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Added value of Diffusion Weighted Image and Apparent diffusion coefficient mapping in differentiation between bone marrow neoplastic infiltration and non-neoplastic complication in hematologic malignancies

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ORIGINAL STUDY

Added value of diffusion-weighted image and apparent diffusion coefficient mapping in differentiation between bone marrow neoplastic infiltration and nonneoplastic complication in hematologic malignancies

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Abstract

Background: **Hematological malignancies, including lymphomas, leukemia, and multiple myeloma, commonly infiltrate the bone marrow. Commonly observed post-treatment complications that affect bone marrow include osteonecrosis, osteomyelitis, ischemic infarction, pathological fractures, and avascular necrosis. These complications frequently occur secondary to chemotherapy, radiotherapy, and high doses of corticosteroids.**

MRI is considered the gold standard imaging modality for the assessment of bone marrow due to its high-contrast resolution without radiation exposure.

In hematological malignancies, distinguishing benign from malignant bone marrow changes remains notoriously challenging.

Diffusion-weighted images (DWI) are highly sensitive sequences for assessing the mobility of free water molecules reflecting microvascular changes. It may provide a promising alternative sequence devoid of contrast.

The study aimed to evaluate the overadded value of DWI and apparent diffusion coefficient (ADC) in differentiation between bone marrow neoplastic infiltration and benign complication in hematologic malignancies.

Patients and methods: **The retrospective study included 150 patients with pathologically proven hematological malignancy with bone marrow lesions.**

All patients underwent a 1.5-T MRI standard protocol with a diffusion-weighted sequence. The gold standard criteria were used to assess pathological neoplastic infiltration. In addition, a 2-year follow-up was conducted for cases of non-neoplastic infiltration where there were single or tiny suspicious lesions that could not be biopsied due to inaccessibility or unsuitability. An MRI follow-up should be conducted within a period of 3−6 months to confirm the final diagnosis.

Results: **Among the 150 patients, 63 (42%) were diagnosed with leukemia, while 72 (48%) were diagnosed with multiple myeloma. Out of the total, 15 (10%) patients were diagnosed with lymphoma, 90 (60.0%) patients had neoplastic infiltrations, and 60 (40.0%) patients experienced non-neoplastic complications.**

The qualitative DWI showed a restricted bright signal in 93.3% of the neoplastic infiltration, and 85% of non-neoplastic complications were facilitated the dark signal, with a significant *P* value of 0.001.

Conclusions: **The ADC map demonstrated a significant decrease in ADC value in cases of neoplastic infiltration in bone marrow. The optimal cutoff ADC value for detecting neoplastic infiltration was found to be less than 0.95, with a sensitivity of 96.6% and specificity of 89.5%.**

Keywords: Haematological malignancies, Bone marrow, Diffusion weighted images, and ADC mapping

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1. Background

Hematological malignancies, such as lymphomas, leukemia, multiple myeloma, and dendritic cell neoplasms, commonly invade the bone marrow and the cortical and cancellous bone [1,2].

Post-treatment complications of various chemotherapy regimens, radiotherapy, and protocols involving high doses of corticosteroids include osteonecrosis, osteomyelitis, ischemic infarction, pathological fractures, and avascular necrosis that are possible complications of different chemotherapy regimens, radiotherapy, as well as protocols with high doses of corticosteroids [3,4].

The appearance of normal bone marrow on MRI varies due to dynamic compositional changes, including red and yellow marrow as well as trabecular bone. These changes occur in response to normal aging, hematologic demand, high doses of steroids, chemotherapy, or radiotherapy. All of these may affect the specificity of imaging interpretation, elevating false-positive results [5].

MRI is considered a gold standard imaging modality in bone marrow assessment due to its ability to scan the whole body and differentiate hematopoietic and fatty marrow with high-contrast resolution. Furthermore, it eliminates the risk of radiation exposure with a high level of sensitivity but limited specificity [1,6].

Pathological bone marrow-infiltrative disorders usually elicit high STIR WI signal compared with red or yellow marrow due to the high water content of the neoplastic cells using the skeletal muscles and discs as an internal standard. This is evidenced in more enhancement than healthy marrow in post-contrast sequences [7].

In hematological malignancies, determining whether the bone marrow changes are benign or malignant remains notoriously challenging [8].

Diffusion-weighted images (DWI) is highly sensitive to the mobility of free water molecules, reflecting microvascular changes. The apparent diffusion coefficient (ADC) is a sequence acquired at varying b values (range from 0 to 1000 s/mm^2) and assessed quantitatively [9]. In cases of DWIs with high *b* values, the lesion can be identified as restricted when it shows high SI with corresponding low ADC values on the ADC map. It may provide a possible promising alternative non-contrast-based sequence [10].

The current study aimed to assess the added value of DWI and ADC in distinguishing between neoplastic infiltration of the bone marrow and benign/non-neoplastic complications in hematologic malignancies.

2. Patients and methods

A retrospective cohort study conducted between January 2019 and January 2022 included patients diagnosed with hematological malignancies with bone marrow lesions confirmed by histopathology. The study has been approved by our Institutional Review Board (IRB).

2.1. Inclusion criteria

This study included patients with pathologically proven hematological malignancies with bone marrow lesions either initially or during the course of treatment. Malignancies were either detected by imaging modalities or clinically suspected.

2.2. Exclusion criteria

(1) Patients with no available pathology.
(2) Musculoskeletal metabolic or systemic diseases.

2.3. MRI technique

The MRI examination was performed using a magnetic resonance system (Achieva 1.5T; Phillips Medical Systems, The Netherlands). Sedation was administered to pediatric unstable patients under the age of 7. All patients were scanned using the standard protocols using dedicated coils.

Using multiplanar MRI sequences without contrast:

Axial and coronal T1, sagittal, axial, and coronal T2 WI with coronal fat-suppressed images of STIR.

Diffusion-weighted (DW) sequence with multiple *b* values:

In the spine and extremity (0, 400, and 800 s/mm^2).

In the skull and maxillofacial (0 and 1000 s/mm^2).

The images were transferred to a workstation (Philips extended workstation). ADC maps were calculated with the MRI system. ADC values were expressed in mm^2/s.

Gadolinium-enhanced T1-WI axial, sagittal, and coronal postcontrast T1 fat sat thrive.

2.4. Imaging evaluation

Two expert radiology consultants with 9 and 14 years of experience reviewed the MRIs independently (both were blinded to the final diagnosis). In

case of disagreement, a third qualified radiologist with 20 years of experience was consulted to make the final decision. There was good interobserver agreement.

(1) The morphological MRI features assessed as follows:
   (a) Site, size, and extensions of marrow lesions.
   (b) Presence of associated soft tissue component.
   (c) Signal and enhancement pattern of bone marrow lesions in T1 and T2 and post-contrast sequences compared with skeletal muscles in appendicular skeleton and intervertebral discs in spinal lesions.
      (a) Infiltrative lesions were considered if bone marrow lesions are hypointense in T1 and hyper in STIR compared with skeletal muscles and intervertebral discs, with more avid postcontrast enhancement in lesions compared with normal red marrow [7].
      (b) Noninfiltrative/benign lesions were considered if bone marrow lesions were slightly hyperintense in T1 and hypointense in STIR compared with skeletal muscles and intervertebral discs with no or postcontrast enhancement as or minimally less than the normal bone marrow [7].

(2) Furthermore, the diffusion and ADC map sequences were analyzed for the characterization of the lesions.
   (a) The ROIs were placed first on DWI and then autocopied to ADC maps by the software. At least three measurements were performed, excluding the necrotic portions as well as the margins of the lesion. Regarding the qualitative assessment, at least one value was recorded for each *b* value. The ADC value was automatically calculated as well.
   (b) Regarding the qualitative assessment, signal intensity of the lesion on DWI bone marrow lesion was reported as restricted diffusion (bright signal) or facilitated diffusion (low signal).
(3) The final diagnosis was reported and compared with pathological data in neoplastic infiltration and two-year follow-ups for non-neoplastic infiltration, while single or tiny suspicious lesions not accessible/suitable for biopsy 3–6-month MRI follow-up to confirm the final diagnosis [11].

3. Results

A total of 150 patients were included in this retrospective study: 87 (58%) patients were males, and 63 (42%) patients were females. The age of patients ranged from 5 to 68 years, with a mean age of 34.24 ± 1.27.

Out of the 150 patients, 63 (42%) patients had pathologically proven leukemia (42 ALL and 21 AML), 72 (48%) had multiple myeloma, and 15 (10%) patients had lymphoma. The axial skeleton was the affected site in 39 (26%) patients. In addition, 111 (74%) patients had bone marrow lesions at the appendicular skeleton, and 57 (38%) patients had bone marrow lesions at both the axial and appendicular skeleton.

Single bone marrow lesions were observed in 27 (18%) patients, 33 (22%) patients had two to three lesions, and 90 (60%) patients had four or more lesions.

3.1. Category of bone marrow lesions

(1) Among the 150 patients, neoplastic infiltrations were observed in 90 (60%) of them; multiple myeloma affected 72/90 (80%) (Fig. 1), AML 8/90 (9%), ALL (4%) (40%) (Fig. 2), and lymphomas affected 6/90 (7%) (Fig. 3).
(1) Sixty (40.0%) patients experienced nonneoplastic complications: 20/60 (33%) red marrow reconversion, 19/60 (32%) bone infarction (Fig. 4), 13 (22%) AVN (Fig. 5), and 8/60 13% osteomyelitis.

3.2. Conventional and diffusion-weighed-MRI

In the neoplastic marrow infiltration $n = 78$ (86.6%) had a high signal in T2WIs, whereas $n = 81$ (90%) had a low signal in T1WI. In total ($n = 90$), 100% demonstrated enhancement.

In the nonneoplastic complication, $n = 51$ (85%) had a high signal in T2WIs. Additionally, all the nonneoplastic complications ($n = 60$) (100%) had low signal in T1WI, $n = 8$ demonstrated enhancement in all osteomyelitis cases.

The qualitative DWI revealed a restricted bright signal in high *b* values (800 or 1000) in $n = 84$ (93.3%) of the neoplastic infiltration. In $n = 51$ (85%) of nonneoplastic complications were facilitated, with a significant *P* value of 0.001 (Table 1).

The ADC map in neoplastic bone marrow infiltration revealed a significantly lower ADC value mean of 0.98 ± 0.76 than in non-neoplastic infiltration, which was 1.24 ± 0.34, with a *P* value of 0.010 (Table 2) (Fig. 6).

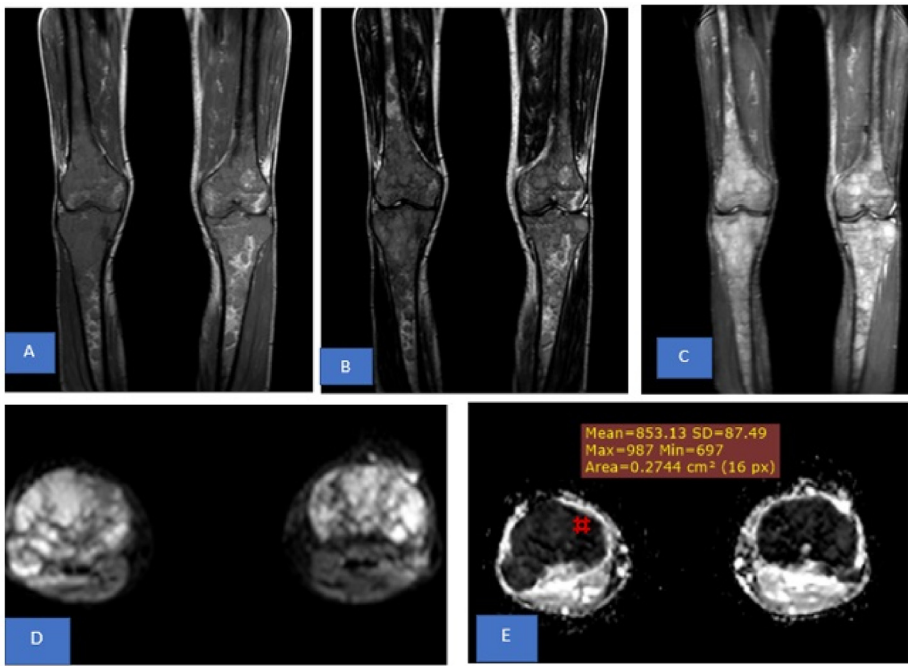

Fig. 1. A case of MM both knee MRI showing low T1 (a), and high T2 and STIR (b, c), restricted on DWIs (d), and low ADC (e) denoting bilateral diffuse intramedullary infiltration of the examined bones. ADC, apparent diffusion coefficient; DWI, diffusion-weighted image.

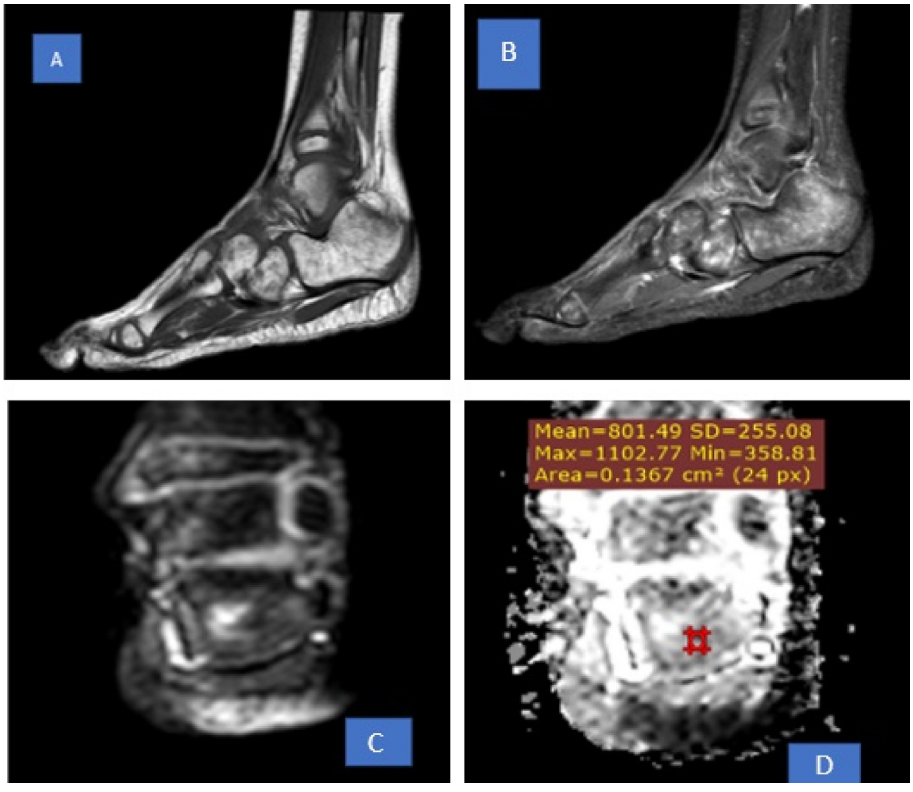

Fig. 2. MRI of the left foot and ankle in a case of leukemia showing low T1-SI (a), high TIRM (b), restricted diffusion (c), and low ADC (d), denoting leukemic infiltration (e). ADC, apparent diffusion coefficient.

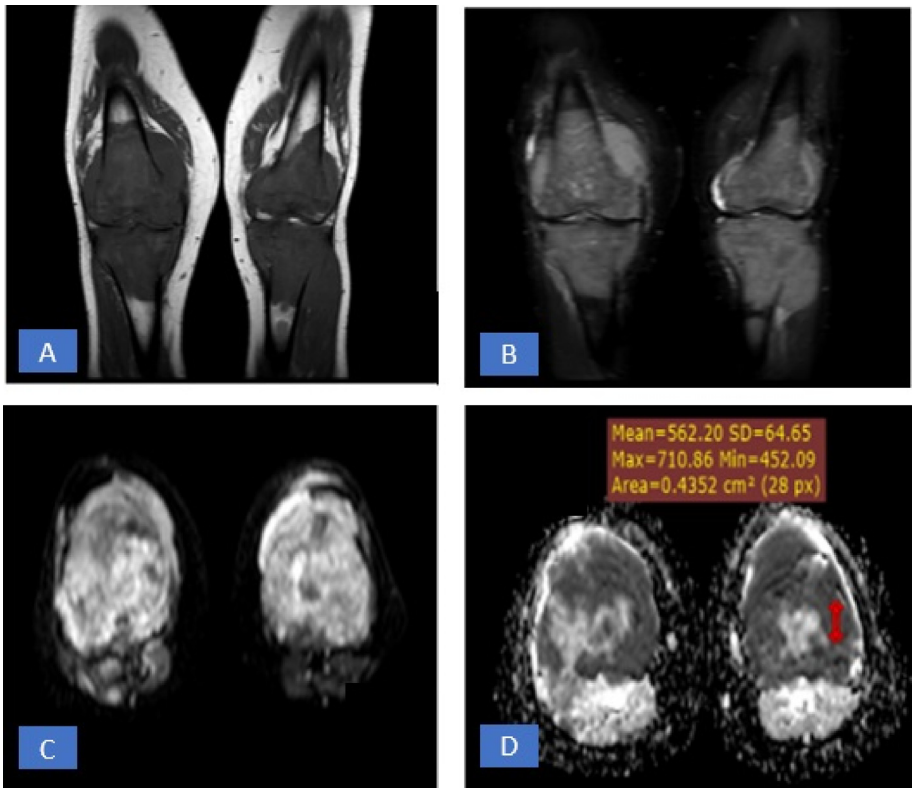

Fig. 3. MRI of both knees in a testicular lymphoma patient showing low T1 (a), high STIR (b), restricted diffusion (c), and low ADC (d), denoting lymphomatous infiltration. ADC, apparent diffusion coefficient.

The best cutoff value for the detection of neoplastic infiltration was ADC less than 0.95×10^{-3} mm^2/s, with a sensitivity of 96.6% and a specificity of 89.5% (Table 3) (Fig. 7).

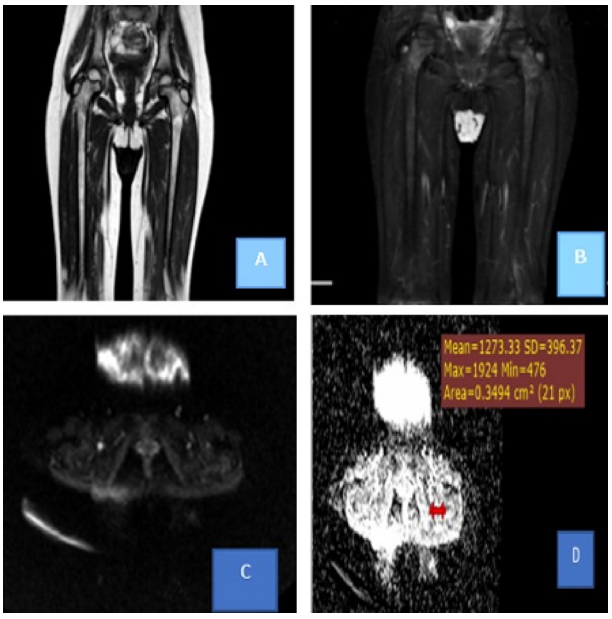

Fig. 4. Bilateral hip MRI of a known case of leukemia showing low T1 (a), high STIR (b), facilitated diffusion (c), and high ADC value (d), denoting bone infarcts. ADC, apparent diffusion coefficient.

4. Discussion

In our study, we found that leukemia is the most common neoplasm causing bone marrow infiltration, accounting for 42%. This finding is consistent with previous studies by Cao *et al*. [12], Riccio *et al*. [13], Maarek *et al*. [14], and Eisa *et al*. [15].

With respect to the site of the lesion, this study examined patients with bone marrow lesions on the axial skeleton (26 cases), the appendicular skeleton (74% cases), and both the axial and appendicular skeletons (38% cases). This finding is consistent with the research conducted by Riccio *et al*. [13] where 23.2% of lesions were detected in the axial skeleton and 76.7% were detected in the appendicular skeleton.

Regarding the category of the diseased bone marrow in this study, out of the 150 patients, 60.0% have neoplastic infiltrations, and 40.0% have non-neoplastic complications, which aligns with Eisa *et al*. [15]. The study found that 55.5% had neoplastic infiltrations, and 44.4% had nonneoplastic complications.

The ADC value was found to be significantly lower in cases of neoplastic infiltration compared with nonneoplastic complications. The mean ADC value for neoplastic infiltration was 0.98×10^{-3} mm^2/s, while it was 1.24×10^{3} mm^2/s for nonneoplastic complications. This finding is consistent with the

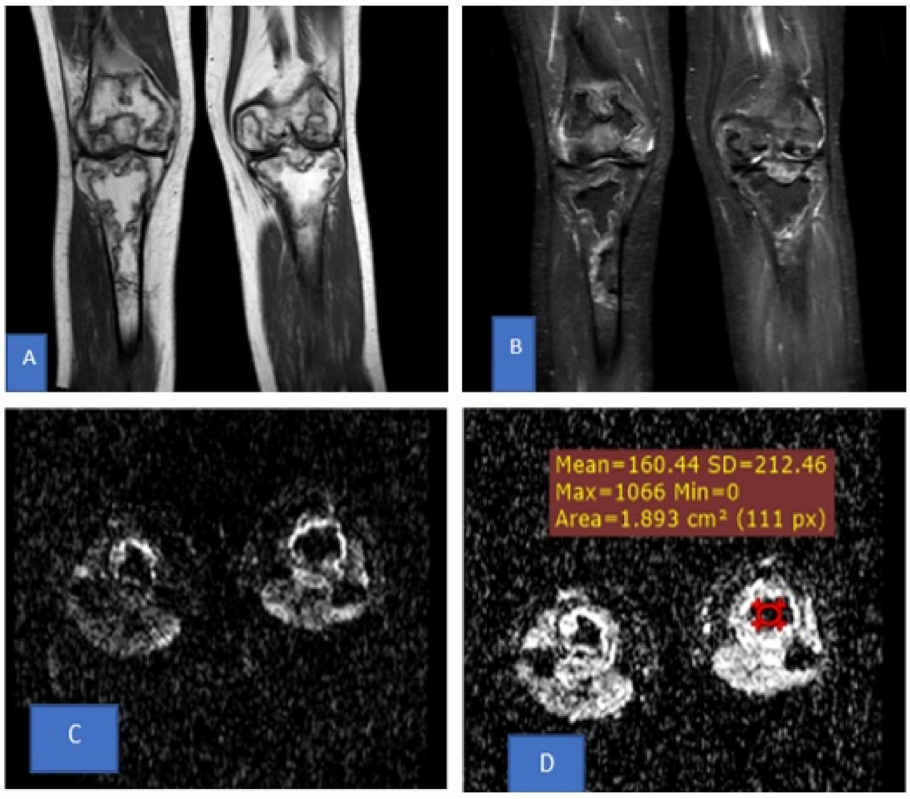

Fig. 5. A known case of leukemia under treatment showing low T1 (a), high STIR (b), with reactive serpentine interface line, facilitated diffusion (c), and high ADC values, denoting AVN. ADC, apparent diffusion coefficient.

Table 1. Conventional and diffusion-weighed-MRI in neoplastic infiltration and nonneoplastic complication.

	Neoplastic infiltration				*P* value
	Count	%	Count	%	
DWIs					
Restricted	84	93.3	9	15	<0.001
Facilitated	6	6.7	51	85.5	
T1					
Low	81	93.1	60	100.0	0.512
Intermediate	9	6.9	0	0.0	
T2					
High	78	89.7	51	89.5	0.093
Low	0	0.0	9	10.5	
Intermediate	12	10.3	0	0.0	

DWI, diffusion-weighted images.

results reported by Cao *et al*. [12]. Similarly, Eisa *et al*. [15] reported significantly lower ADC values in neoplastic infiltration (mean of 0.5 $\times$ 10^{-3} mm^2/s) compared with nonneoplastic complications (mean of 1.7 $\times$ 10^{-3} mm^2/s). The ADC value was significantly lower in neoplastic infiltration than in nonneoplastic complications, with a mean of 0.5 versus 1.7 $\times$ 10^{-3} mm^2/s.

According to our results, the best cutoff value for detecting neoplastic infiltration was ADC less than 0.95 $\times$ 10^{-3} mm^2/s with a sensitivity of 96.6% and specificity of 89.5%, which is consistent with Cao *et al*. [12] study where the ADC value was less than 0.85 $\times$ 10^{-3} mm^2/s with a statistically significant *P* value less than 0.001. These findings are in agreement with Eisa *et al*. [15] and Maarek *et al*. [14] regarding the high sensitivity and specificity of DWI with ADC mapping.

The qualitative DWI revealed a restricted bright signal in high *b* values in 96.6% of the neoplastic infiltration and nine cases of nonneoplastic complications ($n = 9$). This finding is statistically significant with a *P* value of 0.001, which is consistent with the results reported by Eisa *et al*. [15]. They found that the qualitative DWI showed a restricted

Table 2. Apparent diffusion coefficient value of neoplastic infiltration and nonneoplastic complications.

	Neoplastic infiltration					Nonneoplastic complication					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	*P* value
ADC map	0.98	0.76	0.70	0.30	3.20	1.24	0.34	1.30	0.30	2.00	0.010

ADC, apparent diffusion coefficient.

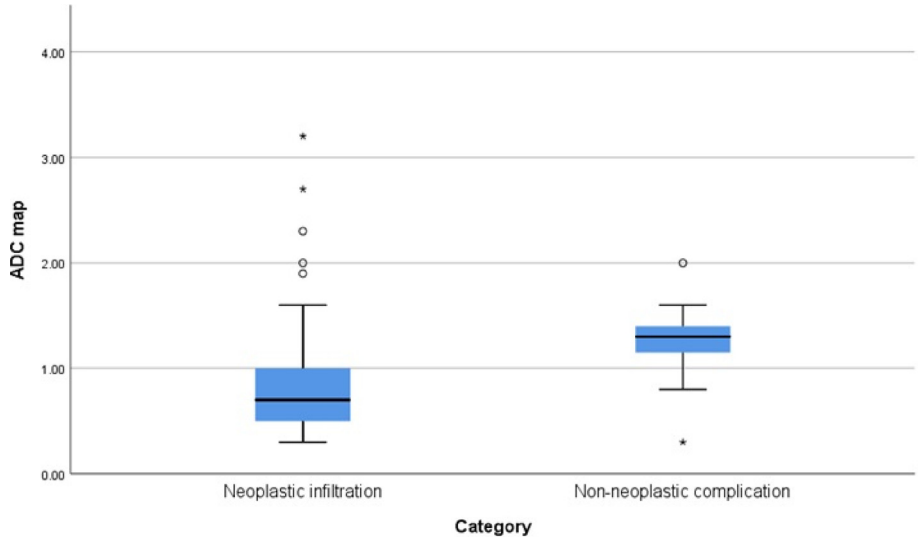

Fig. 6. Comparison between neoplastic infiltration and nonneoplastic complication.

Table 3. Cutoff value, specificity, and sensitivity of apparent diffusion coefficient.

Area under the curve	*P* value	95% confidence interval		Cutoff	Sensitivity %	Specificity %
		Lower bound	Upper bound			
0.722	0.006	0.563	0.882	<0.95	96.6	89.5

bright signal in high *b* values of 100% neoplastic infiltration and 11% nonneoplastic complications, with a significant *P* value of 0.001.

False-positive cases were detected in three pediatric leukemic patients with bone marrow lesions at the humeral and femoral bones. These lesions exhibited restricted diffusion with a low ADC value of 0.3 × 10^{-3} mm^2/s and pathologically proved to be bone infarctions. This may be due to the abundance of red marrow in the pediatric age group in the long bone heads and proximal diaphysis.

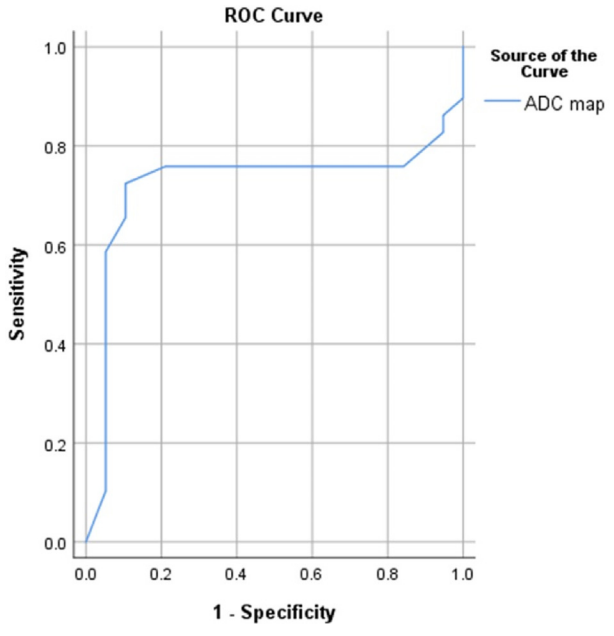

Fig. 7. ROC curve. ROC, receiver operating characteristic.

False-negative cases were detected in six multiple myeloma patients, affecting the sternal, calvarial, and pelvic bones, showing facilitated diffusion with a high ADC value of 1.9 × 3^{-3} mm^2/s. All these lesions were small, less than 5 mm, and doubtful in conventional MRI. Therefore, according to the recommendation of the International Myeloma Working Group, these patients underwent a 3–6 month follow-up that showed progression. This may be due to the small size of the lesion to be adopted to ROI size.

4.1. Limitations

This study is a retrospective study with a heterogeneous group of patients, including pediatric and adult groups with different types of bone marrow neoplasms, so further study on the pediatric age group is recommended.

4.2. Conclusion

MRI is the gold standard modality in the assessment of bone marrow and differentiation between neoplastic infiltration and nonneoplastic complications of bone marrow hematological malignancies.

DWI can add value to MRI studies in patients with hematological malignancy in bone marrow lesions by offering a quantitative and qualitative approach. It can differentiate between neoplastic infiltration and nonneoplastic complications with a cutoff value of ADC less than 0.95×10^{-3}, with high sensitivity and specificity.

Conflicts of interest

There are no conflicts of interest.

Institutional review board (IRB) approval number

The institutional committee's ethical criteria were followed during all proceedings. The faculty of medicine, Helwan university ethical committee approved the study (no. 106-2023) at 17.10.2023.

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