicate a different pathophysiological process. Inherited or metabolic bone disorders—including hypophosphatasia, X-linked hypophosphatemia, pycnodysostosis, and osteopetrosis—have also been implicated in AFF-like presentations, highlighting a multifactorial etiology [1,2].

Despite their rarity, AFFs have significant clinical implications, including high rates of delayed union and nonunion (reported in 26–39% of cases), as well as bilateral involvement in 28–44% of cases [4]. Nevertheless, for most patients, the benefits of anti-resorptive therapy in reducing fragility fracture risk outweigh the relatively low incidence of AFFs, particularly when accompanied by appropriate clinical monitoring and preventive strategies.

2. Methods

A structured survey instrument was developed to evaluate the current level of consensus regarding the diagnosis and management of AFFs across member nations and regions of the AFOS. The primary objectives were twofold: (1) to synthesize region-specific clinical perspectives, and (2) to develop standardized, expert-driven recommendations for the management of AFFs in patients with osteoporosis across Asia.

The survey addressed 10 domains of clinical relevance:

1. Incidence of AFFs in each member nation/region
2. Contributing risk factors for AFFs
3. Proposed pathophysiological mechanisms
4. Diagnostic criteria and radiological features
5. Screening and preventive strategies
6. Post-fracture osteoporosis management
7. treatment approaches for incomplete AFFs
8. Standard of care for complete AFFs
9. Indications for teriparatide therapy in AFFs
10. Criteria for prophylactic intramedullary nailing

Participants were recognized national experts in osteoporosis and skeletal health, representing Japan, South Korea, Hong Kong, Macau, Taiwan, Thailand, Malaysia, Singapore, Vietnam, and the Philippines.

Survey responses were analyzed in conjunction with an extensive manual review of current literature conducted by the principal investigator. A structured consensus-building process was implemented to develop evidence-informed recommendations. While relevant data from North American and European cohorts were included to provide context, priority was given to region-specific findings to ensure relevance to Asian populations. The resulting guidance aims to optimize the diagnosis, treatment, and prevention of AFFs within the distinct demographic, anatomical, and therapeutic landscape of Asia.

3. Results

Survey participation and national guidelines

Responses were received from eight of the ten AFOS member nations/regions. Among these, four countries—Thailand, Malaysia, South Korea, and Hong Kong—reported the existence of formal national guidelines, position statements, or consensus documents specifically addressing AFFs management.

- Thailand [8], Malaysia [9], and Hong Kong [10] incorporate AFFs protocols within their broader national osteoporosis guidelines.
- South Korea has issued a dedicated position statement focused on AFFs prevention and clinical management [11].

All frameworks referenced above uniformly endorse the 2013 revised case definition proposed by the ASBMR Task Force (Table 1) [1].

3.1. Epidemiology

AFFs are rare, and reliable epidemiologic data were limited prior to the establishment of standardized diagnostic criteria. Early documentation primarily consisted of case series involving femoral shaft stress fractures. The link between long-term bisphosphonate therapy and AFFs was initially proposed in 2005 [12] and substantiated by subsequent studies between 2007 and 2009 [13,14]. ASBMR convened task forces in 2010 [15] and 2013 [1] to formalize the definition of AFFs and delineate associated risk factors.

AFFs incidence is closely related to bisphosphonate treatment duration.

- Incidence rates increase with treatment duration: 1.78, 38.9, and 107.5 per 100,000 person-years after ≥ 2, 6, and 7 years of therapy, respectively [16].
- Discontinuation of bisphosphonates reduces AFFs risk by approximately 70% [17].
- Despite the increased risk, absolute incidence remains low, typically between 3.0 and 9.8 per 100,000 person-years [18].

Notably, Asian women exhibit significantly higher AFFs incidence (18.7 per 100,000 person-years) compared with their Caucasian counterparts (7.6 per 100,000), potentially reflecting anatomical differences in femoral and pelvic morphology [19].

Regional data highlights.

- South Korea: A retrospective cohort study of 10,338 bisphosphonate users identified 13 AFFs cases, yielding an incidence of 85.9 per 100,000 person-years (age-adjusted: 72.7; 95% CI: 29.1–175.8) [20].
- Japan: Nationwide surveillance in 2023 conducted by the Japanese Orthopaedic Association reported 745 confirmed AFFs (803 fractures), with an AFF-to-proximal femur fracture ratio of 0.52%.
- Thailand: A radiographic review of 865 subtrochanteric and shaft fractures identified AFFs in 5.7% of cases, underscoring the importance of detailed imaging to distinguish AFFs from traumatic fractures [21].

3.2. Risk factors

AFFs are recognized as a multifactorial condition, both radiographic and clinically distinct from conventional osteoporotic fractures. Data from eight AFOS member countries (Japan, South Korea, Hong Kong, Taiwan, Thailand, Malaysia, Singapore, and the Philippines) identified four principal categories of risk (Table 2).

a) Prolonged bisphosphonate therapy
   - Duration-dependent risk is well-established:
     - Hazard Ratio (HR) of 8.86 (95% CI: 2.79–28.2) for 3 to 5 years
     - HR of 43.51 (95% CI: 13.70–138.15) for ≥ 8 years [22].
   - Suppression of osteoclastic activity compromises microdamage repair and leads to alterations in bone quality [15,23].
   - AFFs can occur in bisphosphonate-naïve individuals; therefore, cases in long-term users are more accurately described as 'bisphosphonate-associated' rather than 'bisphosphonate-induced'.
   - Case reports from Malaysia have documented AFFs in patients on prolonged bisphosphonate therapy [24–26],
   - Though involvement of the femoral neck is rare. Kim et al. [27] report an incomplete atypical femoral neck fracture in a patient without trauma but with prolonged bisphosphonate use and suppressed bone turnover.

b) Femoral and hip geometry

Table 2
Risk factors for atypical femoral fractures (AFFs).

Category	Risk Factor	Details/Notes
1. Medication Use	**Prolonged Bisphosphonate Therapy**	- Strong duration-dependent risk: • HR 8.86 for 3–5 years • HR 43.51 for ≥ 8 years - Suppresses bone turnover → impaired microdamage repair - Described as "associated," not "induced"
	Denosumab	- Risk considered low but similar to bisphosphonates - Bilateral/recurrent AFFs reported, especially after prior AFFs
	Chronic Corticosteroid Use	- HR 2.28 for ≥ 1 year of use - Alters bone metabolism and increases fragility
	Other Pharmacologic Agents	- Proton pump inhibitors (PPIs) - Other drugs affecting bone turnover
2. Skeletal Anatomy	**Femoral and Hip Geometry**	- Increased femoral bowing and coxa vara - Reduces neck-shaft angle, raising lateral cortical stress - More common in Asian women
	High Bone Mineral Density (BMD)	- Seen in AFF patients vs those with typical fragility fractures
3. Comorbid Conditions	**Systemic Diseases**	- Rheumatoid arthritis and other autoimmune/collagen vascular diseases - Chronic kidney disease - Diabetes mellitus - Asthma and COPD - Osteomalacia, vitamin D deficiency
	High Body Mass Index (BMI)	- Elevated BMI may increase mechanical stress on bones
4. Ethnicity/ Genetics	**Asian Ethnicity**	- Higher AFF incidence in Japan, South Korea, Thailand - Possibly due to anatomical variations and pharmacogenetics

Table 1
ASBMR task force 2013 revised case definition of AFFs.

Major features (at least four of five Major Features must be present)
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
The fracture is non-comminuted or minimally comminuted
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site
Minor features (while not diagnostic, these factors associate with AFF)
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

Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, periprosthetic fractures, and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (eg, Paget's disease, fibrous dysplasia).

- Asian populations may be predisposed to AFFs due to anatomical variations such as increased femoral bowing and coxa vara, which increase lateral cortical stress [28].
- A study from Queen Mary Hospital demonstrated that patients with AFFs had longer durations of bisphosphonate use, higher bone mineral density (BMD), and more acute femoral neck-shaft angles compared to those with typical fragility fractures ($P < 0.05$) [29].

c) Pharmacologic agents
- Chronic corticosteroid use ($\geq$ 1 year) is associated with a significantly elevated AFFs risk (HR: 2.28; 95% CI: 1.51–3.43) [22].
- Additional agents implicated include proton pump inhibitors and other medications affecting bone metabolism [30].

d) Comorbid conditions
- AFF has been associated with several systemic comorbidities, including:
  - Elevated body mass index (BMI)
  - Rheumatoid arthritis and other collagen vascular diseases
  - Chronic kidney disease
  - Asthma and chronic obstructive pulmonary disease
  - Vitamin D deficiency and diabetes mellitus [31,32].

3.3. Diagnosis

Early recognition of AFFs requires high clinical suspicion, particularly in patients on prolonged anti-resorptive therapy presenting with localized, persistent dull pain in the thigh, hip, groin, or knee—often occurring weeks to months before fracture. Complete AFFs typically occur with minimal trauma, such as during routine ambulation or rising from a seated position.

Recommended imaging modalities.

- Plain radiographs: Anteroposterior and lateral full-length femoral radiographs are the first-line imaging modality. Bilateral imaging is essential due to a 28–40% incidence of contralateral involvement [1,33].
- Dual-Energy X-ray Absorptiometry (DXA): extended femoral views may assist in early detection of cortical changes.
- Computed Tomography (CT): indicated when plain radiographs or DXA reveal a fracture line. CT offers detailed visualization of cortical lucency and periosteal thickening [30].
- Magnetic Resonance Imaging (MRI): useful when:
  1. Radiographs and DXA fail to reveal definitive fractures
  2. Lateral cortical thickening is present without cortical lucency
  3. Bone marrow edema alone suggests a stress reaction
  4. Edema with cortical lucency confirms incomplete AFFs [1].

Diagnostic criteria:

Most AFOS member nations have adopted the ASBMR 2013 revised case definition, which stratifies features into major (required) and minor (supportive) components [30]. This standardization supports consistent diagnostic protocols and promotes regional harmonization of clinical practice.

3.4. Prevention and screening

Patients on long-term bisphosphonate therapy should be clinically reassessed after 3–5 years to determine whether to continue treatment or initiate a drug holiday [34,35]. Notably, the risk of AFFs declines to baseline levels within approximately one year after discontinuation of bisphosphonate therapy [36].

Emerging imaging modalities are recommended for early detection of femoral cortical changes predictive of AFFs. Although not yet commonly used, these approaches show considerable promise. Notably, extended femoral imaging by DXA allows qualitative and quantitative evaluation of cortical thickening [37]. Van de Laarschot et al. reported cortical beaking—a radiologic precursor to AFFs—in 4.3% (12/282) of patients on anti-resorptive therapy using this method, with a positive predictive value of 83.3% [4].

The International Society for Clinical Densitometry (ISCD) currently recommends the following screening measures for patients on anti-resorptive agents [37].

- Routine bilateral full-length femoral imaging is recommended after three years of continuous therapy, especially in patients concurrently on glucocorticoids.
- Bilateral femoral imaging is mandatory in patients on anti-resorptive therapy presenting with groin, thigh, or hip pain, to exclude impending or incomplete AFFs.

3.5. Management of AFFs

Management of AFFs necessitates a comprehensive, multidisciplinary approach that integrates timely diagnosis, risk factor modification, individualized treatment, and long-term skeletal monitoring. Core components include.

- Contralateral femoral imaging – warranted due to bilateral involvement in approximately 25% of cases.
- Metabolic evaluation – to reassess fracture risk and identify secondary causes of osteoporosis.
- Nutritional optimization – ensuring adequate calcium intake and correcting vitamin D insufficiency or deficiency.
- Lifestyle modification – including smoking cessation and reduction of excessive alcohol consumption.
- Long-term surveillance – ongoing monitoring of both affected and contralateral femurs for progression or new fractures.

3.5.1. Management of AFFs

Four AFOS member countries—Thailand, Malaysia, South Korea, and Hong Kong—have published formal national or regional guidelines on AFFs management. Treatment strategies for incomplete AFFs should be individualized based on clinical symptoms and imaging findings.

- Symptomatic patients with functional impairment:

Patients with weight-bearing pain and radiographic findings—such as periosteal reaction, lateral cortical thickening, or the characteristic “dreaded black line”—are candidates for prophylactic intramedullary (IM) nailing. This intervention significantly reduces the risk of progression to complete fracture. Early surgical management achieves union rates of up to 97%, compared to a 47% progression rate with non-operative treatment [38–42,46].

- Mildly symptomatic patients without functional limitation:

An initial trial of conservative management may be appropriate, including non-weight-bearing measures, use of assistive devices, and serial radiographic monitoring. Surgical intervention should be reconsidered if there is no clinical or radiographic improvement within 2–3 months.

- Asymptomatic patients with incidental radiographic findings:

Isolated cortical thickening without associated pain may be managed conservatively through activity modification and periodic imaging. MRI or bone scintigraphy can be utilized to assess for bone marrow edema or metabolic activity suggestive of a stress reaction.

In Japan, treatment decisions are often guided by radiographic patterns: subtrochanteric fractures are more likely to require surgical intervention than diaphyseal fractures, and the presence of a radiolucent

line strongly favors operative management.

Although not universally included in treatment guidelines, teriparatide (recombinant PTH 1–34) has demonstrated potential benefits in selected cases, including reduced rates of delayed union and nonunion, and accelerated fracture healing [4,10,11,43–45]. Despite the lack of randomized controlled trials, it is increasingly used in clinical practice as an adjunct to surgical management.

3.5.2. Management of complete AFFs

IM nailing remains the standard of care for complete AFFs, preferred over plate fixation due to superior biomechanical stability and improved healing outcomes. It should span the entire femur—from the subtrochanteric region to the distal metaphysis—to facilitate indirect healing through callus formation.

Unlike plate fixation, which relies on primary healing often compromised by bisphosphonate therapy, IM nailing offers a load-sharing construct that promotes bone regeneration. A systematic review of 733 AFFs from 77 studies reported lower reoperation rates with IM nailing (12.9%) versus plate fixation (31.3%) [46].

The 2024 OSHK guideline for postmenopausal osteoporosis recommends surgical repair using closed or open reduction, followed by long IM nail fixation with dynamic locking [10,47].

The 2023 Position Statement by the Korean Society for Bone and Mineral Research emphasizes intraoperative caution. Iatrogenic fractures may occur during nail insertion across sclerotic cortex. Over-reaming of the canal is strongly advised to mitigate this risk. When such fractures occur, they are associated with increased risks of delayed healing or nonunion [11,48–50].

3.5.3. Surgical considerations in excessive femoral bowing

Excessive anterolateral femoral bowing, frequently seen in Asian populations, presents a technical challenge for IM nailing due to mismatch between the implant and native femoral curvature [51].

3.5.3.1. Nail customization. Preoperative planning should assess the degree of femoral bowing (mild, moderate, or severe) using a line from the greater trochanter to the intercondylar notch. Customized nail curvature reduces the risk of cortical breach or iatrogenic fracture.

3.5.3.2. Entry point modification. Using a lateral entry point at the tip of the greater trochanter, rather than the traditional piriformis fossa, has shown improved outcomes. One comparative study demonstrated significantly shorter healing times with lateral entry (17.8 vs 21.2 weeks; $P = 0.02$) [11]. Kim et al. reported similar union rates and faster healing in patients with severe bowing treated with lateral entry nails [52].

3.5.3.3. Alternative fixation strategies. When IM nailing is not feasible, plate fixation using minimally invasive plate osteosynthesis (MIPO) principles may be considered. To ensure adequate mechanical stability, the plate should extend along the full femoral length [53].

3.6. Osteoporosis management following AFFs

The management of osteoporosis after AFFs requires an individualized strategy that supports fracture healing while preventing future fractures and minimizing medication-related complications.

3.6.1. Discontinuation of anti-resorptive therapy

Prompt cessation of anti-resorptive agents, including bisphosphonates and denosumab, is cornerstone of post-AFFs management. Continued therapy after an AFFs elevates the risk of contralateral fracture [54]. Clinicians should explicitly counsel patients to discontinue treatment, especially those on oral bisphosphonates who may inadvertently continue therapy via pre-filled pill organizers.

Bisphosphonates demonstrate prolonged skeletal retention. For example, alendronate and risedronate can be detected in urine months after discontinuation [55], and a single zoledronic acid infusion may suppress bone turnover markers for up to four years [56].

Discontinuation of denosumab presents unique challenge due to rebound bone resorption, resulting in rapid bone loss and increased risk of spontaneous vertebral fractures [57–59]. The FREEDOM trial reported vertebral fracture rates of 6.66 per 100 person-years after three years of denosumab, rising to 10.73 per 100 person-years with prolonged use [59]. To mitigate rebound risk, a bisphosphonate “bridge” (eg, alendronate or zoledronic acid) is commonly administered post-denosumab, especially after brief exposure [60,61]. However, recommending bisphosphonate therapy following denosumab-associated AFF may warrant careful consideration, especially since a substantial proportion of these patients may have had prior bisphosphonate exposure. In this study [62], nearly 30% of denosumab-associated AFF cases involved previous use of bisphosphonates. Given that transitioning from bisphosphonate to denosumab—a more potent anti-resorptive agent—may increase the risk of AFF, reintroducing bisphosphonate after a denosumab-related AFF could potentially exacerbate the underlying pathophysiology rather than mitigate it. Alternatives such as raloxifene and anabolic agents (teriparatide, romosozumab) are being explored. The DATA-Switch study demonstrated that teriparatide following denosumab resulted in hip BMD decline, whereas romosozumab maintained hip BMD and increased spinal BMD.

Delayed specialist referral, especially without a Fracture Liaison Service (FLS), can hinder effective post-denosumab management. Although delayed anabolic therapy may improve outcomes, all anabolic agents carry a risk of rapid BMD loss upon discontinuation. Thus, proactive treatment planning prior to denosumab initiation is crucial, with decisions guided by cumulative anti-resorptive exposure and fracture risk.

3.6.2. Evaluation of secondary osteoporosis

A thorough evaluation for secondary causes of bone fragility is essential in the post-AFFs population. Although there are practical challenges, it is essential—especially in high-risk individuals without previous metabolic assessment.

Considerations include.

- History of bariatric surgery or malabsorptive gastrointestinal disorders
- Trace mineral deficiencies (eg, copper) that may contribute to neuropathy and falls
- Vitamin D or calcium malabsorption
- Hypercalciuria, often undetected without 24-h urine calcium testing—even in the absence of nephrolithiasis [63].
- Normocalcemic hyperparathyroidism, warranting investigation after confirming vitamin D sufficiency [64].

A comprehensive differential diagnosis is essential, as emphasized by Mizra & Canalis [65] and Lewiecki [66]. Identifying and addressing underlying causes may restore skeletal integrity and potentially obviate the need for pharmacologic therapy.

3.6.3. Consideration of anabolic therapy

Anabolic agents provide dual benefits in the management of AFFs, by both enhancing fracture healing and improving bone density in the post-fracture period. Among these agents, teriparatide is the most extensively studied.

According to systematic reviews conducted by the European Calcified Tissue Society, teriparatide use has been associated with significantly improved healing outcomes.

- Healing rates increased from 51% to 76% in surgically treated complete AFFs.

- Incomplete AFFs treated with prophylactic surgery, healing rates improved from 43% to 90% [4].

While much of the current evidence stems from case series and observational studies, the data consistently support a role for anabolic therapy in both acute fracture healing and long-term skeletal management following AFFs.

Beyond teriparatide, romosozumab has emerged as a valuable option, particularly in patients transitioning from denosumab therapy. Romosozumab not only helps maintain hip BMD but also provides additional benefit by increasing spinal BMD [67]. This makes it a strategic agent in patients at high risk of further skeletal deterioration, especially those with a history of prolonged anti-resorptive use.

To optimize bone remodeling while potentially reducing cost and side effects, cyclical teriparatide regimens have been proposed. In one study, alternating three-month on/off cycles of teriparatide successfully maintained bone turnover dynamics, though BMD gains were smaller compared to continuous therapy followed by anti-resorptive consolidation [68].

Despite the theoretical appeal, these regimens are not FDA-approved, and their use may be limited by reimbursement and regulatory challenges. Further research is needed to establish their efficacy and long-term outcomes in both fracture healing and osteoporosis management.

Given the rapid decline in BMD observed after discontinuation of anabolic agents, implementing maintenance therapy is critical to preserving treatment gains and preventing future fractures. In select postmenopausal women, raloxifene may be a suitable option following teriparatide, particularly for those at lower fracture risk or with contraindications to more potent anti-resorptives.

It is also important to consider the duration limitations of anabolic agents: both teriparatide and abaloparatide are approved for maximum of two years, while romosozumab is limited to one year of use due to safety concerns and regulatory guidelines. Therefore, strategic treatment plan—often involving transition to an anti-resorptive agent—is essential to ensure long-term skeletal health.

In patients who continue to exhibit high fracture risk—even after healing from AFFs and correction of secondary causes of osteoporosis—sequential or cyclical anabolic therapy approach may represent rational long-term strategy. Although cost and limited access remain significant barriers, particularly in healthcare systems with restrictive reimbursement policies, this strategy remains clinically viable in carefully selected patients. Individualized treatment planning, guided by ongoing risk assessment and patient preference, is essential to maximize benefit while navigating these constraints.

Summary of key points and clinical recommendations for AFFs in Asian Populations across multiple categories and topics is presented in Table 3.

Table 3
Key points & clinical recommendations for AFFs in Asian populations.

Area	Recommendation
1. Early Recognition & Diagnosis	• Maintain high clinical suspicion in patients on long-term anti- resorptives with thigh/groin pain • Use **bilateral femoral imaging** (X-ray, MRI, extended femoral DXA) to detect incomplete or bilateral AFFs early
2. Risk Assessment & Therapy Modification	• Regularly evaluate duration/type of anti-resorptive therapy • Consider **drug holidays** or **alternative agents** (eg, anabolic therapies) where appropriate • **Individualize therapy** for those with prior AFFs or prolonged exposure to bisphosphonates or denosumab
3. Surgical Management	• Use **prophylactic intramedullary nailing** for symptomatic or high-risk incomplete AFFs. • For **complete AFFs**, prefer **long intramedullary nails**; consider **plate fixation** if femoral anatomy (eg, bowing) complicates nailing • In **PAFFs**, choose fixation based on implant stability, location, and bone quality
4. Pharmacologic Management Post-AFFs	• **Avoid abrupt discontinuation of denosumab** to prevent rebound fractures; consider bridging with bisphosphonates, raloxifene, or anabolic agents • Use **anabolic agents** (eg, teriparatide, romosozumab) to promote healing and increase BMD, ensuring appropriate sequencing to avoid rebound bone loss
5. Surveillance & Follow- up	• Integrate **routine imaging surveillance** into long-term osteoporosis care for patients on anti-resorptives • Ensure **close follow-up** (clinical and radiographic) for conservatively managed patients to detect progression
6. Multidisciplinary & Individualized Care	• Promote **team-based care** involving endocrinologists, orthopedists, radiologists, and primary care providers • Provide **patient education** on symptoms, adherence, and importance of follow-up • Tailor management plans to **individual risk profiles** and local practice settings

4. Discussion

4.1. Regional perspective on atypical femoral fractures

This multinational survey conducted across AFOS member countries provides valuable insight into real-world clinical practices in the diagnosis and management of AFFs in Asia. While international consensus, particularly the 2013 ASBMR criteria [1] continues to guide recognition of AFFs, our findings reveal substantial variability in local interpretation, clinical decision-making and therapeutic approaches. These discrepancies likely reflect differences in clinician awareness, healthcare infrastructure, drug accessibility and national guidelines.

AFFs represent a rare but serious complication of long-term anti-resorptive therapy, particularly bisphosphonates and denosumab [6,13,17,81,82]. In a large cohort of 196,129 women, the hazard ratio for AFF increased substantially with longer bisphosphonate duration, and Asian ethnicity was associated with a higher risk than White women (HR for Asians vs Whites = 4.84) [1]. Further, clinical reviews have highlighted that although AFFs are uncommon, they are increasingly recognized and may alter the risk and benefit calculus of osteoporosis treatment [12,26,82].

Importantly, many AFOS clinicians report encountering similar fracture morphologies at non-femoral sites (eg, humerus, tibia, ulna) in patients on long-term anti-resorptive therapy. A recent systematic review found 151 atypical fractures in 114 published cases at non-classical sites, reinforcing the idea of a systemic skeletal effect of suppressed bone turnover [21]. While the ASBMR definition remains anatomically specific to the femur [1], these emerging data support a broader clinical concept.

4.2. Ethnic and anatomical risk factors in Asian populations

Several large population studies from Japan [8], Korea [20,80], and Thailand [21] confirm an increased incidence of AFFs in Asian populations, a finding consistently reflected in our survey responses. For example, in a multi-ethnic US cohort of women initiating bisphosphonates (N = 48,390), Asian women had an age-adjusted hazard ratio of 8.5 compared with white women for AFFs [19].

The pathophysiology behind this elevated risk is likely multifactorial. Anatomical studies have shown that factors such as greater femoral bowing and decreased neck-shaft angles, particularly in Asian women, may concentrate mechanical stress on the lateral femoral cortex [18,28,79,80]. For instance, the study concluded that Asian ethnicity remained an independent predictor of AFF status even after adjusting for femoral

geometry [18,79]. This biomechanical predisposition, combined with prolonged suppression of bone turnover, may explain why Asian populations appear more susceptible to AFFs under long-term anti-resorptive therapy.

Our survey results also reaffirm the dose- and duration-dependent relationship between anti-resorptive therapy and AFF risk—especially with bisphosphonates [4,6,17,81]. While denosumab has also been implicated, evidence suggests its absolute risk remains low and may be comparable to bisphosphonates [10,20,83]. Nevertheless, case reports of bilateral or recurrent AFFs after denosumab initiation (especially following prior AFF) emphasize the need for careful individualized pharmacologic planning [10,81].

4.3. Diagnostic strategies and the role of imaging

Timely diagnosis of AFFs is critical to preventing fracture progression and bilateral involvement. Across AFOS countries, there is increasing awareness of the importance of imaging—particularly in patients presenting with thigh or groin pain while on anti-resorptive therapy. Bilateral femoral radiographs remain first-line; however, MRI is especially sensitive for detecting early or incomplete AFFs when radiographs are inconclusive [37].

Moreover, regulatory bodies such as the European Medicines Agency have recommended periodic review of long-term bisphosphonate users and emphasized that AFFs, although rare, may occur after minimal trauma and require high clinical suspicion [14,25].

4.4. Treatment approaches for incomplete and complete AFFs

Management of incomplete AFFs remains an area of clinical debate and survey-derived practice variation. Many clinicians favor prophylactic intramedullary nailing for symptomatic patients or those with high-risk radiographic features (lateral beaking, cortical lucency) [38,46,71]. Meanwhile, conservative management might be appropriate for asymptomatic, low-risk individuals but requires rigorous monitoring due to risk of progression [4].

Complete AFFs are generally managed with IM nailing, which supports callus-mediated healing—a process less reliant on bone remodeling than direct cortical healing [46]. However, in patients with pronounced femoral bowing—common in Asian populations—standard IM nailing may not be optimal due to implant-anatomy mismatch [6,51–53]. In such cases, plate fixation may provide an alternative, though evidence suggests higher complication rates [53].

4.5. Evolving concepts: periprosthetic atypical femoral fractures (PAFFs)

A growing area of interest is the identification of atypical features in periprosthetic femoral fractures (PAFFs). Although current ASBMR definitions exclude fractures adjacent to arthroplasty implants [1], recent studies suggest that PAFFs may share pathophysiology with classic AFFs in long-term anti-resorptive users [72,73]. These fractures pose distinct biomechanical and surgical challenges due to implant presence and altered local loading, underscoring the need for further clinical research and tailored guidelines.

4.6. Osteoporosis management after AFFs: therapeutic dilemma

Post-fracture osteoporosis management is a complex challenge. While discontinuation of anti-resorptive agents is typically recommended following AFFs, the risk of rebound bone loss and vertebral fractures—particularly after denosumab withdrawal—is significant [57,59,70]. Bridging strategies using bisphosphonates, raloxifene or anabolic agents may mitigate that risk [60,61].

Anabolic therapies, especially teriparatide, have shown promise in enhancing fracture healing and reducing future fracture risk [43–45,74]. However, treatment sequencing remains critical: for instance, a direct switch from denosumab to teriparatide may produce rapid cortical bone loss and increased fracture risk [75,76]. Access challenges for anabolic therapies (cost, reimbursement, regulatory approval) continue to limit their use in many Asian countries [77].

4.7. Toward standardization: future directions

Ultimately, our survey underscores the need for standardized protocols across Asia for diagnosis, management and follow-up of AFFs. Routine bilateral femoral imaging, particularly among long-term anti-resorptive users presenting with prodromal pain, should be embedded into national osteoporosis care pathways [37,78].

Additionally, the expanding recognition of AFF-like fractures at non-femoral sites and in periprosthetic settings suggests that current classification criteria may need updating [21,69].

Further research is warranted to clarify optimal therapeutic strategies following AFF, including drug sequencing and the role of anabolic agents in prevention and healing. As our understanding of AFFs pathophysiology advances, regionally tailored guidelines that reflect the unique skeletal and ethnic characteristics of Asian populations will be critical in improving patient outcomes.

4.8. Limitations

This survey-based study, while comprehensive and multinational in scope, has several inherent limitations. First, as a cross-sectional survey of clinical practices among AFOS member countries, the findings rely on self-reported data, which may be subject to recall bias and reporting inaccuracies. Variability in healthcare infrastructure and resource availability across regions may also influence responses, potentially limiting the generalizability of the results to broader Asian populations or other global settings.

Second, the survey captures clinical practice patterns rather than patient-level outcomes, which constrains the ability to directly correlate specific diagnostic or therapeutic approaches with efficacy or safety profiles. Consequently, while the data highlight prevailing trends and regional differences, they do not provide definitive evidence regarding optimal management strategies for AFFs.

Third, heterogeneity in the interpretation and application of the 2013 ASBMR AFF case definition among respondents may have influenced diagnostic and treatment choices, especially in regions where localized guidelines or adaptations exist. This variability underscores the need for further harmonization and validation of AFFs diagnostic criteria in diverse populations.

Finally, evolving therapeutic options, including anabolic agents and novel surgical techniques, continue to emerge. The survey may not fully capture the most recent advances or the extent of their integration into routine clinical practice, particularly in resource-limited settings.

Future prospective studies with standardized data collection and patient outcome measures are warranted to complement these findings and guide evidence-based, region-specific recommendations for the management of AFFs.

5. Conclusions

This multinational survey provides important insights into current practices for the diagnosis and management of AFFs across diverse Asian populations. The results highlight both shared clinical strategies and region-specific variations, influenced by genetic predisposition, anatomical factors, and healthcare infrastructure. AFFs represent distinct clinical condition with multifactorial pathophysiology, requiring early identification, individualized management, and coordinated multidisciplinary care.

The elevated incidence of AFFs in Asian populations underscores the need for regionalized clinical guidelines that account for specific risk factors and optimize both surveillance and treatment approaches.

Although anti-resorptive therapies remain integral to osteoporosis management, their association with AFFs necessitates careful risk stratification, vigilant monitoring, and consideration of alternative or sequential options, including anabolic agents, particularly in high-risk individuals.

Advances in imaging, surgical intervention, and pharmacotherapy have improved management outcomes; however, continued research is essential to refine clinical algorithms and enhance patient care. Integrating standardized surveillance protocols and promoting international collaboration will be critical in addressing the unique challenges of AFF within the Asian context and improving long-term musculoskeletal health outcomes.

CRediT author statement

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Declaration of generative AI in scientific writing

The authors did not use generative AI or AI-assisted technologies in the preparation of this manuscript.

Conflicts of interest

Chung-Hwan Chen reports lecture fees from Amgen. Julie Li-Yu reports lecture fees and/or honoraria from Zuellig Pharma. Linsey Gani reports lecture fees from Amgen, DKSH, Servier, Zuellig; Advisory board member of Viatris, Organon. Satoshi Mori reports lecture fees from Amgen, Asahi-Kasei Pharma, Astellas Pharma. Ching-Lung Cheung reports research support from Amgen, MSD, and Sanofi. The other authors declare no competing interests.

Acknowledgments

We gratefully acknowledge the valuable contributions of the following experts who participated in this survey and shared their expertise. From Thailand: Thanut Valleenukul, Thawee Songpatanasilp, Unnop Jaisamrarn, Surapong Anuraklekha, Varalak Srinonprasert, Sumapa Chaiamnuay, Aasis Unnanuntana, Lalita Wattanachanya, Hataikarn Nimitphong, Noratep Kulachote, Ong-art Phruetthiphat, Rahat Jarayabhand, Tanawat Amphansap, Ekasame Vanitcharoenkul, Pojchong Chotiyarnwong, Natthinee Charatcharoenwitthaya. From South Korea: Kwang-kyoun Kim. From Malaysia: Swan Sim Yeap, Sharmila Sunita Paramasivam. From Taiwan: Chung-Hwan Chen. From the Philippines: Julie Li-Yu, Mark Anthony Sandoval. From Singapore: Linsey Gani. From Japan: Satoshi Mori. From Hong Kong: Ching-Lung Cheung. Their insights and contributions were essential to the development and completion of this manuscript. **ORCID** Thanut Valleenukul: 0009-0009-9777-5411. Thawee Songpatanasilp: 0000-0002-0612-5299. Unnop Jaisamrarn: 0000-0003-2412-9805. Surapong Anuraklekha: 0009-0006-1027-367X. Varalak Srinonprasert: 0000-0001-5311-7657. Sumapa Chaiamnuay: 0000-0001-6056-3559. Aasis Unnanuntana: 0000-0002-5742-298X. Lalita Wattanachanya: 0009-0007-2400-4697. Hataikarn Nimitphong: 0000-0003-0151-1622. Noratep Kulachote: 0000-0002-8643-8198. Ong-art Phruetthiphat: 0000-0001-7903-9685. Rahat Jarayabhand: 0000-0003-3873-2584. Tanawat Amphansap: 0000-0003-2148-3921. Ekasame Vanitcharoenkul: 0000-0002-6472-7511. Pojchong Chotiyarnwong: 0000-0002-0287-222X. Natthinee Charatcharoenwitthaya: 0000-0002-6472-7511. Kwang-kyoun Kim: 0000-0002-6844-5431. Swan Sim Yeap: 0000-0002-0474-3667. Sharmila Sunita Paramasivam: 0000-0003-3470-7015. Chung-Hwan Chen: 0000-0001-8941-4792. Julie Li-Yu: 0000-0002-1626-9747. Mark Anthony Sandoval: 0000-0003-0622-8287. Linsey Gani: 0000-0002-3699-2406. Satoshi Mori: 0000-0002-7660-5562. Ching-Lung Cheung: 0000-0002-6233-9144.

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