



# Reliability and diagnostic utility of radiographs in patients with incomplete atypical femoral fractures

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## Abstract

**Objective** The aim of this study was to evaluate the sensitivity and specificity of radiographs in identifying incomplete atypical femoral fractures and to determine interobserver and intra-observer reliability.

**Materials and methods** Anterior–posterior and lateral radiographs of 10 femurs with incomplete atypical femoral fractures confirmed using bone scintigraphy and magnetic resonance imaging, and 40 femurs without incomplete atypical femoral fractures confirmed using bone scintigraphy, were reviewed by 4 orthopedic surgeons and 4 radiology specialists. Sensitivity, specificity, accuracy, positive predictive value, and negative predictive value were calculated to determine a diagnosis of incomplete atypical femoral fractures. Interobserver reliability was measured using Fleiss' kappa value, and intra-observer reliability was ascertained using Cohen's kappa statistic.

**Results** Mean sensitivity, specificity, accuracy, and the positive and negative predictive values were found to be 89, 89, 89, 67, and 97% respectively, in diagnosing incomplete atypical femoral fractures using radiographs. Interobserver reliability was found to be at a good level (Fleiss' kappa = 0.66, standard error = 0.03, 95% confidence interval = 0.61–0.71). Intra-observer Cohen's kappa values ranged from 0.53 to 0.91.

**Conclusion** The use of radiography was satisfactory in identifying incomplete atypical femoral fractures, and the level of interobserver agreement was found to be good. As radiographs are associated with low positive predictive values, an advanced imaging method should be used when an increase in femoral cortical thickness is the only contributory factor to suspicion of an incomplete atypical femoral fracture.

**Keywords** Diagnostic accuracy · Femoral fractures · Insufficiency fractures · Reliability · Sensitivity and specificity

## Introduction

Osteoporosis is a common disease in the elderly population. The increased risk of bone fractures causes significant morbidity and mortality in these patients, and it poses an economic burden on healthcare systems [1–3]. Bisphosphonates are the most commonly used antiresorptive agents for osteoporosis treatment, and these drugs are potent inhibitors of osteoclast-mediated bone resorption [4, 5]. The efficacy of bisphosphonates in reducing the risk of osteoporotic fractures has been demonstrated in extensive clinical studies and, generally, they have been found to be safe

[6]. However, after 2005, an increasing number of atypical subtrochanteric and femoral diaphysis fractures have been reported. The long-term use of bisphosphonates is thought to be the cause of these fractures [7–11].

The American Society of Bone and Mineral Research (ASBMR) formed a task force related to atypical femoral fractures (AFFs), and the first report about these fractures was completed in 2010 [12]. In 2013, the diagnostic criteria were reviewed, and the ASBMR working group defined complete AFFs as noncomminuted, transverse, or short oblique subtrochanteric or femoral shaft fractures that extend across the entire femoral shaft, often with the formation of a medial spike [13]. The periosteal or endosteal thickening of the lateral cortex, in the form of “beaking” or “flaring,” is a major feature, whereas a generalized increase in the cortical thickness of the femoral diaphysis is a minor feature in the case definition of AFFs.

The long-term exposure of bisphosphonates leads to impaired bone quality with the suppression of bone remodeling

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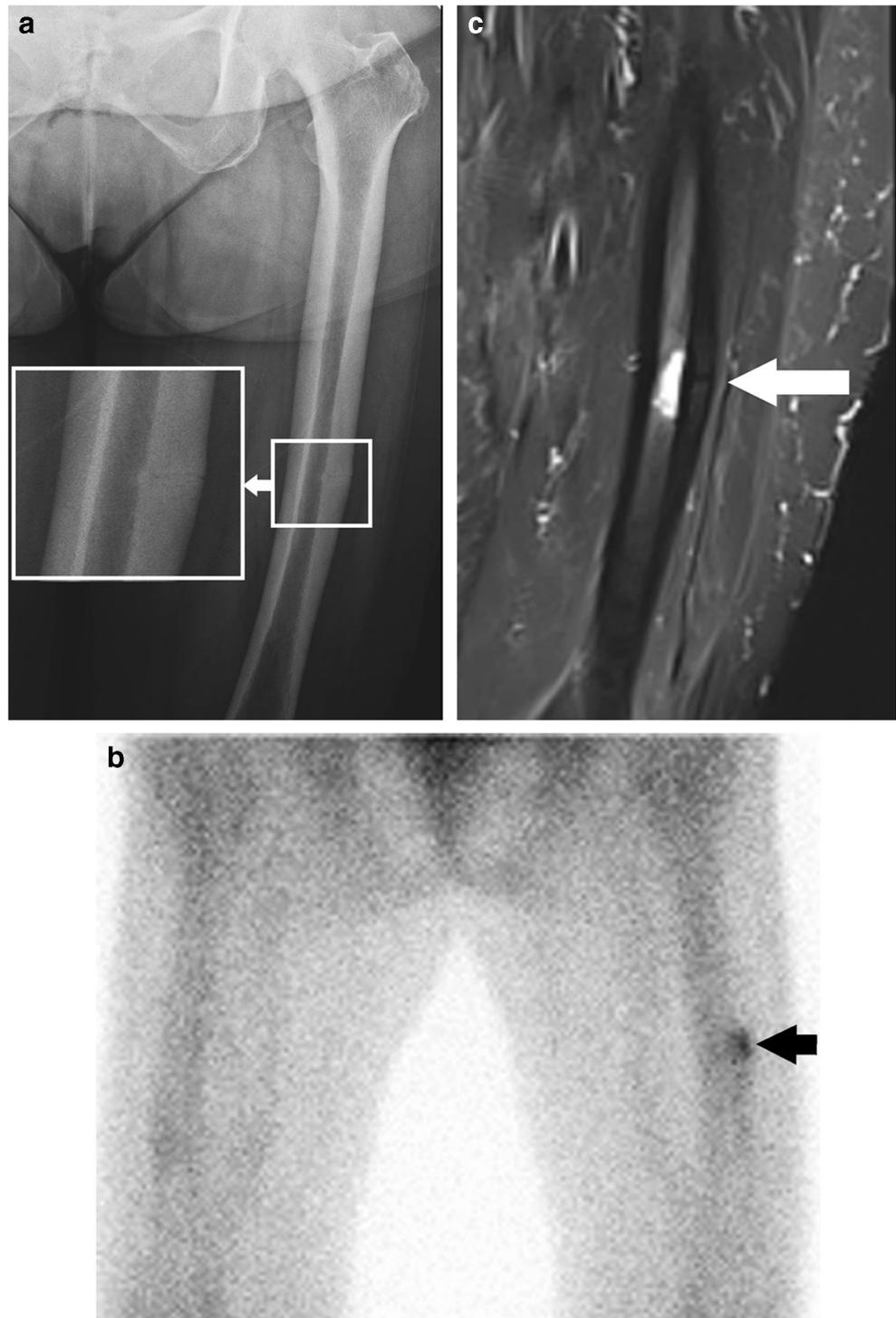
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and accumulation of microdamage, particularly at sites of high bone turnover [14]. Incomplete AFFs (iAFFs) may also be encountered in the form of an insufficiency fracture at the lateral cortex of the subtrochanteric or diaphyseal region of the femur. In contrast to typical stress fractures, in which the compressive load of the femur passes to the medial surface, iAFFs occur along

the lateral cortex of the femur, where the exposure to tensile forces is high [15].

The radiological features of an iAFF may vary as focal cortical thickening, radiolucency as a dreaded black line, striations or cavities [16]. Variations in the appearance of an iAFF can be interpreted differently in individual evaluations. Although several studies have evaluated the sensitivity,

**Fig. 1** **a** A woman aged 72 years presented with left thigh and knee pain, had been taking alendronate therapy for 8 years, and was diagnosed with an incomplete atypical femoral fracture in the left femur. Focal cortical thickening and a lucent line at the mid-diaphysis of the left femur (*white arrow* shows enlargement of the *white box*) is seen. Note that, without exception, all observers evaluated this radiograph as an incomplete fracture in both reviews. **b** Increased isotope uptake is seen at the lateral cortex of the left mid-diaphyseal femur (*black arrow*) with technetium-99 m bone scintigraphy of the same patient. **c** Coronal T2 MRI shows incomplete fracture line (*white arrow*) and adjacent bone marrow edema



specificity, and reliability of diagnostic imaging procedures for complete AFFs, to the best of our knowledge, similar studies have not been performed in this regard for iAFFs [17, 18]. The aim of this study was to evaluate the sensitivity and specificity of radiographs in identifying iAFFs and to determine interobserver and intra-observer reliability.

## Materials and methods

Approval for this study was granted by the Institutional Ethics Committee and informed consent waived for the retrospective review of medical records. A total of 24 consecutive patients presented to our clinic with complete AFFs between January 2014 and May 2018. The contralateral femur of the patients was examined, and iAFFs were identified in 6 of the patients. In addition, iAFFs were suspected in 13 patients with a history of long-term bisphosphonate use who presented at the outpatient polyclinic with knee or thigh pain. Bilateral femoral radiographs were obtained from these patients to conduct a comparison with the asymptomatic side. An incomplete fracture was detected in 4 of the 13 patients, and none of them had bilateral involvement.

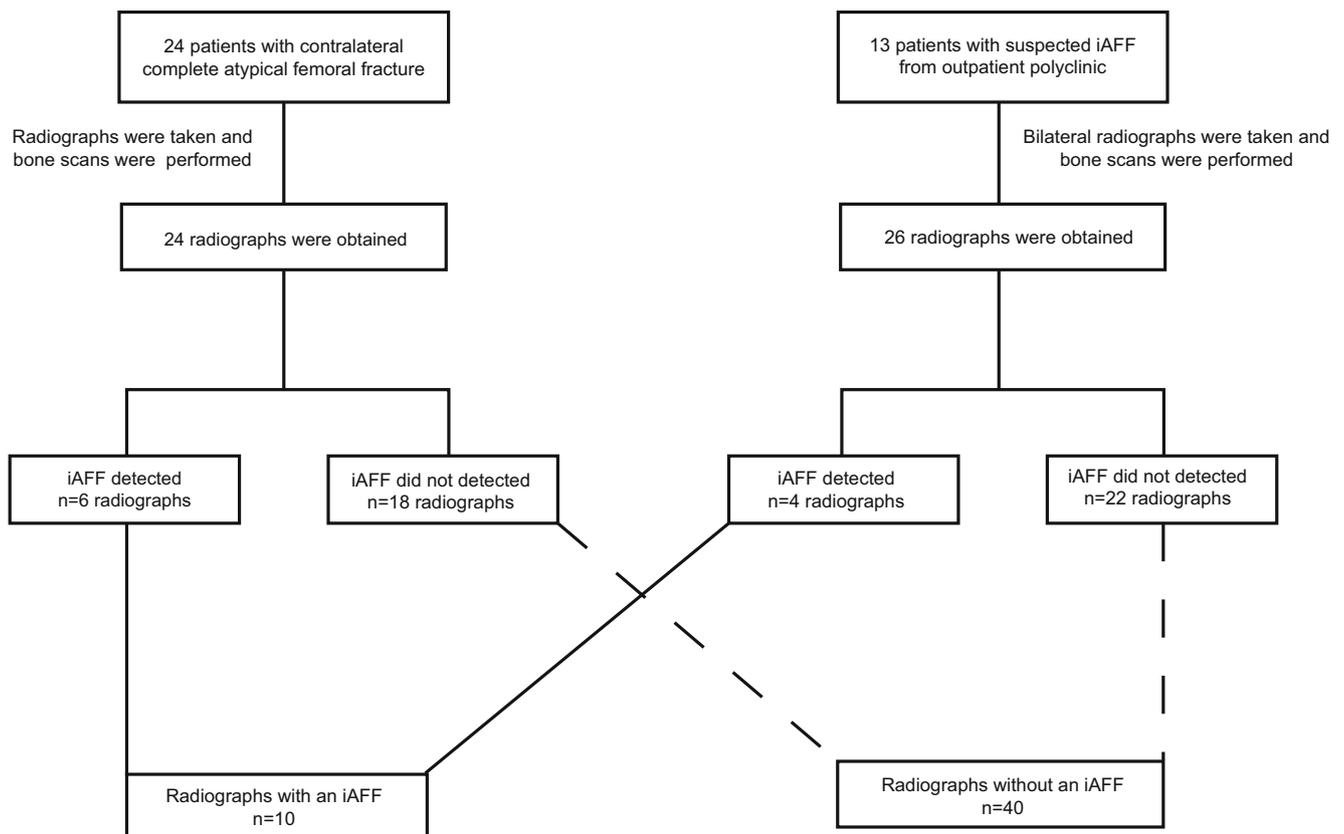
Evidence of an iAFF was confirmed in all cases using technetium-99 m bone scintigraphy, along with radiography. Presence of focally increased isotope uptake at the suspected

area was accepted as an iAFF. Magnetic resonance imaging (MRI) was also performed for 7 of the 10 patients in whom iAFF was detected and bone marrow edema was seen in all these cases (Fig. 1). MRI could not be performed for 3 patients; 2 of them had a cardiac implant, and 1 of them did not consent to undergo the MRI owing to claustrophobia. Lack of evidence of focally increased isotope uptake on the bone scans was accepted as a negative diagnosis, and a further MRI examination was not performed for these cases.

High-resolution digital images of the anterior–posterior and lateral radiographs of 50 femurs of 37 patients (10 femurs with iAFFs and 40 femurs without iAFFs) were included in this study. The flow diagram of the radiographs used in the study is shown in Fig. 2.

All 37 patients were women aged >50 years old (mean  $67.1 \pm 6.9$  years), and all of them had been receiving bisphosphonate treatment for >5 years (mean  $7.5 \pm 1.4$  years). The characteristics of patients with and without iAFFs are given in Table 1.

None of the images included any clinical information related to the patients. The radiographs were numbered using a random sequence and evaluated separately by four independent orthopedic surgeons and four radiology specialists with clinical experience ranging from 10 to 22 years. Before the evaluation, the observers were informed about the radiological characteristics of AFFs related to bisphosphonate treatment,



**Fig. 2** The flow diagram of radiographs used in this study. *iAFF* incomplete atypical femoral fracture

**Table 1** Characteristics of patients with and without an incomplete atypical femoral fracture (iAFF)

	iAFF ( <i>n</i> = 10)	Non-iAFF ( <i>n</i> = 27)	<i>p</i> * value
Age ± SD (years) (range)	69.3 ± 4.3 (62–76)	68.9 ± 7.7 (57–82)	0.853
Female gender (%)	10 (100%)	40 (100%)	N/A
Duration of BP treatment ± SD, years (range)	7.8 ± 0.9 (7–10)	7.7 ± 1.7 (5–12)	0.674

BP bisphosphonate, SD standard deviation, N/A not applicable, as all the patients were women

\*Statistical differences in continuous variables were calculated using the Mann–Whitney *U* test

and they were shown images of iAFFs from the literature [9, 13, 15]. When performing the assessments, the observers were blinded to the age of the patients, duration of bisphosphonate use, pain, and other personal clinical information. The observers were asked to evaluate the presence or absence of iAFFs according to the 2013 ASBMR criteria (Table 2) and to mark the location of an identified iAFF with a digital marker. The evaluations of the observers were recorded on standard data collection forms, and the data obtained from the forms were recorded electronically by two different researchers to prevent errors. Two weeks after the first evaluation, the same radiographs presented in a different sequence were evaluated once again by the observers.

Sensitivity, specificity, accuracy, and the positive and negative predictive values in the determination of iAFFs were calculated for each observer. Interobserver and intra-observer reliability were measured using Fleiss' kappa and Cohen's kappa respectively. The kappa values were evaluated as <0 poor agreement, 0.01–0.20 agreement at an insignificant level, 0.21–0.40 weak agreement, 0.41–0.60 moderate agreement, 0.61–0.80 good agreement, and 0.81–1.00 very good agreement [19]. The data obtained in this study were analyzed using IBM SPSS Statistics for Windows, version 22 (IBM, Armonk, NY, USA).

## Results

Mean sensitivity 89% (range = 70–100%), specificity 89% (range = 85–95%), accuracy 89% (range = 86–92%), positive predictive value 67% (range = 60–80%), and negative predictive value 97% (range = 93–100%) were reported for the

identification of iAFFs using radiography. The orthopedic surgeons and radiology specialists demonstrated similar diagnostic accuracy in detecting iAFFs. The diagnostic statistical values of each observer are shown in Table 3.

Overall interobserver reliability in identifying iAFFs was found to be at a good level (Fleiss' kappa = 0.66, standard error = 0.03, 95% confidence interval = 0.61–0.71). The interobserver reliability within orthopedic surgeons and radiology specialists showed similar results (Fleiss' kappa = 0.67, standard error = 0.06, 95% confidence interval = 0.55–0.78, and Fleiss' kappa = 0.63, standard error = 0.06, 95% confidence interval = 0.51–0.74 respectively). The intra-observer Cohen's kappa values ranged from 0.53 to 0.91 (Table 4).

## Discussion

In recent years, the frequency of AFFs, which are thought to be due to the prolonged use of bisphosphonates, is increasing [20]. The ASBMR formed a task force related to AFFs and defined the major and minor characteristics of these fractures [12, 13]. The characteristics of iAFFs are described as lateral cortex involvement only, periosteal or endosteal thickening of the lateral cortex, the presence of unilateral or bilateral prodromal symptoms, and generalized cortical thickening in the femur diaphysis.

The radiographic appearance of iAFFs varies as they are characterized by a wide range of features. Focal elevations that resemble bumps on the lateral cortex of the femur are frequently the only sign of an iAFF on early radiographs. Sometimes, a transverse radiolucent line in a “mound”-shaped focal elevation, defined as the “dreaded black line,” is

**Table 2** American Society of Bone and Mineral Research Task Force 2013 revised case definitions for atypical femoral fractures [13]

Major features	Minor features
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less	Generalized increase in the cortical thickness of the femoral diaphysis
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	Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex	Bilateral incomplete or complete femoral diaphysis fractures
The fracture is noncomminuted or minimally comminuted	Delayed fracture healing
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”)	

**Table 3** Sensitivity, specificity, positive predictive value, and negative predictive value of the radiographs for each observer

	True-positive ( <i>n</i> = 10)	True-negative ( <i>n</i> = 40)	False-positive	False-negative	Sensitivity (%)	Specificity (%)	Accuracy (%)	Positive predictive value (%)	Negative predictive value (%)
OS 1	10	34	6	0	100	85	88	63	100
OS 2	10	35	5	0	100	88	90	67	100
OS 3	8	38	2	2	80	95	92	80	95
OS 4	8	36	4	2	80	90	88	67	95
Mean diagnostic values of orthopedic surgeons ± SD					90 ± 12	90 ± 4	90 ± 2	69 ± 8	97 ± 3
RS 1	9	35	5	1	90	88	88	64	97
RS 2	10	35	5	0	100	88	90	67	100
RS 3	7	37	3	3	70	93	88	80	93
RS 4	9	34	6	1	90	85	86	60	97
Mean diagnostic values of radiology specialists ± SD					88 ± 13	88 ± 3	88 ± 2	65 ± 4	97 ± 3
Mean diagnostic values of all observers ± SD					89 ± 11	89 ± 4	89 ± 2	67 ± 6	97 ± 3

OS orthopedic surgeon, RS radiology specialist, SD standard deviation

apparent [9, 16]. Although several studies have evaluated the diagnostic accuracy and interobserver reliability of radiographs for complete AFF, to the best of our knowledge, similar studies have not been performed in this regard on iAFFs [17, 18]. Therefore, we aimed to evaluate the diagnostic accuracy, interobserver reliability, and intra-observer reliability of radiography in diagnosing iAFFs.

We used radiographs of 10 iAFFs and 40 radiographs of femurs without iAFFs in a similar age group for this study. It can be difficult to diagnose an iAFF in patients with extreme lateral femoral bowing or generalized cortical thickening of the femur. Accordingly, advanced imaging methods with high sensitivity, such as bone scintigraphy or MRI, were used to confirm a diagnosis of iAFFs in the study [21].

In global medical diagnostic testing, a positive predictive value >90%, sensitivity >85%, and specificity >85% are usually considered to be “high” [22, 23]. Sensitivity, specificity, and

accuracy were high (89%), the positive predictive value was low (67%), and the negative predictive value was high (97%) in the current study in diagnosing iAFFs using radiography. These results indicate that the radiographs exhibit a satisfactory level of effectiveness in the screening of the iAFFs.

Although the “false-negative” assessment rate among observers was low (Fig. 3), numerous “false-positive” interpretations of iAFFs were made during the analysis, as reflected by the low mean positive predictive value. When we reviewed the “false-positive” cases, we observed that some observers marked diffuse cortical thickenings (Fig. 4) as iAFFs.

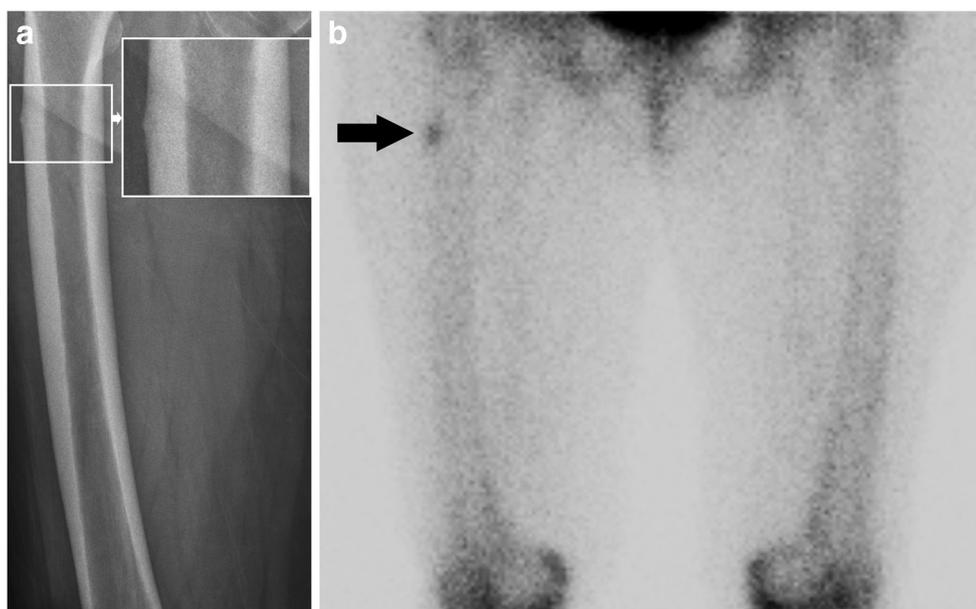
We think that there is a lack of clarity in the definition of diffuse cortical thickening according to the ASBMR criteria, and uncertainty about the diagnostic importance of cortical thickening. Moreover, the presence of diffuse cortical thickening in AFFs is also controversial. Niimi et al. found no significant difference with respect to femoral cortical thickening between osteoporotic patients with long-term bisphosphonate use and those not receiving bisphosphonate treatment [24]. In addition, Koeppen et al. compared femoral cortical thickenings in patients aged >55 years with ordinary femoral fractures and those with AFF, and they found no significant difference; therefore, they recommended that this criterion should be revised [25]. Within the ASBMR criteria, there are clinical criteria, such as prodromal syndrome, in addition to the radiological criteria. Another reason for a low positive predictive value may be that the observers had no clinical information about the patients. In our opinion, if an iAFF is suspected both clinically and radiologically, it would be reasonable to use an advanced imaging modality.

When the interobserver reliability was evaluated, the kappa values were found to be at a good level of agreement. In a more detailed examination of the intra-observer kappa values, the agreement was found to be at a moderate level in 1 orthopedic

**Table 4** Intra-observer reliabilities of each observer for the determination of iAFFs

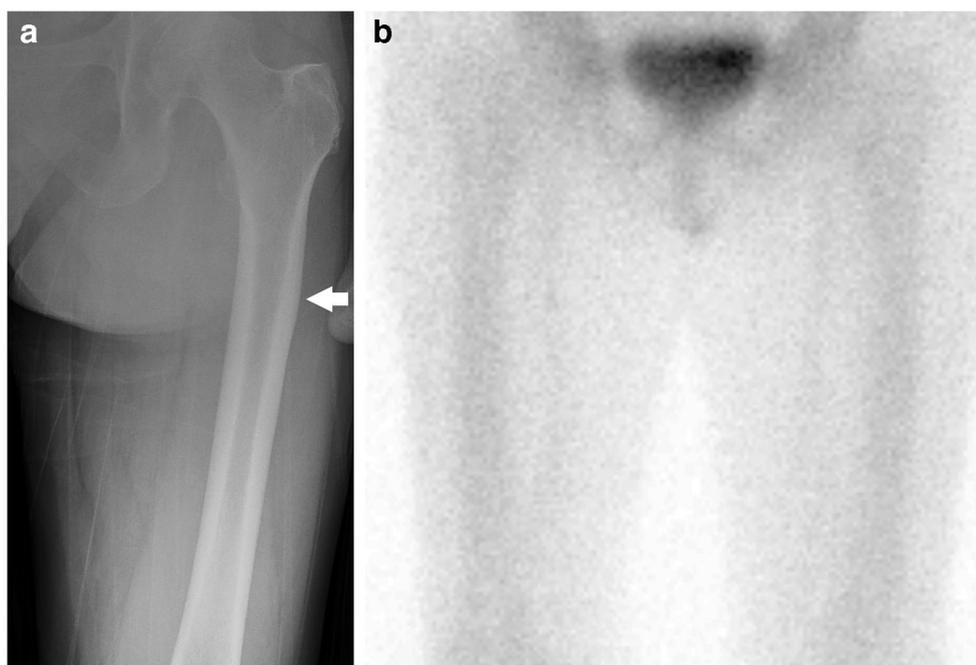
	Cohen's kappa	SE	Minimum – maximum (95% CI)	<i>p</i> value
OS 1	0.91	0.06	(0.79–1.00)	<0.001
OS 2	0.53	0.13	(0.34–0.82)	<0.001
OS 3	0.65	0.14	(0.37–0.93)	<0.001
OS 4	0.88	0.08	(0.73–1.00)	<0.001
RS 1	0.67	0.12	(0.44–0.91)	<0.001
RS 2	0.75	0.11	(0.54–0.95)	<0.001
RS 3	0.73	0.13	(0.48–0.98)	<0.001
RS 4	0.91	0.07	(0.77–1.00)	<0.001

CI confidence interval, OS orthopedic surgeon, RS radiology specialist, SE standard error



**Fig. 3** **a** A woman aged 64 years presented with right hip pain, and had been taking alendronate therapy for 8 years. The radiographic image was rated false-negative for the diagnosis of an iAFF by several observers. The radiographic image of the right femur shows small periosteal focal cortical thickening (*white arrow* shows enlargement of the *white box*) at the subtrochanteric region. Two orthopedic surgeons (OS3 and OS4) and three radiology specialists (RS1, RS3, and RS4) interpreted this

radiograph as normal in the first evaluation. In the second evaluation, no incomplete fracture was detected by three orthopedic surgeons (OS2, OS3, and OS4) and two radiology specialists (RS1 and RS2). **b** Increased isotope uptake is seen at the lateral cortex of the right subtrochanteric region (*black arrow*) with technetium-99 m bone scintigraphy of the same patient. Unfortunately, MRI could not be performed owing to the patient suffering from claustrophobia



**Fig. 4** **a** A woman aged 75 years presented with hip and back pain, and had been taking alendronate therapy for 9 years. The radiographic image was rated false-positive for the diagnosis of an iAFF by several observers. Increased cortical thickness along the subtrochanteric region of the proximal femur (*white arrow*) is seen on radiography. Two orthopedic surgeons (OS1 and OS2) and two radiology specialists (RS2 and RS4) marked the subtrochanteric area as an iAFF in the first evaluation. In

the second review, the same orthopedic surgeons and one radiology specialist (RS2) interpreted the same area as an incomplete atypical fracture. **b** Bone scintigraphy examination was performed owing to the increased cortical thickness of the right femur and a suspected iAFF. No increased isotope uptake in the two femurs was observed and the patient was evaluated as not having an incomplete fracture

surgeon, at a good level in 1 orthopedic surgeon and 3 radiology specialists, and at a very good level in 2 orthopedic surgeons and 1 radiology specialist. Based on these results, it can be interpreted that the observers made similar judgements for the same cases.

Adams et al. evaluated the sensitivity, specificity, and reliability of the radiological characteristics of complete AFFs as defined by the ASBMR criteria. According to that study, the two most sensitive fracture characteristics in the differentiation of AFFs were a transverse fracture pattern in the lateral cortex and a lack of comminution (94 and 93% respectively), and the determination of generalized cortical thickening exhibited the lowest sensitivity (49%) [17]. Moreover, interobserver reliability for the identification of generalized cortical thickening was evaluated as “weak” ( $\kappa = 0.16$ ).

The current study had both limitations and strengths. We think that the use of advanced imaging methods for the confirmation of the presence or absence of iAFFs is more objective than the determination of AFFs by a committee decision using only the radiographs. The limitations of this study are that no power analysis was performed before the study and the number of radiographs with iAFFs was small. In addition, the observers only evaluated the radiographs of one femur for each patient, whereas in clinical practice, a comparison with the contralateral side assists in the diagnosis of an . If the observers in the current study had been able to compare the images with those obtained for the contralateral side, their findings on diffuse cortical thickening might have been considerably enhanced, leading to a lower false-positive rate and higher mean positive predictive value.

In conclusion, the use of radiography was satisfactory in identifying iAFFs, and the level of interobserver agreement was found to be good. As radiographs are associated with low positive predictive values, an advanced imaging method should be used when an increase in femoral cortical thickness is the only contributory factor to a suspected iAFF.

## Compliance with ethical standards

**Conflicts of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All of the procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

**Informed consent** The need to obtain informed consent was waived as this research comprised a retrospective review of the medical records.

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