Improving the Diagnosis of Ipsilateral Femoral Neck and Shaft Fractures

A New Imaging Protocol

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Background: Despite increased awareness of ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures and advanced imaging with thin-cut high-resolution computed tomography (CT), failure of diagnosis remains problematic. The purpose of the present study was to determine if the preoperative diagnosis of ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures can be improved with magnetic resonance imaging (MRI) compared with radiographic and CT imaging.

Methods: In response to delayed diagnoses of femoral neck fractures despite thin-cut high-resolution CT, our institutional imaging protocol for acute, high-energy femoral shaft fractures was altered to include rapid limited-sequence MRI to evaluate for occult femoral neck fractures. All patients received standard radiographic imaging as well as thin-cut high-resolution pelvic CT imaging upon presentation. Rapid limited-sequence MRI of the pelvis was obtained to evaluate for an occult femoral neck fracture.

Results: Thirty-seven consecutive patients with 39 acute, high-energy femoral shaft fractures resulting from blunt trauma were included. The average age of the patients was 29.1 years (range, 14 to 82 years). Ten (25.6%) of the 39 femoral shaft fractures were open. Two femoral shaft fractures (5.1%) were associated with ipsilateral femoral neck fractures that were detected on radiographs, and no MRI was performed. None of the remaining 37 femoral shaft fractures were associated with a femoral neck fracture that was identified on CT imaging. Thirty-three (89.2%) of 37 patients underwent pelvic MRI to evaluate the ipsilateral femoral neck. Four (12.1%) of those 33 patients were diagnosed with a femoral neck fracture (2 complete, 2 incomplete) that was not identified on thin-cut high-resolution CT or radiographic imaging.

Conclusions: Rapid limited-sequence MRI of the pelvis for patients with femoral shaft fractures identified femoral neck fractures that were not diagnosed on thin-cut high-resolution CT in 12% of our patients. Our results suggest that the frequency of femoral neck fractures may be underrepresented on CT imaging; rapid limited-sequence MRI was feasible without delaying definitive treatment even in polytraumatized patients.

Level of Evidence: Diagnostic Level III. See Instructions for Authors for a complete description of levels of evidence.

The association of ipsilateral femoral neck fractures with high-energy femoral shaft fractures is well known[1-4]. Despite this recognition, the rate of delay in diagnosis is still unacceptably high, with some studies showing that as many as 57% of femoral neck fractures are identified either during or after surgery[5-8]. Morphologically, the femoral neck fracture is most commonly nondisplaced or minimally displaced, vertically oriented, and, possibly, along radiographic lines of tension and compression[7,9,10]. These characteristics often create difficulties with visualization on radiographic and computed tomography (CT) imaging. These injuries frequently occur in young patients[3,11], and the consequences of missing a femoral neck fracture and subsequent displacement (unplanned reoperation, osteonecrosis of the femoral head, nonunion, etc.) can be devastating[12,13].

Because of the importance of this injury, many imaging techniques have been suggested to decrease the rate of missed or delayed diagnosis of ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures[6,8,14,15]. Tornetta et al. reported improved diagnosis of femoral neck fractures in association with the use of 2-mm thin-cut high-resolution CT imaging of the ipsilateral hip[10]. Other suggested modalities

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include dedicated intraoperative hip radiographs made after definitive fixation of the femoral shaft as well as dynamic stress fluoroscopy of the hip[5]. Despite these improvements, diagnosing an ipsilateral femoral neck fracture in the preoperative time period remains a challenge.

Magnetic resonance imaging (MRI) has been identified as the preferred imaging modality to detect femoral neck stress fractures in cases in which a fracture is suspected but no definitive fracture is visualized on radiographic or CT imaging[15-20]. However, standard MRI can be a time-consuming study and is often not feasible in the case of a polytraumatized patient. In conjunction with our radiology department, we initiated a rapid limited-sequence MRI protocol to be used specifically for patients with high-energy femoral shaft fractures due to a blunt traumatic mechanism. We hypothesized that the diagnosis of ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures due to blunt trauma could be improved with rapid limited-sequence MRI.

Materials and Methods

Beginning in September 2018, our institution's imaging protocol for high-energy femoral shaft fractures due to blunt trauma was altered to include rapid limited-sequence MRI of the pelvis and the proximal parts of the femora to assist in diagnosing acute ipsilateral femoral neck fractures. This change was made in response to prior delayed diagnoses of femoral neck fractures despite the use of thin-cut (2-mm) high-resolution CT scanning, intraoperative fluoroscopy with static evaluation of the hip, and dedicated hip radiographs made prior to the cessation of anesthesia. Demographic data, the mechanism of injury, radiographic data, and data on associated injuries were obtained from electronic medical records. Patients with femoral shaft fractures due to low-energy falls or ballistic mechanisms were excluded. Institutional review board approval was obtained for retrospective analysis of the records of all patients who were managed following this change in our institutional protocol.

According to the protocol, all patients with acute, high-energy femoral shaft fractures and blunt trauma who presented to our level-I trauma center emergency department were to receive standard radiographic imaging of the hip and femur as well as thin-cut high-resolution pelvic CT imaging at the time of presentation. These patients were stabilized and placed in skeletal traction in the emergency department. A CT examination using thin-cut (2-mm) images was performed, typically with use of reformatted images from a CT examination of the chest, abdomen, and pelvis that was performed as part of our general trauma protocol. The CT examination was performed on a single-source 128-slice scanner with helical acquisition and subsequent thin reformation of the pelvis and proximal parts of the femora in all trauma patients. Three-dimensional reformats were also available in all cases.

If a patient was diagnosed with an ipsilateral femoral neck fracture on radiographic or CT imaging, no MRI was indicated. If a patient did not have a definitive femoral neck fracture on hip radiographs or thin-cut, high-resolution CT imaging, rapid limited-sequence MRI of the pelvis was performed. An MRI protocol was developed that consisted of a large-field-of-view image of the pelvis and the proximal parts of both femora. Images were restricted to coronal non-fat-suppressed T1 and coronal short tau inversion recovery (STIR) sequences. The large-field-of-view images adequately covered the proximal parts of the femora, typically just proximal to the middle part of the shaft. These limited short sequences take <10 minutes for the entire study. Coronal imaging was chosen because we believed that the vertical nature of femoral neck fractures would be best visualized in this plane of imaging and also because of the scan time required to cover a large field of view. To limit the amount of time the patient spent inside the MRI scanner, sagittal and axial images were not obtained. In all cases but 1, the region of interest (i.e., the proximal parts of the femora) was imaged using CT scans after identification of a femoral shaft fracture.

All patients were managed and cared for by multiple services in the acute traumatic setting, with the trauma surgery service being the primary team. MRI studies were ordered after standard imaging modalities were obtained and the patient was assessed and deemed stable for MRI by the primary team. If the MRI could not be completed by the planned time of the surgery, it was omitted so that surgery was not delayed.

Results

Thirty-seven consecutive patients (28 male and 9 female) presented with 39 acute high-energy femoral shaft fractures. The average age of the patients was 29.1 years (range, 14 to 82 years). Two patients sustained a bilateral femoral shaft fracture. The mechanisms of injury included 24 motor-vehicle accidents (with 4 patients being ejected), 5 motorcycle accidents, 5 auto-pedestrian collisions, 2 all-terrain-vehicle injuries, 1 fall from >8 ft (>2.4 m), 1 crush injury, and 1 trampoline accident. Ten (25.6%) of the 39 femoral shaft fractures were open, with all being classified Gustilo-Anderson type 3A[21].

Nineteen (51.4%) of the 37 patients had ipsilateral extremity trauma, and 19 (51.4%) had additional trauma to an extremity other than the one with the femoral shaft fracture. Sixteen patients (43.2%) sustained head trauma, 11 (29.7%) sustained spine trauma, 16 (43.2%) sustained chest trauma, and 14 (37.8%) had intra-abdominal injuries. Four patients (10.8%) had isolated femoral shaft fractures at the time of the initial evaluation.

Two (5.1%) of the 39 femoral shaft fractures were associated with ipsilateral femoral neck fractures that were identified on initial radiographs, so no MRI was performed for these patients according to the protocol. Of the remaining 37 femoral shaft fractures, 36 (97.3%) were evaluated with CT imaging as part of the initial trauma evaluation to assess the ipsilateral femoral neck. Two patients had 3-mm cuts, 2 had 5-mm cuts, and all others had 2-mm fine cuts. None of these 36 patients who underwent pelvic CT imaging, which included imaging of the proximal parts of the femora, were diagnosed with a definitive femoral neck fracture.

Thirty-three (89.2%) of the 37 patients without a femoral neck fracture identified on initial radiographic imaging underwent large-field-of-view pelvic and proximal femoral MRI to evaluate the ipsilateral femoral neck. Four patients did not undergo MRI: 2 patients could not safely undergo MRI because of retained metallic foreign bodies from prior ballistic injuries, 1 patient was in extremis and was too unstable for the imaging study prior to definitive orthopaedic surgical intervention, and 1 patient did not undergo MRI because the protocol was not followed. For the 33 patients who underwent MRI, the average time from emergency room triage to MRI of the pelvis was 17 hours and 29 minutes (range, 1 hour and 42 minutes to 89 hours). Six patients underwent the MRI >24 hours after triage: 4 of these patients underwent MRI after the placement of an external fixator, and the other 2 underwent MRI after fixation of the femoral shaft. Excluding these 6 patients, the average time to MRI was 11 hours and 25 minutes from triage. No patient had an adverse event in the MRI scanner.

Ipsilateral femoral neck fractures that were not identified on CT with 2-mm thin cuts or radiographs were identified on MRI scans in 4 (10.8%) of 37 femoral shaft fractures in 35 patients. Two of these fractures were complete, and 2 were incomplete (Figs. 1 and 2). Surgical plans were altered preoperatively to include femoral neck stabilization for 3 of the 4 patients, and postoperative rehabilitation protocols were modified with protected weight-bearing once a femoral neck fracture was diagnosed and definitive fixation had occurred. Femoral neck fractures presented as linear edema with a subtle increase in signal on the heavily T2-weighted STIR images. Only minimal change (a subtle hypointense linear line) was identified on the non-fat-suppressed T1-weighted images.

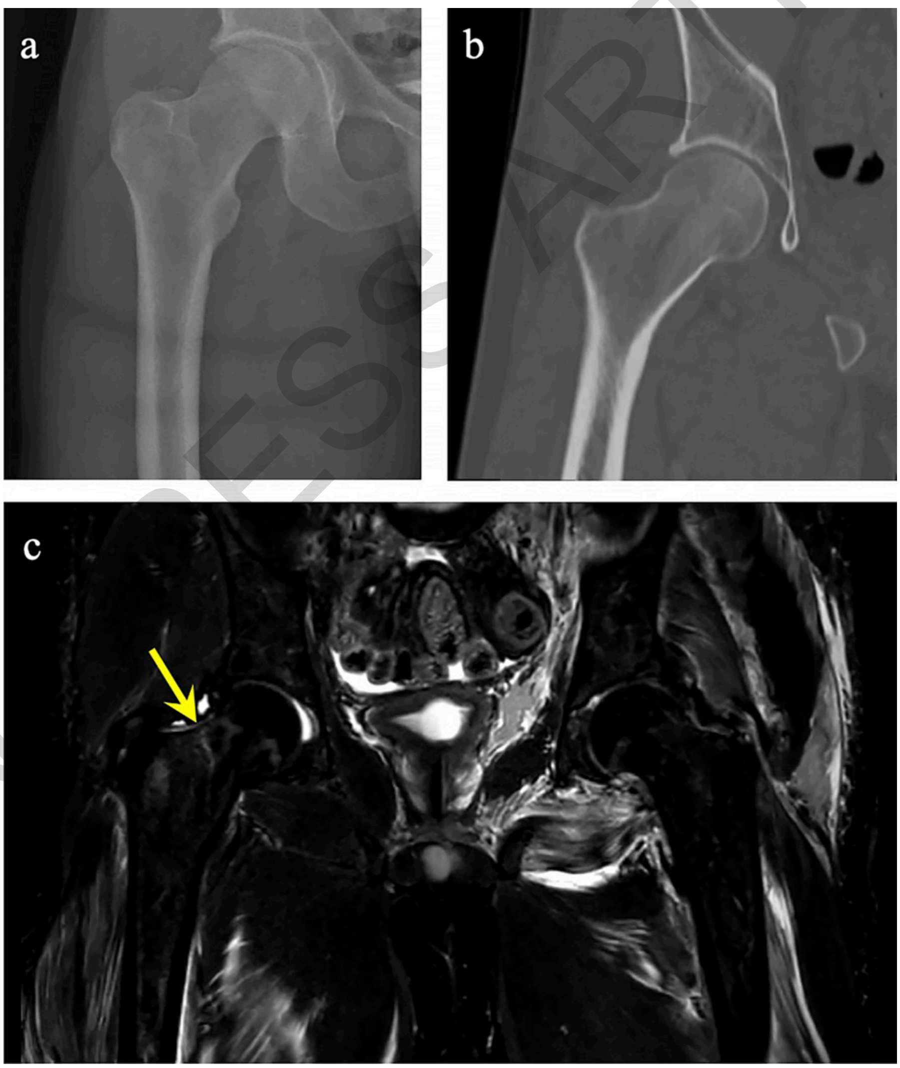

Fig. 1

Figs. 1-A, 1-B, and 1-C A 26-year-old male patient with incomplete femoral neck fracture. **Figs. 1-A and 1-B** Anteroposterior radiograph and coronal thin-cut high-resolution CT image of the hip demonstrating no identifiable femoral neck fracture. **Fig. 1-C** Coronal STIR MRI scan demonstrating an incomplete tension-sided femoral neck fracture (arrow).

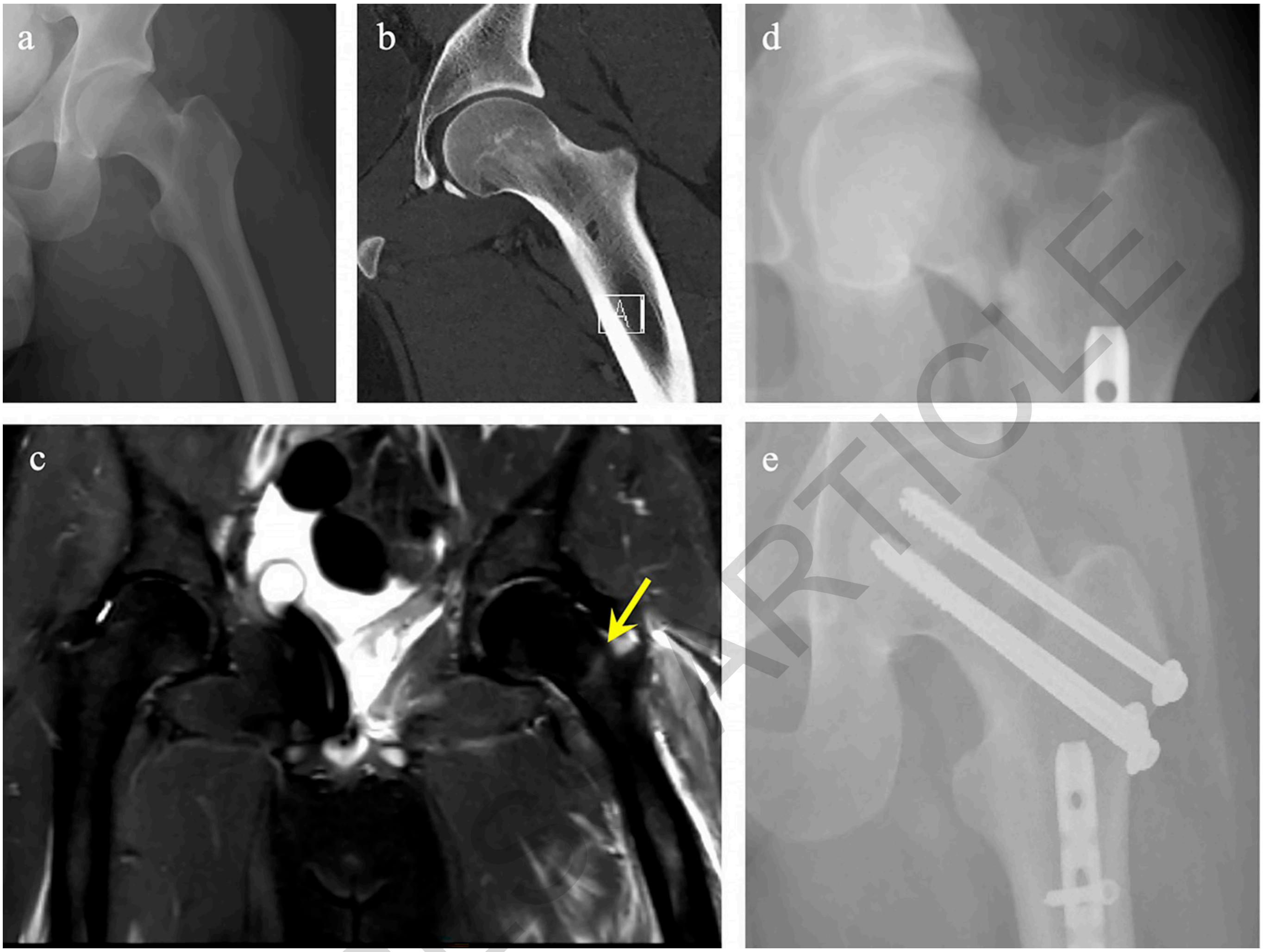

Fig. 2

Figs. 2-A through 2-E A 20-year-old male patient with an MRI-diagnosed femoral neck fracture that was initially untreated and subsequently displaced. **Figs. 2-A and 2-B** Anteroposterior hip radiograph (**Fig. 2-A**) and coronal thin-cut high-resolution CT image (**Fig. 2-B**) demonstrating no identifiable femoral neck fracture. **Fig. 2-C** Coronal STIR MRI scan demonstrating a complete femoral neck fracture (arrow). **Fig. 2-D** Anteroposterior radiograph of the hip, made 2 weeks postoperatively, demonstrating a displaced femoral neck fracture. **Fig. 2-E** Anteroposterior radiograph of the hip, made after open reduction and internal fixation of the femoral neck fracture.

In the early stages after the initiation of the protocol, the MRI scan for 1 patient was misinterpreted as showing no fracture (Fig. 2). However, this interpretation was amended after review by a fellowship-trained musculoskeletal radiologist. The femoral neck fracture was not fixed during the initial procedure for the femoral shaft fracture. The patient subsequently returned to the clinic with a displaced femoral neck fracture and underwent open reduction and internal fixation. The other 3 femoral neck fractures that were identified on MRI were addressed at the same time as the femoral shaft fractures. The second complete fracture and 1 of the incomplete fractures were stabilized with a retrograde femoral intramedullary nail and cannulated screws, and the remaining incomplete femoral neck fracture was stabilized with a reconstruction femoral nail.

Postoperative follow-up was available for 34 of 37 patients, including 28 patients with 30 high-energy femoral shaft fractures that were not associated with ipsilateral femoral neck fractures identified on MRI. After a mean duration of follow-up of 66 days (range, 14 to 128 days), no patient was found to have an undiagnosed femoral neck fracture on the basis of clinical examination and radiographic imaging.

Discussion

The diagnosis of ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures has continued to remain a challenge. In a series of 2,897 femoral neck fractures associated with 91 ipsilateral femoral shaft fractures, 24 femoral neck fractures were initially undiagnosed[7]. One proposed explanation was that the orientation of the fracture along radiographic tension and compression lines may increase the difficulty of visualizing the fracture on radiographic and CT images. This varied axial fracture geometry was highlighted in a series of high-energy femoral neck fractures[9]. Although thin-cut high-resolution CT imaging has been reported to be the most effective imaging modality, a recent study questioned whether this improved detection is due to actual detection of a fracture or to observational bias[6]. In a blinded assessment of diagnosing femoral neck fractures with use of radiographic or CT imaging, CT had a rate of missed femoral neck fractures similar to that of radiography, with a sensitivity of up to 64%[6]. The importance of identifying femoral neck fractures preoperatively cannot be overstated with regard to preoperative planning, preventing delayed diagnosis, and reducing complications that can arise in association with displaced fractures. In order to minimize the uncertainty regarding the existence of a femoral neck fracture in patients with high-energy femoral shaft fractures, including patients with equivocal findings on CT scanning, we developed a protocol that includes rapid limited-sequence MRI. The MRI protocol consisted of a large-field-of-view image of the pelvis and the proximal parts of both femora. Images were restricted to coronal non-fat-suppressed T1-weighted and coronal STIR sequences. The large-field-of-view images adequately covered the proximal parts of the femora, typically just proximal to the middle of the shaft. These sequences had a high matrix and isovolumetric voxel size with parallel imaging and compressed sense to reduce time.

With use of standard imaging techniques, our observed rate of ipsilateral femoral neck fractures was 5.1% (2 of 39), which is consistent with previous studies[14]. However, when including MRI, our rate of diagnosis of ipsilateral femoral neck fractures increased to 15.4% (6 of 39). The increased rate of diagnosis is likely due to the increased sensitivity of this imaging modality. To our knowledge, we are the first to describe the use of MRI to diagnose ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures, and we were able to accurately diagnose 2 incomplete femoral neck fractures in addition to the 2 complete fractures. Of the fractures identified on MRI, the 2 complete fractures were basicervical and vertically oriented and the 2 incomplete fractures consisted of an inferomedial femoral head impaction fracture with extension into the femoral neck and an incomplete superolateral femoral neck fracture. None of the 4 additional fractures were identified on CT imaging, and the 2 incomplete fractures may not have been visualized on static radiographic images after stabilization of the femoral shaft fracture or dynamic stress fluoroscopy because of their incomplete nature. An early failure of preoperative detection led to a displaced femoral neck fracture in the postoperative period. That fracture was not recognized on preoperative imaging because of our own learning curve in interpreting these images. While unfortunate, that case does show the value of this MRI sequence in the preoperative period. Detecting these fractures preoperatively is imperative and, in all cases but 1, allowed for additional preoperative planning, proper patient discussions, postoperative rehabilitation, and stabilization of fractures prior to completion of an incomplete fracture or displacement of a nondisplaced fracture.

Interpreting novel imaging studies during the management of polytraumatized patients can be challenging. The MRI sequence developed for this protocol includes the contralateral (typically uninjured) hip for evaluation. After reviewing images with our musculoskeletal radiologist, we were able to define fractures of the femoral neck as any evidence of linear edema, either complete or incomplete.

There is also a high rate of associated multisystem injuries in these patients, between 75% and 100%[14]. Our study showed that even though 89.2% of patients had associated trauma, 89% of all indicated patients could be evaluated with MRI. This high percentage of MRI obtained in multiply injured patients was due to the rapid nature of the coronal-only images acquired in an expedient fashion. The MRI did not compromise the overall care of these acutely injured patients. Only 1 patient could not undergo MRI prior to surgery because of a tenuous physiological condition. Additionally, patients who were in skeletal traction simply had the external traction device (e.g., traction bow) removed prior to the MRI and replaced after completion of the MRI; traction did not prevent any patient from undergoing MRI. Likewise, all patients who underwent initial external fixation of the femur for damage control prior to MRI were able to undergo MRI uneventfully.

The limitations of the present study include the possibility that the rapid-sequence coronal images obtained in our MRI protocol may not capture femoral neck fractures that could be diagnosed with sagittal or axial MRI. However, Steele et al. recently reviewed femoral neck stress fractures and demonstrated that MRI sequences limited to STIR and T1-weighted coronal sequences were adequate for fracture evaluation[17]. We were able to implement the MRI protocol for the evaluation of our trauma patients, but we recognize that there are patient conditions and situations that will restrict its use. An additional weakness is the lack of long-term follow-up and outcomes of these patients. However, records were available for follow-up on 28 patients (30 femoral shaft fractures) who were not found to have ipsilateral femoral neck fractures. At an average of 66 days after injury, no patients with a negative MRI were found to have a missed femoral neck fracture. The addition of MRI to the workup of these patients did add cost to their care, and a formal cost analysis was not performed for the present study. The present study included no control group of patients who were managed prior to the addition of the MRI for femoral neck fracture identification and thus we are unable to compare the full difference between the standard imaging assessment of these patients and the addition of the MRI examination. A larger, prospective study with comparative diagnostic groups and cost analysis is needed.

To our knowledge, this is the first study in which MRI has been used to assess for ipsilateral femoral neck fractures in patients with high-energy femoral shaft fractures. MRI was able to accurately and consistently identify femoral neck fractures in patients with high-energy femoral shaft fractures that were not otherwise identified on hip radiographs and thin-cut high-resolution CT scans. We found that the preoperative diagnosis of femoral neck fractures can be improved with use of our novel protocol involving rapid limited-sequence MRI. We also demonstrated that a majority of patients with these high-energy injuries, even those with multiple injuries, can safely undergo this imaging modality in an expedient manner. ■

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References

1. Swiontkowski MF. Ipsilateral femoral shaft and hip fractures. Orthop Clin North Am. 1987 Jan;18(1):73-84.
2. Wiss DA, Sima W, Brien WW. Ipsilateral fractures of the femoral neck and shaft. J Orthop Trauma. 1992;6(2):159-66.
3. Wolinsky PR, Johnson KD. Ipsilateral femoral neck and shaft fractures. Clin Orthop Relat Res. 1995 Sep;318:81-90.
4. Swiontkowski MF, Hansen ST Jr, Kellam J. Ipsilateral fractures of the femoral neck and shaft. A treatment protocol. J Bone Joint Surg Am. 1984 Feb;66(2):260-8.
5. Avilucea FR, Joyce D, Mir HR. Dynamic stress fluoroscopy for evaluation of the femoral neck after intramedullary nails: improved sensitivity for identifying occult fractures. J Orthop Trauma. 2019 Feb;33(2):88-91.
6. O'Toole RV, Dancy L, Dietz AR, Pollak AN, Johnson AJ, Osgood G, Nascone JW, Sciadini MF, Castillo RC. Diagnosis of femoral neck fracture associated with femoral shaft fracture: blinded comparison of computed tomography and plain radiography. J Orthop Trauma. 2013 Jun;27(6):325-30.
7. Cannada LK, Viehe T, Cates CA, Norris RJ, Zura RD, Dedmond B, Obremskey W, Bosse MJ; Southeastern Fracture Consortium. A retrospective review of high-energy femoral neck-shaft fractures. J Orthop Trauma. 2009 Apr;23(4):254-60.
8. Hak DJ, Mauffrey C, Hake M, Hammerberg EM, Stahel PF. Ipsilateral femoral neck and shaft fractures: current diagnostic and treatment strategies. Orthopedics. 2015 Apr;38(4):247-51.
9. Collinge CA, Mir H, Reddix R. Fracture morphology of high shear angle "vertical" femoral neck fractures in young adult patients. J Orthop Trauma. 2014 May;28(5):270-5.
10. Tornetta P 3rd, Kain MSH, Creevy WR. Diagnosis of femoral neck fractures in patients with a femoral shaft fracture. Improvement with a standard protocol. J Bone Joint Surg Am. 2007 Jan;89(1):39-43.
11. Alho A. Concurrent ipsilateral fractures of the hip and femoral shaft: a meta-analysis of 659 cases. Acta Orthop Scand. 1996 Feb;67(1):19-28.
12. Damany DS, Parker MJ, Chojnowski A. Complications after intracapsular hip fractures in young adults. A meta-analysis of 18 published studies involving 564 fractures. Injury. 2005 Jan;36(1):131-41.
13. Slobogean GP, Sprague SA, Scott T, Bhandari M. Complications following young femoral neck fractures. Injury. 2015 Mar;46(3):484-91. Epub 2014 Oct 31.
14. Jones CB, Walker JB. Diagnosis and management of ipsilateral femoral neck and shaft fractures. J Am Acad Orthop Surg. 2018 Nov 1;26(21):e448-54.
15. Sadozai Z, Davies R, Warner J. The sensitivity of CT scans in diagnosing occult femoral neck fractures. Injury. 2016 Dec;47(12):2769-71. Epub 2016 Oct 18.
16. Shin AY, Morin WD, Gorman JD, Jones SB, Lapinsky AS. The superiority of magnetic resonance imaging in differentiating the cause of hip pain in endurance athletes. Am J Sports Med. 1996 Mar-Apr;24(2):168-76.
17. Steele CE, Cochran G, Renninger C, Deafenbaugh B, Kuhn KM. Femoral neck stress fractures: MRI risk factors for progression. J Bone Joint Surg Am. 2018 Sep 5;100(17):1496-502.
18. Pejic A, Hansson S, Rogmark C. Magnetic resonance imaging for verifying hip fracture diagnosis why, when and how? Injury. 2017 Mar;48(3):687-91. Epub 2017 Jan 17.
19. Shin AY, Morin WD, Gorman JD, Jones SB, Lapinsky AS. The superiority of magnetic resonance imaging in differentiating the cause of hip pain in endurance athletes. Am J Sports Med. 1996 Mar-Apr;24(2):168-76.
20. Guanche CA, Kozin SH, Levy AS, Brody LA. The use of MRI in the diagnosis of occult hip fractures in the elderly: a preliminary review. Orthopedics. 1994 Apr;17(4):327-30.
21. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bones: retrospective and prospective analyses. J Bone Joint Surg Am. 1976 Jun;58(4):453-8.