




Ghost Sign on Diffusion-Weighted Imaging Generated Apparent Diffusion Coefficient Map: Additional MRI Diagnostic Marker for Extremity Osteomyelitis

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Abstract

Objective The aim of this study was to determine the sensitivity and specificity and inter-reader reliability of previously known “ghost sign” and “penumbra sign” on T1-weighted (T1W) imaging and “ghost sign” on apparent diffusion coefficient (ADC) map in osteomyelitis (OM) of the extremities.

Materials and Methods In this cross-sectional retrospective study, two fellowship-trained musculoskeletal readers blinded to final diagnosis of OM versus no OM were asked to report the penumbra sign and ghost sign on T1W images and ghost sign on ADC map, as well as diagnosis of OM. Cohen’s kappa was used. Diagnostic performance measures including sensitivity, specificity, and accuracy were calculated.

Results A sample of 178 magnetic resonance imaging (MRI) scans of pathology-proven cases were included in this study, with 41 being positive for OM and 137 being negative for OM. There was a fair inter-reader agreement for imaging signs, and moderate agreement of 0.60 for OM. The sensitivities of the penumbra sign on T1W imaging, ghost sign on T1W imaging, and ghost sign on ADC map for OM are 3.7, 9.8, and 19.5%, respectively, while their respective specificities are 98.9, 97.8, and 94.5%, respectively. All three imaging signs showed a similar (good) accuracy of 76 to 78%.

Conclusion The ghost sign on ADC can be used as an additional marker for OM and is a similarly highly specific but a more sensitive sign for OM than the conventionally used penumbra sign and ghost sign on T1W imaging.

Keywords

- ▶ osteomyelitis
- ▶ MRI
- ▶ ghost sign
- ▶ DWI
- ▶ penumbra sign

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Key Points

- The ghost sign on ADC can be used as a helpful indicator of osteomyelitis.
- Across two fellowship-trained musculoskeletal readers, there was a fair inter-reader agreement for imaging signs and moderate agreement for OM.
- The ghost sign on ADC is a similarly highly specific but a more sensitive sign for osteomyelitis than the conventionally used penumbra sign and ghost sign on T1W imaging. All three imaging signs showed a similar (good) accuracy of 76 to 78%.

Introduction

Osteomyelitis (OM) is an infection of the bone secondary to direct inoculation, hematogenous seeding, or contiguous spread of microbial organisms, most commonly from *Staphylococcus aureus*.¹ This condition manifests as an inflammatory destruction of the bone, with many cases occurring in men, older individuals, and diabetes mellitus patients. Adult OM commonly occurs in the setting of regional trauma, surgery, or infected skin ulcerations. While the incidence of OM has not been characterized consistently, it has been increasing over time, contributing to an estimated amount of up to 1 in 675 hospital admissions in the United States annually.²

Cases of OM secondary to contiguous spread from ulcerations are growing in frequency as the older population is increasing in the United States and increasingly develops comorbidities, such as diabetes mellitus and immunocompromised status.³ Diabetic patients encompass as high as a 25% lifetime risk of developing diabetic foot ulcers. Approximately 20% of these patients with diabetic foot ulcers progress to diabetic foot osteomyelitis (DFO). Treatments for DFO patients range from antibiotic therapy and local wound care to surgical debridement and/or amputation. As such, DFO management entails substantial health care and economic burdens, with Medicare spending ranging anywhere from \$9 to 13 billion annually to care for these patients.⁴ Therefore, timely and accurate diagnosis of OM is critical for prompt treatment, mitigating the need for more aggressive surgical interventions, and to improve patient outcomes and overall quality of life.

According to the American College of Radiology (ACR) appropriateness criteria, patients suspected of OM of the extremities should be screened by plain radiographic imaging with magnetic resonance imaging (MRI) reserved as the more definitive imaging modality.⁵ Diagnosis can then be confirmed via bone biopsy and/or cultures.⁶ MRI is very useful due to its high sensitivity, excellent anatomic detail, and ability to determine the extent of the disease.⁷⁻⁹ In particular, the “ghost sign” on T1-weighted (T1W) MRI sequence is reported to be a useful indicator of OM. The ghost sign refers to the phenomenon that the infected bone seems to disappear and blend into surrounding soft tissues due to increasing infiltration and hypointensity of the marrow and cortical erosion while bone may be still apparent on T2W imaging.¹⁰⁻¹² Similarly, the “penumbra sign” has been described as rim of hyperintensity on T1W images around a subacute abscess cavity in the bone due to a highly vascu-

larized granulation tissue rim and it assists in differentiation of infection from bone tumor.^{13,14} These signs have been reported in small sample sizes in previous studies without a case-control assessment or inter-reader analysis.

Diffusion-weighted imaging (DWI) has become increasingly used as a diagnostic tool due to its incremental role in assessing the presence of bone or soft-tissue lesions. Combined with quantitative parameters such as the apparent diffusion coefficient (ADC), DWI has the potential to improve characterization of these lesions over conventional MRI, especially for determination of soft-tissue or intraosseous abscess.^{9,15-17} Of note, ADC maps have been found to display a “ghost sign,” that is, disappearance of black bone on ADC map and appearance of diffuse hyperintensity compared to normal adjacent bones in the setting of OM due to diffusion enhancement.¹⁸ Due to fat suppression used on DWI, the bones and muscles are hypointense on ADC maps. The ghost sign on ADC is seen as disappearance of bony and marrow outlines with diffuse hyperintense signal. This sign on ADC map is an early sign of acute OM and can be present despite normal contours of bone on T1W and T2W images (►Fig. 1). In the authors' experience, simple vasogenic or reactive edema without OM preserves the DWI signal with minimal hyperintensity and the ghost sign is not apparent. However, there is no systematic study assessing its value in the diagnosis of OM or DFO and inter-reader assessment.

The purpose of this study was to determine the sensitivity and specificity and inter-reader reliability of previously known “ghost sign” and “penumbra sign” on T1W imaging and “ghost sign” on ADC map in extremity OM. We hypothesized that the presence of the “ghost sign” on ADC map has higher diagnostic accuracy and sensitivity than the one on T1W imaging.

Materials and Methods

This study was a cross-sectional, retrospective, multireader evaluation that was conducted in adherence to the institutional review board (IRB) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations. The study received local institutional IRB approval and informed consent was waived.

Patients

An electronic search was conducted in the local institutional Picture Archival and Communications System (PACS) to identify MRI and radiographic studies of extremity OM between the period of June 2015 and May 2019. Keywords

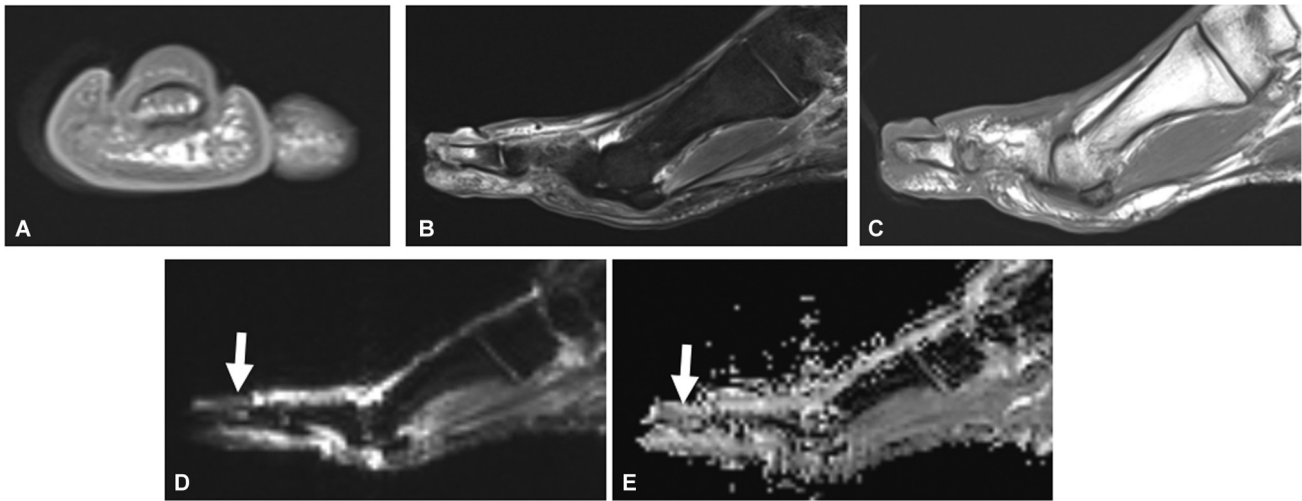


Fig. 1 Patient with proven osteomyelitis of the first distal phalanx. (A) Axial T1-weighted (T1W), (B) sagittal short tau inversion recovery (STIR), and (C) T1W images of the first distal phalanx lacking the “ghost sign.” Corresponding (D) sagittal diffusion-weighted imaging (DWI) and (E) apparent diffusion coefficient (ADC) map of the first distal phalanx showing the “ghost sign” (arrows).

used include OM, extremity, foot, ankle, and MRI. The inclusion criteria were all sexes, aged ≥ 14 years, both upper and lower extremities, at least two-view radiographic imaging and complete MRI with and without contrast and DWI, and a diagnosis of OM that is either confirmed or excluded by pathology reference standards via surgery or CT-guided biopsy and/or bone cultures within 1 week of the MRI included. The exclusion criteria included patients with incomplete imaging as determined by a senior radiologist and patients with metal in field of view degrading the imaging resolution. In our setup, both radiologists and podiatrists perform bone biopsies in all stages of disease severity. There was no bias placed in selection criteria and OM cases were in different stages of severity. Cultures were available in abscess and OM cases as an additional finding and not as an exclusive finding. From there, patients' cases with complete sets of multiplanar T1W, T2W, pre- and postcontrast, and DWI were chosen by a senior radiologist for inter-reader analysis and diagnostic accuracy assessment. A consecutive sample of 227 patients was identified with 157 patient cases containing a complete set of MRIs with DWI. The senior radiologist created a PowerPoint presentation for the readers with a final total of 178 cases using imaging from the 157 unique patients. Cases that utilized imaging from the same patient depicted different areas of interest.

Radiograph and Magnetic Resonance Imaging

The imaging protocol is outlined in ► **Table 1**. There were both 1.5- and 3-T MRI protocols but with similar imaging parameters, all obtained on Aera and Skyra Siemens scanners (Erlangen, Germany). A final total of 178 scans were identified, with 81 scans performed on the 1.5-T MRI machine and 97 scans performed on the 3-T MRI machine.

Imaging Review

Two attending radiologists, both with more than 5 years of postmusculoskeletal fellowship experience in OM imaging, were trained using 10 scans from the sample set. These scans

were also included in the final data set. All scans were read blinded to the final diagnosis and other readers' interpretations. During the readings, the readers were asked to interpret the conventional and DWI MR images of each scan and document their findings onto a provided data sheet (created on Microsoft Excel). The readers were asked to document the following findings: the presence of the penumbra and ghost signs on T1W imaging, ghost sign on ADC, and the presence of OM. The findings were independently assessed on both conventional and DWI sequences.

Statistics

The inter-reader agreement in characterizing the penumbra sign on T1, ghost sign on T1, ghost sign on ADC, and OM diagnosis was assessed using Cohen's kappa. Cohen's kappa was interpreted as slight agreement: 0.00 to 0.20; fair agreement: 0.21 to 0.40; moderate agreement: 0.41 to 0.60; substantial agreement: 0.61 to 0.80; and almost perfect agreement: 0.81 to 1.00.¹⁹ A *p*-value less than 0.05 was considered significant. All analyses were done in SAS 9.4 (SAS Institute, Inc, Cary, NC). Diagnostic performance measures for detecting OM including sensitivity, specificity, and overall accuracy were calculated for each sign for the readers using the final pathology as the reference standard.

Results

A final sample of 178 MRI pathology-proven extremity cases were included in this study, with 41 being positive for OM and 137 being negative for OM. Of the 41 positive OM cases, 39 were direct spread and 2 were hematogenous spread. Three cases were positive for intraosseous abscess (► **Table 2**). The percentage of cases with samples obtained from surgical biopsy and imaging-guided radiology procedures were 94.6 and 5.4%, respectively. Case distribution of the imaging signs can be found in ► **Table 3**.

The regions of interest showcased in the cases included the shoulder ($n=9$), humerus ($n=2$), elbow ($n=1$), wrist

Table 1 Infection MRI protocol

MR sequence	2D/3D	Slice thickness/gap (mm)	Pixel size (F × P), mm	TR (repetition time), ms	TE (echo time), ms	Other
Three-plane scout	2D	5		8	4	
Coronal T2W DIXON	2D	4/0.4	0.5 × 0.6	3,000–4,500	40–45	
Sagittal STIR	2D	4/0.4	0.5 × 0.6	3000–4,500	30–35	
Sagittal T1W TSE	2D	4/0.4	0.5 × 0.6	450–600	6–9	
Axial T2W DIXON	2D	3–4/0.4	0.5 × 0.6	3,000–4,500	40–45	
Axial T1W TSE	2D	3–4/0.4	0.5 × 0.6	450–600	6–9	
Axial T1W DIXON or VIBE PRE	3D	1.5 ISO/0	Acquired ISO	Lowest	Lowest	
Axial T1W DIXON or VIBE POST	3D	1.5	Acquired ISO	Lowest	Lowest	Isotropic
Axial DWI	2D	4/0	2 × 2	2,500–4,500	65–70	B: 50, 400, 800 ADC map send to PACS

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FS, fast (turbo) spin; MRI, magnetic resonance imaging; PACS, Picture Archival and Communications System; STIR, short tau inversion recovery; TSE, turbo spin echo.

Table 2 Demographics data

Patient population	
Male (mean age ± SD)	54.7 ± 13.0
Female (mean age ± SD)	55.3 ± 14.1
Sample case distribution	
Lower extremity	
Ankle	7
Femur	11
Foot	112
Hip	5
Knee	14
Tibia/fibula	11
Upper extremity	
Elbow	1
Shoulder	9
Wrist	2
Hand	4
Humerus	2

Table 3 Case distribution of osteomyelitis, penumbra sign, and ghost sign

Presence	Number of cases
Osteomyelitis	41
Penumbra sign	5
Ghost sign on T1	9
Ghost sign on ADC	11

Abbreviation: ADC, apparent diffusion coefficient.

(*n* = 2), hand (*n* = 4), hip (*n* = 5), femur (*n* = 11), knee (*n* = 14), tibia/fibula (*n* = 11), ankle (*n* = 7), and foot (*n* = 112). A few selected cases can be seen in ►Figs. 1–4. Of the 157 unique patients, 97 were males and 60 were females. The average ages of the men and women in this study were 54.7 ± 13.0 and 55.3 ± 14.1 years, respectively (►Table 2).

Inter-Reader Agreement

Among the two readers, there was a fair inter-reader agreement of 0.33 (95% confidence interval [CI]: [–0.15, 0.63]) for the penumbra sign on T1W, slight agreement of 0.11 (95% CI: [–0.14, 0.37]) for the ghost sign on T1W, fair agreement of 0.26 (95% CI: [0.05, 0.49]) for the ghost sign on ADC, and moderate agreement of 0.60 (95% CI: [0.49, 0.71]) for OM.

Diagnostic Performance and Confidence Level

The analysis can be found in ►Table 4. The mean sensitivity, specificity, and accuracy of the two readers for the penumbra sign on T1W were 3.7, 98.9, and 77.0%, respectively. The mean sensitivity, specificity, and accuracy of the ghost sign on T1W were 9.8, 97.8, and 77.5%, respectively. For the ghost sign on ADC, the mean sensitivity, specificity, and accuracy were 19.5, 94.5, and 77.3% respectively. The diagnostic accuracy for OM on conventional MRI plus DWI was 76.4% for reader 1 and 67.4% for reader 2 (►Figs. 1–4).

Discussion

This study of 178 pathology-proven scans suspicious for OM finds fair agreements for previously described MRI signs of OM and intraosseous abscess and moderate agreement for OM. This is the first report of inter-reader reliability of these MRI signs as interpreted by fellowship-trained radiologists. The ghost sign on ADC was also found to be a highly specific

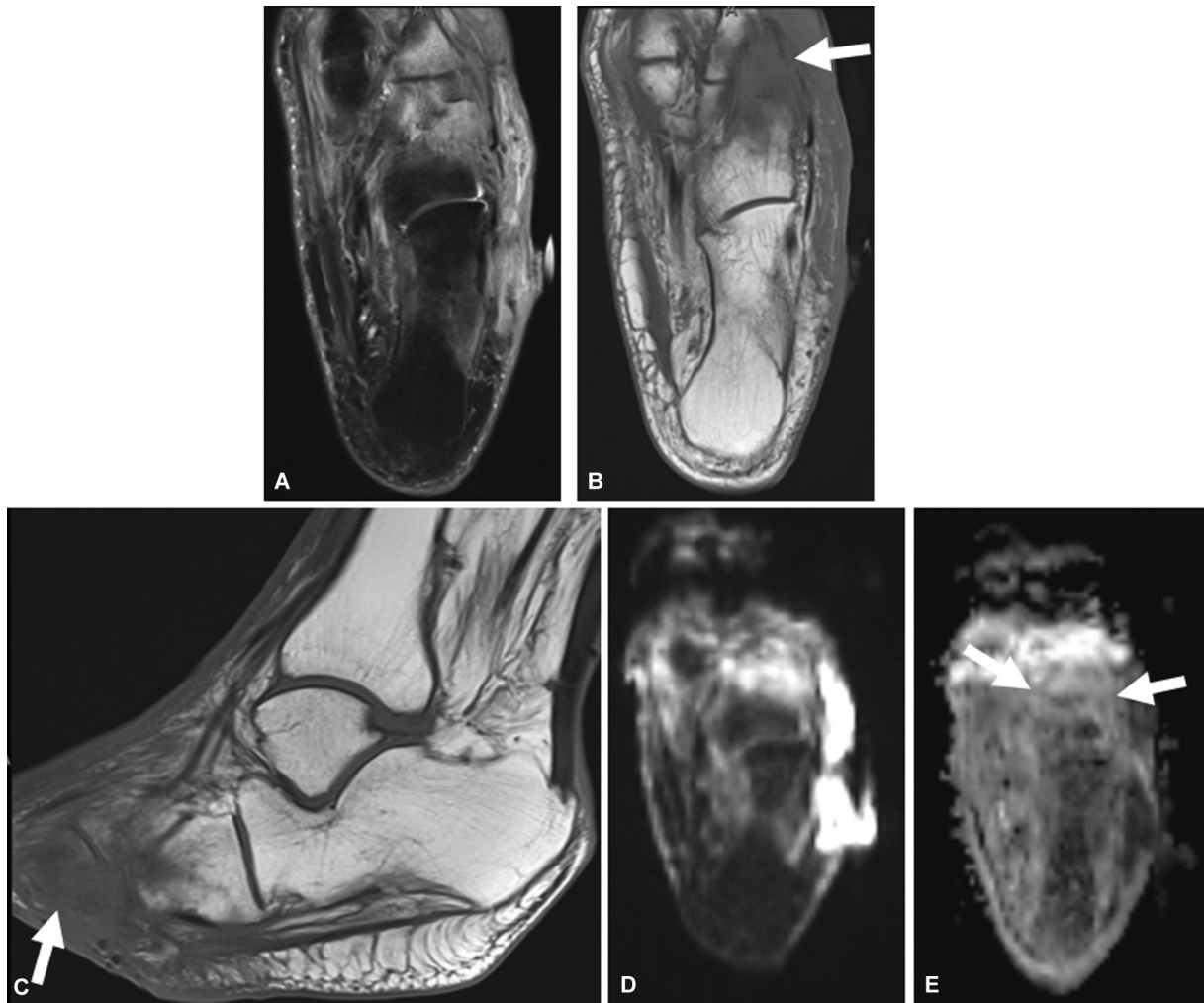


Fig. 2 Patient with osteomyelitis of the left third through fifth residual metatarsal bases and cuboid, status post partial amputation of the foot. (A) Axial T2-weighted (T2W) Dixon water map, (B) axial T1W, and (C) sagittal T1W images of the left ankle showing the “ghost sign” on T1W image (arrows). (D, E) Corresponding diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map, respectively, of the region of interest showing the “ghost sign” (arrows).

sign for OM like on T1W images and, in addition, showed somewhat more sensitivity on DWI. When present, the penumbra sign on T1W was also a highly specific MRI sign. MRI is currently the modality of choice for patients with radiographs suspicious of OM. Thus, finding the diagnostic accuracy of these previously described signs is imperative.

The strength of this study was a larger case-control sample than previous small-scale studies. The penumbra sign has been shown to be a useful tool in distinguishing infectious processes from bone tumors. This validates the study by McGuinness et al, which found high specificity for this sign but low sensitivity for musculoskeletal infection.¹⁴ However, the previous study did not include controls and the study was limited to OM versus tumors.

In recent years, DWI combined with ADC has increasingly emerged as a useful tool in musculoskeletal MRI for various pathologies.^{20–23} Guirguis et al evaluated the incremental value of DWI over conventional MRI for the diagnosis of OM and found no significant difference between the groups, with a sensitivity and specificity of 0.97 and 0.97, respectively, with conventional MRI and 0.97 and 0.94, respectively, with

the addition of DWI.²⁰ However, another study by Kruk et al found that DWI with quantitative ADC measurements are helpful tools for identifying OM, with calculated cutoff values aiding in the differentiation between abnormal and healthy bone.²⁴ In another work, Guirguis et al described the ghost sign on ADC and its use-case in OM in a review article¹⁸; however, this initial report tested the diagnostic accuracy and found this sign to be useful. This study is one of the first among the current literature to evaluate the diagnostic performance of the ghost sign on ADC. Since readers do not routinely measure the ADC values in infections, qualitatively assessing this imaging sign may assist the diagnosis of OM. It also showed somewhat higher sensitivity and inter-reader agreement than the ghost sign on T1W imaging. Nevertheless, the sensitivity of these signs on both imaging sequences remains low. Thus, considering both T1W and ADC images together during OM evaluation might make these signs useful in practice. High specificity and low sensitivity of this ghost sign may aid in ruling out OM. These signs may also aid in interpretations of less-experienced readers, which were lacking in the Guirguis et al study. There has been

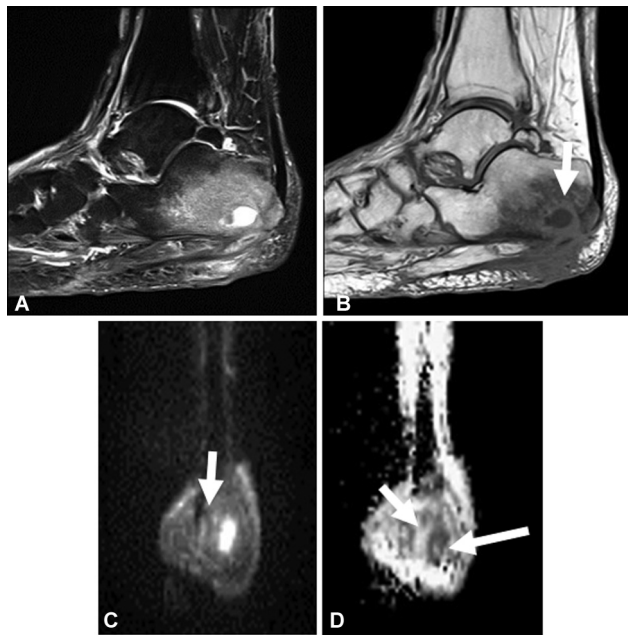


Fig. 3 Patient with calcaneal osteomyelitis and intraosseous abscess. (A) Sagittal short tau inversion recovery (STIR) and (B) T1W images of the left ankle showing the “penumbra sign” (arrow). Corresponding (C) coronal diffusion-weighted imaging (DWI) and (D) apparent diffusion coefficient (ADC) map of the left ankle show the “ghost sign” (small arrow) and diffusion restriction in the region of intraosseous abscess (large arrow).

report of T2 shine-through artifact relative to reactive edema in a review article^{25,26}; however, we would like to point out that the ghost sign shows up as exaggerated hyperintensity on ADC maps as compared to the low signal on T1W images and DWI maps. This also reflects the work done by Kruk et al that the ADC values of reactive edema ($<1.1 \times 10^{-3}$) are lower than that of OM ($>1.3 \times 10^{-3}$).²⁴

There were some limitations present in this study. This study was a retrospective study conducted at a single institution and, as such, the sample cases may not be representative of the general population as the prevalence of OM in our sample was much higher than in the general population. Another limitation of this study was that there were only two readers, which contributed to the fair-moderate inter-reader agreement; however, it was a large sample of 170-plus pathology-proven cases. We also did not ask the readers to interpret separately in two settings—with only conventional MRI and only DWI—as the intent was to determine the initial estimate of the frequency of these signs and their inter-reader reliability. The interobserver agreement was low, and this could be due to insufficiently defined terms, or low

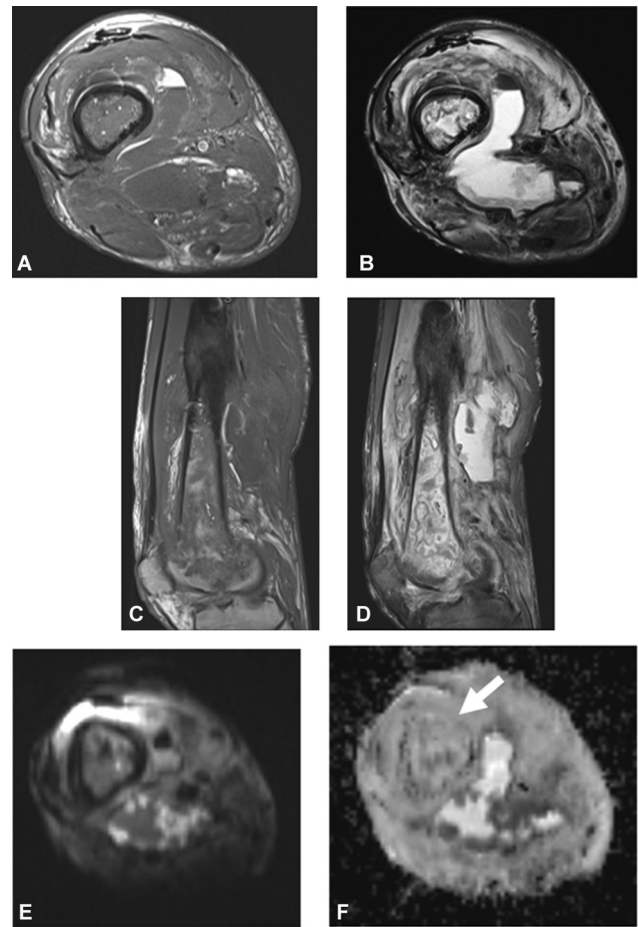


Fig. 4 Patient with soft-tissue abscess and osteomyelitis of the femur. (A) Axial T1-weighted (T1W), (B) axial fat-saturated T2-weighted (fsT2W), (C) sagittal T1W, and (D) sagittal fsT2W images of the femur showing lack of the “ghost sign.” Corresponding (E) diffusion-weighted imaging (DWI) and (F) apparent diffusion coefficient (ADC) map of the region of interest showing the “ghost sign” (arrow).

numbers of training cases. Additionally, it was difficult to blind the readers to other suggestive signs of bony infection, such as ulceration or sinus tracts, thus impacting the resultant sensitivity and specificity calculated for the ghost and penumbra signs. Future studies can include a larger sample size and more readers to better characterize these imaging findings.

Conclusion

To summarize, while inter-reader reliability is limited for previously described three MRI signs for OM, the ghost sign

Table 4 Mean diagnostic performance of penumbra sign on T1, ghost sign on T1, and ghost sign on ADC for osteomyelitis

Statistics	Penumbra sign on T1W	Ghost sign on T1W	Ghost sign on ADC
Sensitivity	3.7%	9.8%	19.5%
Specificity	98.9%	97.8%	94.5%
Accuracy	77.0%	77.5%	77.3%

Abbreviations: ADC, apparent diffusion coefficient; T1W, T1 weighted.

on ADC can be used as an additional marker for OM and is a similarly highly specific and but more sensitive sign for OM than the conventionally used penumbra sign and ghost sign on T1W imaging.

Clinical Relevance

Ghost sign on ADC is a highly specific MRI sign that can be used as an additional marker for identifying infected bone and diagnosing OM by radiologists.

Conflict of Interest

A.C. is a consultant of ICON Medical and TREACE Medical Concepts Inc., receives book royalties from Jaypee and Wolters, and serves as the medical advisor for Image-Biopsy Lab Inc. and receives research grants from Image-Biopsy Lab Inc. and Qure-AI. O.A. and P.P. are consultants for Image Biopsy Lab, Inc. Rest authors declare no conflict of interest.

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