



Contribution of diffusion-weighted MR imaging in follow-up of inflammatory appendiceal mass: Preliminary results and review of the literature

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ABSTRACT

Objective: We aimed to search the contribution of diffusion-weighted imaging (DWI) in follow-up of patients with acute appendicitis associated inflammatory appendiceal mass (IAM). DWI was used as a monitoring imaging method to assess the response of medical treatment.

Materials and methods: 19 patients (mean age, 37+–13.1; age range, 19–69; M/F: 10/9), presented with clinical, laboratory and computed tomography (CT) findings suggestive of IAM were enrolled prospectively in this study. CT and DWI images were evaluated by two radiologists in consensus. b values 0, 500 and 1000 s/mm² were used, and DWI images were analysed both qualitatively and quantitatively. Laboratory parameters were C-reactive protein value and white blood cell count. During follow-up changes in the diameter of IMA and laboratory parameters were correlated with ADC values. Conservative treatment with interval appendectomy and a total conservative approach without surgery were the treatment options during follow-up.

Results: We found statistically significant correlation between the ADC values, maximum IAM diameter and laboratory parameters. During follow-up five surgical procedures were performed: one patient underwent surgery for cecal adenocarcinoma and four underwent interval appendectomy. One patient developed acute relapse of IAM at the sixth month of follow-up.

Conclusion: DWI may be used with a significant success for follow-up of patients with IAM. As a monitoring imaging method, DWI may also aid in determining of most appropriate timing for interval appendectomy as well as may help in diagnosing alternative diagnoses (e.g. malignancy and inflammatory bowel disease) that can mimic IAM.

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1. Introduction

Acute appendicitis (AA) is a common surgical emergency. Prompt and early diagnosis is of crucial importance as delay in the diagnosis may give rise to several complications that may increase morbidity and even, mortality. The prevalence of appendiceal perforation and subsequent development of an appendiceal inflammatory mass (IAM) is reported to range from 2% to 10% [1]. The underlying pathophysiologic mechanism for the devel-

opment of these masses was proposed to be secondary to the response of the patient's inflammatory-immunological response which, finally, aims to wall-off and limit the inflammatory process [1]. The conventional treatment for uncomplicated AA in adults is surgery (open or laparoscopic) with reported overall complication rates of 11.1% and 8.7%, for open and laparoscopic appendectomy, respectively [2]. The mortality is rare which is around 0.5% [3,4]. However, the management of IAM is less clear and several treatments approaches have been proposed [5,6]. Immediate surgical intervention, medical treatment followed by delayed or interval appendectomy or conservative medical treatment without any surgical intervention have all presented as different treatment options. Conservative approach with or without interval appendectomy has recently been advocated as an alternative approach to these patients [2].

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Pre-operative imaging is reported to decrease false-positive appendectomy rates and, therefore, imaging is being utilized more and more commonly in assessment for AA. Ultrasonography (US) and computed tomography (CT) are the workhorse imaging modalities, with CT being more common for the primary evaluation of these patients [6–9]. Among these two modalities CT was reported to be more sensitive than US not only in the primary diagnosis but also for the depiction of the potential complications [10,11]. Despite these advantages, CT use is limited in the pediatric age group and the pregnant patients with US being more commonly employed in these patients [12,13]. MRI, although not very commonly used for this application, several authors reported the benefits of the use of rapid magnetic resonance imaging (MRI) techniques that are particularly applicable in the emergency setting [14–17]. Diffusion-weighted magnetic resonance imaging (DWI) of the abdomen and pelvis has been increasingly used since the 1990s with the introduction of stronger diffusion gradients, faster imaging sequences, and improvements in the MRI hardware [14,15]. Increased cellularity (e.g. tumor, abscess, fibrosis, and cytotoxic edema) and the loss of cell membrane integrity restricts the diffusion and this feature of diffusion may be used in the evaluation of the solid and cystic masses. DWI can be performed in a very short time without any IV use of contrast media allowing quick qualitative assessment. Quantitative assessment can also be done with the creation of apparent diffusion coefficient (ADC) maps from diffusion images obtained at different b values [17–19].

The main goal of this prospective study is to assess the role of DWI to show the progress of inflammation of RLQ mass during follow-up and to show the alternative diagnoses such as cecal adenocarcinoma and inflammatory bowel disease of patients, treated non-surgically, with presumed IAM.

2. Materials and methods

2.1. Patient selection and inclusion criteria

For this prospectively designed study, from August 2014 to May 2016, we scanned 141 patients with CT presenting to emergency department (ED) with symptoms suggestive of acute appendicitis (AA). Among these patients, 19 of them (mean age, 37±13.1; age range, 19–69; M/F: 10/9) manifested with CT findings suggestive of IAM. All 19 patients were placed on medical treatment, based on the decision of the attending surgeon in charge, with IV antibiotics and fluid resuscitation and none of them underwent emergency surgery. This study was approved by the medical ethics committee of our university hospital. Written consent is regularly acquired, after a discussion with the patient regarding the potential benefits and disadvantages of the procedure, and an additional written consent was also obtained before the MRI in all 19 patients. For follow-up of these right lower quadrant (RLQ) masses only DWI study was done with no IV contrast use. Age, gender, clinical characteristics and laboratory findings of patients were noted. The patient characteristics at presentation are shown in Table 1. Control DWI studies were performed at second, third and eighth week in the early follow-up period and after two months from the index study, they were called for a clinical visit and imaging every 3 months.

2.2. Imaging protocols

In the 19 patients the DWI studies were performed with a 1.5-T MR scanner (Magnetom® Aera; Siemens, Erlangen, Germany). The protocol of the DWI was as follows: axial diffusion-weighted single-shot echoplanar sequence (EPI) with fat suppression, without breath holding (TR, 7500; TE 62–80 ms; matrix, 192 × 192; slice thickness, 5 mm; gap, 6 mm; FOV, 400 mm; PAT factor 2; acquisi-

Table 1
Patient characteristics at presentation (n = 19).

	No	Percentage (%)
<i>Gender</i>		
Male	10	52,6
Female	9	47,4
<i>Representation of patients</i>		
Generalized abdominal pain	4	21,1
Right lower quadrant pain	14	73,7
Generalized pelvic pain	1	5,3
<i>Fever</i>		
+	6	31,6
–	13	68,4
<i>Palpable Mass</i>		
+	6	31,6
–	13	68,4
<i>Appendicolith</i>		
+	5	26,3
–	14	73,7

tion time, 3 min; b values 0, 500, and 1000 s/mm²). The scanning area was from the diaphragm to the pelvis, in the supine position.

2.3. Image analysis

Two experienced abdominal radiologists (10 and 5 years) interpreted the CT scans of all 141 patients. Initial and follow-up MRI studies of 19 patients, who were enrolled into this study, were also assessed by the same radiologists. All interpretations were made with consensus. The readers were both aware of the clinical and laboratory findings.

The following CT parameters, at the time of initial presentation, were noted in 19 patients with RLQ masses suggestive of IAM: the diameter, the content of IAM, the presence of appendicolith, surrounding fat stranding and presence of abdominal fluid. CT findings of IAM were generally a perforated Appendix surrounded by neighboring intestinal structures and/or omentum or a complex mass without a visible Appendix in RLQ.

On MRI, the signal intensity of RLQ masses were qualitatively assessed in images acquired at b values of 0, 500 and 1000s/mm². ADC maps were also evaluated on all MRI studies for quantitative evaluation of diffusion restriction.

In all 19 patients, the initial CT and initial-follow-up DWI datasets were evaluated on an independent workstation (Syngo.via, Siemens) for CT postprocessing and ADC map analysis. CT images were evaluated before the DWI analysis. The initial CT scan parameters, mentioned above, were recorded and then the corresponding lesions were again evaluated, this time, on DWI and ADC. In the follow-up MRI studies we mainly evaluated the size (by measuring the longest diameter) and the evolution of the diffusion restriction using ADC maps. ADC values were measured by placing a circular region of interest (ROI) on the lesion. The size of ROI was kept as large as possible covering the hypointense parts of the masses on ADC maps. Same measurements were repeated on the follow-up MRI studies. For each follow-up MRI scan, the readers were aware of previous imaging findings as well as clinical and laboratory findings.

2.4. Clinical analysis, type of conservative therapy and surgical options or other interventions in follow-up period

At presentation, the presence of abdominal pain, fever, detection of a palpable RLQ mass, and levels of C-reactive protein (CRP) and white blood cell (WBC) counts were noted. The same parameters were reassessed in the follow-up visits. During follow-up,

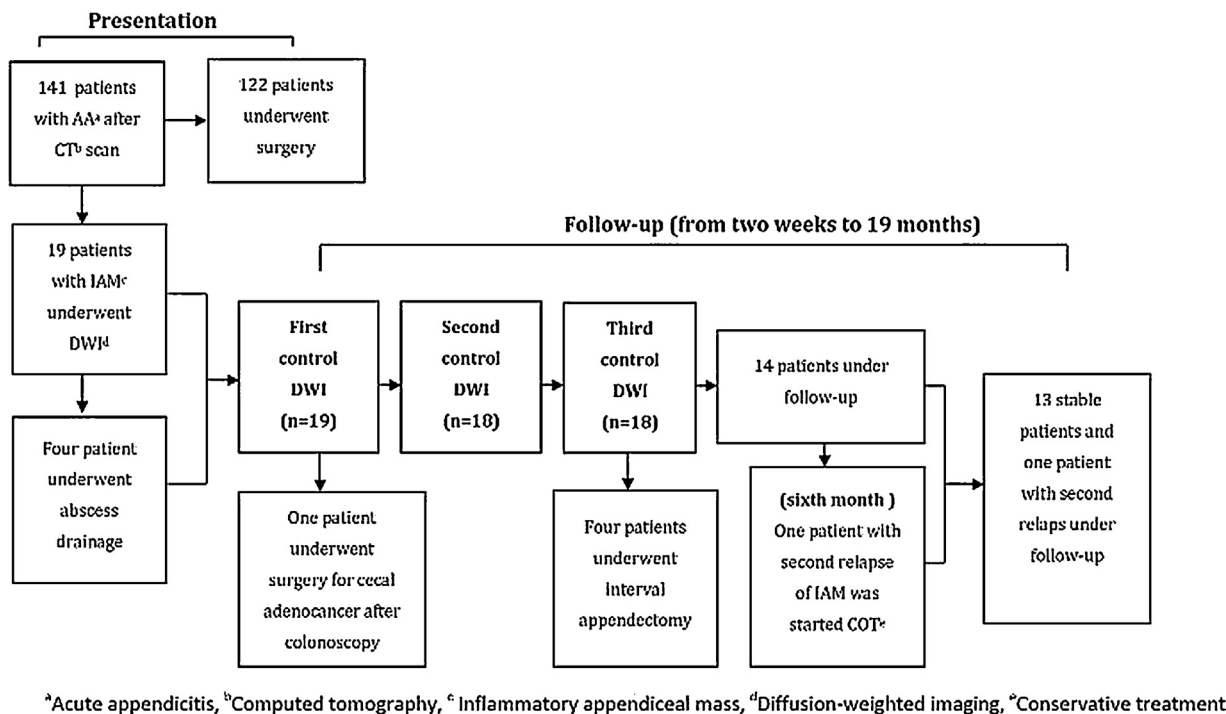


Fig. 1. Patient flow diagram.

laboratory tests were obtained at the same intervals of control DWI. All patients ($n = 19$) were hemodynamically stable and none of them were critically ill at the time of the initial presentation and a conservative therapy was concluded by the attending surgeon in charge. All were initially hospitalized and intravenous (IV) ceftriaxone (1–2 g/day in single daily dose) combined with metronidazole (500 mg, 3 times per day) was started. The in-hospital IV antibiotic treatment was continued for 10 days for each patient. Patients older than 40 years also were planned to have a colonoscopy four weeks after the index episode to rule out an underlying malignancy.

2.5. Statistical analysis

All the data were analyzed using the Statistical Package for the Social Sciences (SPSS 13.0 Statistical Software, SPSS Inc., Chicago, IL, USA). The medians and ranges of age, CRP, WBC and ADC values were calculated. The Kolmogorov–Smirnov test was used to show deviation from normal distribution. Correlation between the mean values of ADC, CRP, WBC and IAM dimension were analyzed using Pearson's correlation analysis. Within each treatment period, changes in CRP, ADC values, WBC counts were tested using repeated measures ANOVA with Greenhouse Geisser correction. Post hoc comparisons between first and each point in control time were performed by Student's *t*-test followed by Bonferroni adjustment of all probability values on the basis of the number of comparisons made in each period. A *p* value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

The patient flow diagram is shown at Fig. 1. The mean follow-up time was $9.23 (\pm 6.07)$ months, ranging from 0.5 to 19 months. Four patients needed percutaneous abscess drainage at the time of initial presentation. Four patients underwent interval appendectomy after their third control MR study, based on the decision of the surgical team. DWI findings of those patients showed com-

plete resolution of IAM, both qualitatively and quantitatively. At surgery, minimal or no adhesions were noted and simple appendectomy was performed in all patients. Histopathological examination of these appendices revealed normal appendices with no inflammatory changes in three cases and minimal inflammatory changes with no evidence of perforation in one patient (Fig. 2). Follow-up of these four patients was discontinued after surgery. One patient developed recurrent appendicitis and IAM at the sixth month and was again placed on medical treatment, based on the patient's will. He was asymptomatic with regression of the IAM revealed by DWI two weeks after the second relapse and was still on follow-up at the time of the writing of this manuscript. The remaining 13 patients completely recovered both clinically and radiologically. They were warned about the potential to develop a relapse in the future, and in the case to apply emergency department as soon as possible.

There were eight patients who were over the age of 40 in our study group and seven of them underwent colonoscopy at the fourth week after the index presentation. One patient needed early colonoscopy as the second week follow-up DWI did not demonstrate any sign of regression (e.g. diameter and ADC values). In this patient, endoscopist detected a mass in the cecum which turned out to be a colonic adenocarcinoma after the biopsy and the patient underwent surgery three weeks after the initial presentation. The remaining patients did not demonstrate any evidence of malignancy on their elective fourth week colonoscopy exams.

Visual assessment of DWI with *b* factors of either 500 or 1000 s/mm² were sufficient to detect RLQ masses against suppressed background signal and they were easily discernible with their hyperintense signal on DWI and corresponding diffusion restriction on ADC maps.

C-reactive protein, WBC, ADC values and IAM dimension were the main parameters that we recorded on the follow-up. The interval evolution of these parameters both at initial presentation and on follow-up scans were presented in Table 2.

CRP, WBC values and IAM dimensions exhibited strong inverse significant correlation with ADC values (CRP, $r = -0.51$, $p < 0.001$;

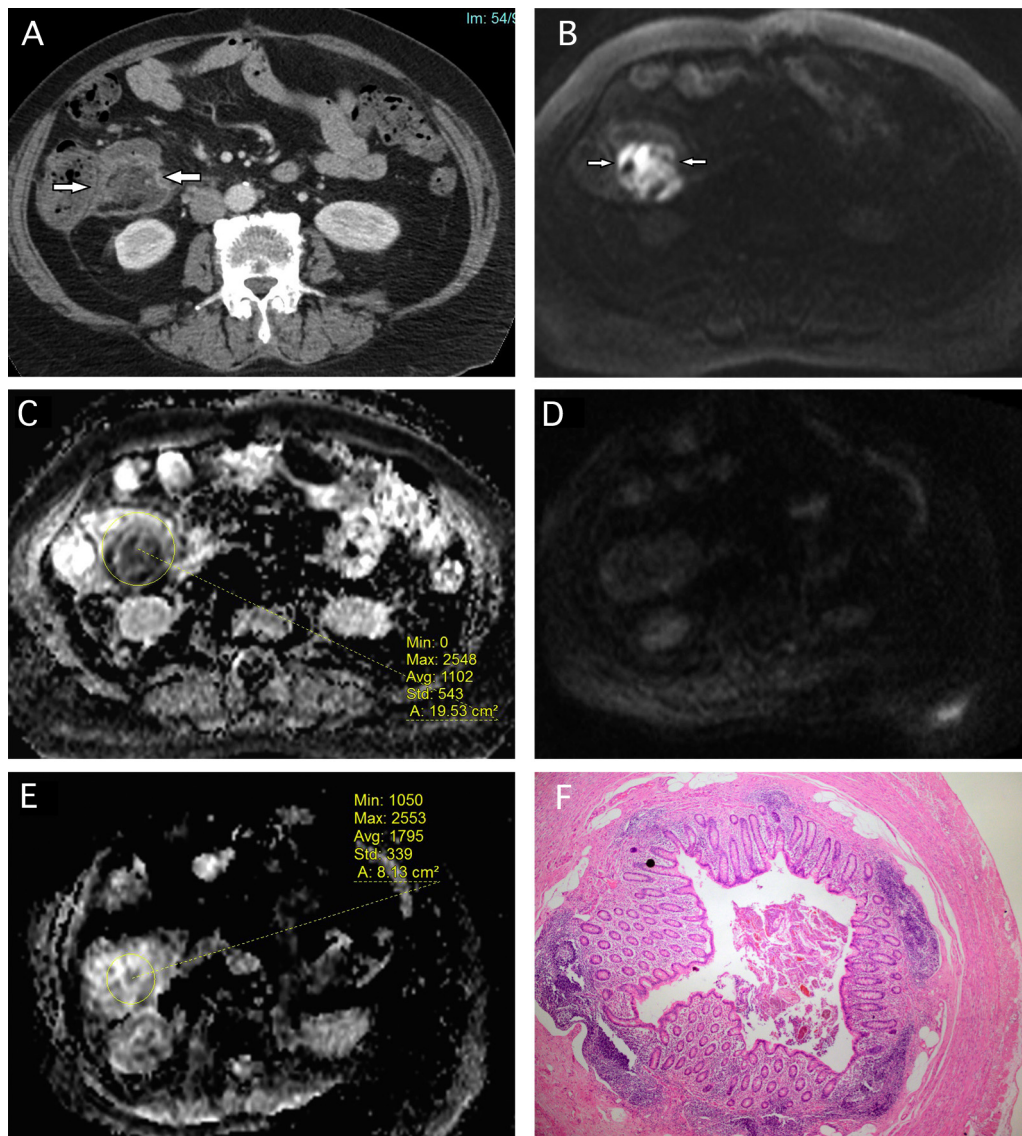


Fig. 2. A 48-year-old male with acute right lower quadrant (RLQ) pain for 4 days. Clinical, laboratory and imaging findings suggested IAM. The patient underwent interval appendectomy at the fourth week of follow-up.

(a) CT at presentation shows a RLQ mass (IAM) bordered by cecum laterally, ileum anteriorly and Gerota fascia posteriorly (arrow). (b, c) DWI (b = 1000) and ADC map at presentation show restricted diffusion (arrow). (d, e) Four weeks after initial presentation, DWI (b = 1000) and ADC map reveal total recovery at the localization of previous IAM, both qualitatively and quantitatively. (f) Microscopy of appendectomy specimen shows no any inflammatory cells.

Table 2
Marker characteristics at presentation and during follow-up.

Marker	Presentation (M ± SD) ^a (n = 19)	First Control (M ± SD) (n = 19)	Second Control (M ± SD) (n = 18) [*]	Third Control (M ± SD) (n = 18)
CRP ^b (mg/L)	9.36 ± 2.73	4.78 ± 0.95	3.76 ± 0.67	3.2 ± 0.49
WBC ^c count (per mL)	14832 ± 2844	9471 ± 1834	8225 ± 1022	8153 ± 1058
IAMdim ^d (cm ²)	27.32 ± 10	11.52 ± 7.89	2.05 ± 3.20	0.46 ± 1.97
ADC ^e (x 10 ⁻³ mm ² /s)	1.20 ± 0.23	1.65 ± 0.21	1.79 ± 0.46	2 ± 0.13

^a Mean ± standard deviation.

^b C-reactive protein.

^c White blood cell count.

^d Inflammatory appendiceal mass diameter.

^e Apparent diffusion coefficient.

^{*} One patient underwent surgery for cecal adenocarcinoma.

WBC, $r = -0.64$, $p < 0.001$; IAM dimension, $r = -0.63$, $p < 0.001$) (Fig. 3). The results of the ANOVA test indicated a significant change in the IAM dimension, ADC value, CRP value and WBC value of 18

patients during follow-up. For each parameter, mean difference at presentation and follow-up was found to be statistically significant ($p < 0.01$).

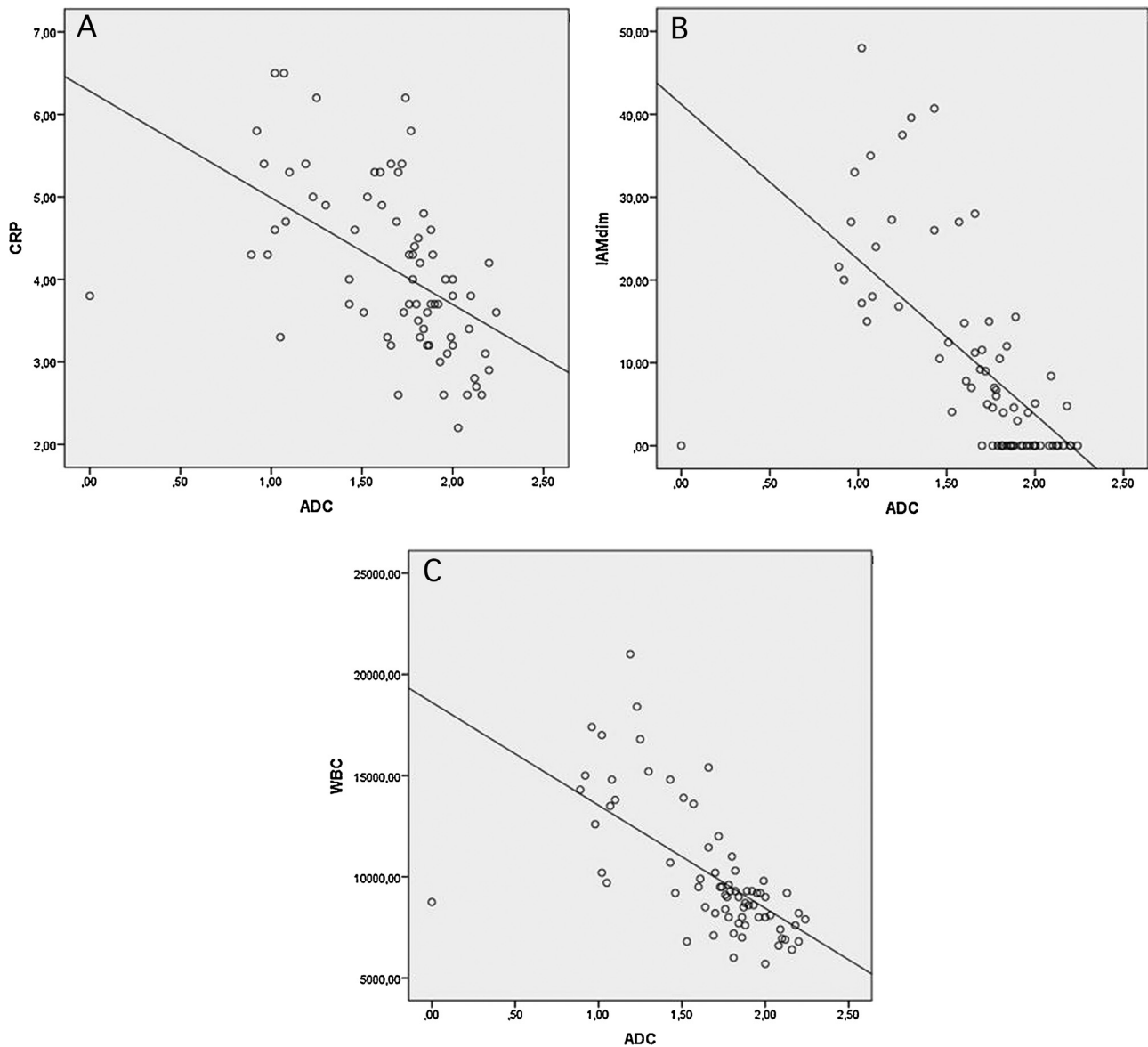


Fig. 3. Graphs show the correlation between (a) CRP and ADC values, (b) WBC and ADC values, (c) IAMdim and ADC values.

4. Discussion

Solely based on clinical findings, the diagnosis of IAM may be challenging and imaging is almost always needed for the diagnosis. CT is the most commonly utilized imaging modality in both the diagnosis of appendicitis as well as its complications [20–24]. The extent and anatomic relationships of IAM is well-depicted with CT which also helps the selection of the appropriate treatment approach [2,25]. In the present study, CT clearly demonstrated a RLQ mass in 19 patients, thought to be an IAM, that was also compatible with a clinical history of pain starting in the last few days.

Based on the surgical literature, the conventional management of acute appendicitis without IAM is immediate surgery, while the management of acute appendicitis with IAM is controversial. Immediate surgery, interval appendectomy after 6–12 weeks of conservative medical therapy (Ochsner method) and complete conservative therapy without surgery were all reported as viable treatment options [26,27].

Despite the fact that while immediate surgery was advocated as a treatment approach, the operative morbidity of patients with IAM is more than three times higher than emergency surgery in non-complicated appendicitis. Emergency surgery in IAM cases may necessitate the extending of the surgical resection field and may lead to ileocecal resection and right-sided hemicolectomy. It should also be kept in mind that cecal malignancies may mimic IAM, both, clinically and radiologically [28,29]. Conservative management, with or without interval appendectomy, was reported to have less morbidity, shorter hospital stay, lower rates of wound infection. Ileus and reoperation rates are also less common compared to immediate surgery [28,29]. The need for interval appendectomy after successful conservative treatment has recently been questioned as the risk of recurrent appendiceal inflammation may be low [1,2]. However, it also be noted that there also other research results that advocate the use of early appendectomy in these patients. In these reports, the authors proposed that the postponement of emergency surgery in these cases may delay the early diagnosis and intervention for other diseases mimicking IAM

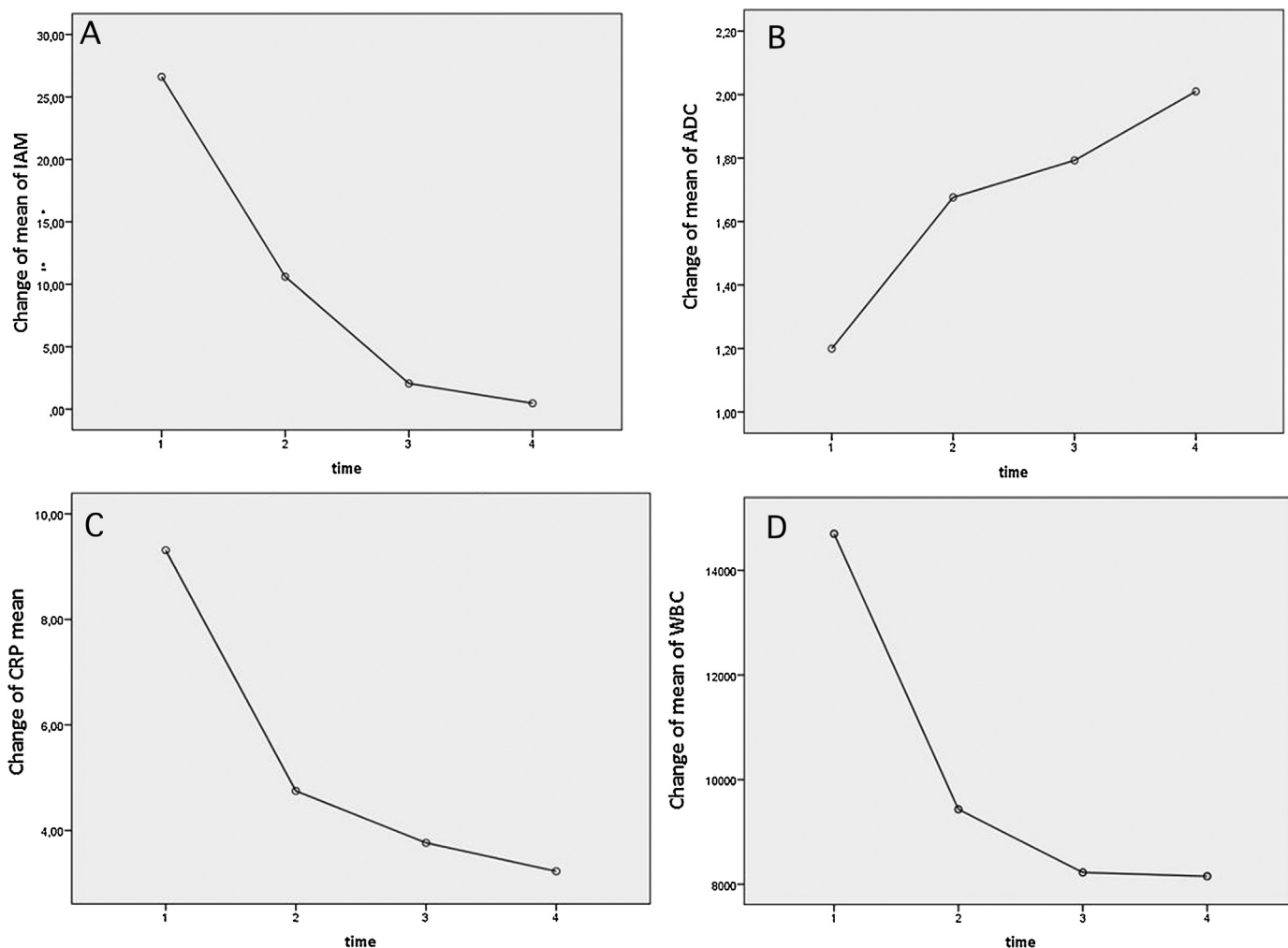


Fig. 4. Graphs show the change of (a) IAM dimension, (b) ADC mean, (c) CRP mean, (d) WBC mean.

such as Crohn's disease and cecal cancer [26,28,29]. Despite these counter arguments, the majority of the surgical community appear to prefer Ochsner method in the treatment of these patients [20].

In the modern medical practice, imaging is widely used in the diagnosis of acute appendicitis and, with the use widespread use of modern imaging technology, the false positive appendectomy rates have significantly decreased [10,11]. With this increasing use of imaging, the alternative diagnosis which may mimic AA may be diagnosed with high success rates. In patients placed on conservative medical treatment rather than immediate surgery, imaging plays a fundamental role in the follow-up. Conventionally, CT and US are the most commonly used modalities for this purpose. However, both US and CT has their own disadvantages. US is highly operator dependent and may be less sensitive, especially, in patients with large body habitus. Bowel distension is another limiting factor in US, obscuring the underlying posteriorly located pathologies. CT is an excellent tool for abdominal imaging which can be quickly done in a matter of seconds and is also widely available. However, the main disadvantage of the use of repeat CT scans is the overall radiation dose accumulation, especially in the pediatric age group and the young adults. The cumulative IV contrast load may also be problematic who are allergic or have low renal reserves.

Magnetic resonance imaging may be a perfect fit in these age groups with its lack of radiation and excellent soft tissue resolu-

tion. Unfortunately, MRI also has its own disadvantages such as longer imaging time, lack of local expertise and other logistical challenges. The use of DWI as the only imaging sequence for follow-up of these patients may significantly help to overcome some of the limitations of MRI. DWI is a very quick imaging sequence which also keeps the patients away from the cumulative radiation and contrast burden. DWI provides qualitative and quantitative information at the cellular level and is considered to be a form of functional imaging applications [30–33], but some morphological information may also be acquired. Conventionally, DWI was most commonly used in neuroimaging applications but with the recent advances in MRI technology body applications are becoming more common. Restricted diffusion is commonly observed in case of high cellularity within the lesion (e.g. tumors, abscesses, fibrosis and cytotoxic edema). DWI is sensitive to the microenvironmental changes in tumors at the molecular level that result from treatment and, thus, may predict tumor response to treatment [32]. In the same regard, DWI may also be used for treatment response of infectious-inflammatory processes.

In the present study, we evaluated DWI as an imaging tool to assess the changes of IAM, both qualitatively and quantitatively, during follow-up. We evaluated the relationship between ADC values of IAM and correlated the imaging data with the laboratory results (CRP and WBC). We also used the morphological information, provided by the DWI, for the size assessment of the IAMs.

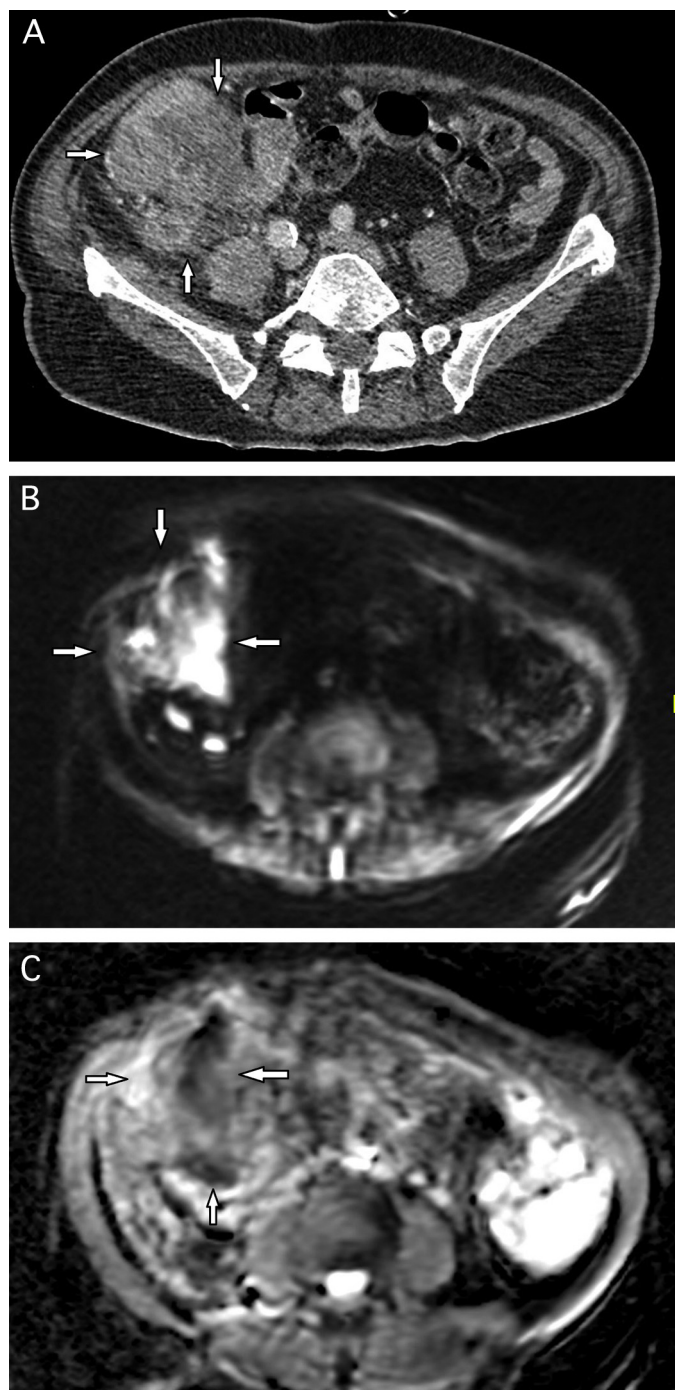


Fig. 5. A 54-year-old male with right lower quadrant (RLQ) pain for last 5 days. Clinical, laboratory and imaging findings were suggestive of IAM at presentation. Although there was relief of pain and improvement of laboratory tests following two weeks antibiotic therapy, on control DWI there was not any change of the RLQ mass (not shown in the figure). Colonoscopy performed at second week of follow-up showed a cecal mass. Surgery revealed cecal adenocarcinoma with appendiceal mucocele. (a) CT at presentation shows a complex RLQ inflammatory mass (arrows). (b, c) DWI ($b=500$) and ADC map at presentation show restricted diffusion of the mass (arrows).

We found statistically significant correlation between the ADC values and the laboratory parameters. We observed that, as the ADC values increase (suggests decreased cellularity within the IAMs) there was normalization of the serum inflammatory markers (i.e., CRP and WBC) and decrease of IAM diameter (Fig. 4). A statistically

significant correlation was noticed between the increase in ADC values and the regression in lesion size and the serum CRP levels ($p < 0.001$). These data may indicate that the utilization of DWI may allow to monitorize the clinical response to conservative therapy by providing both qualitative and quantitative information.

In the present study 4 patients underwent interval appendectomy (21%) while 14 (73%) were followed-up with complete conservative approach. All of interval appendectomies were elective by the decision of the surgeons rather than acute relapse of appendicitis. Simple appendectomy could be achieved in all patients without any aggressive adhesions that might enlarge the surgical extent and increase complications related to surgery. Pathological specimens of appendectomies revealed minimal or no inflammatory cells. Last control DWI of these four patients showed complete resolution of RLQ mass with ADC values ranging from 1.78 to 2.18. These facts point out that DWI with its capability to show inflammation may help in appropriate timing for the safest interval appendectomy. We suggest that further studies with higher number of patients are needed to disclose the role of DWI that may show whether a cut-off ADC value could be obtained for most appropriate timing regarding interval appendectomy. In one patient thought to have IAM, colonoscopy was decided following first control DWI because of persistent findings of mass on DWI with no change of ADC values despite improvement of clinical and laboratory findings. Colonoscopy revealed a complicated cecal adenocarcinoma with appendiceal mucocele (Fig. 5). None of our patient underwent immediate surgery. One patient had developed acute relapse of IAM at the sixth month of follow-up with sudden right lower quadrant pain (Fig. 6). The patient underwent DWI that revealed IAM with diffusion restriction. Since the patient was stable and there was no accompanying abscess, surgeons decided to start conservative therapy with intravenous antibiotics again. In this patient, DWI could give satisfactory information regarding clinical and laboratory findings without need of any other imaging modality. It is also a remarkable point that DWI may especially avoid an additional contrast-enhanced CT scan that might be needed in follow-up. As shown in this case, DWI may be an efficient imaging modality for evaluation of acute relapses of IAM, but this point must be investigated with further studies.

The present study has several limitations. We enrolled limited number of patients into this study which may decrease the accuracy of our findings. Larger patient groups with longer follow-up periods may be enrolled into future studies, based on the information provided in this study, for better statistical assessment. An important limitation of this study is, so far we have not found a patient with inflammatory bowel disease, that was one of the major concerns as pointed out at the beginning of the paper. But it should be kept in mind that, this study is preliminary and with expanded studies, DWI may have a role in differential diagnosis during follow-up of suggested IAM. We also did not include other MRI sequences that provide morphological information which could have better identified the lesion borders, especially with the use of IV contrast. However, this inclusion of other MRI sequences would go against our aim in this study as we tried to implement the quickest MRI method without the use of IV contrast media.

As for final words, we think that DWI may be used with a significant success for the follow-up of patients with IAM, who were placed on medical management rather than emergency surgery. Its use may be even more beneficial in patients over the age of 40, where the risk of malignancy is increased and malignancy may mimic acute appendicitis associated IAM. The lack of radiation in MRI follow-up may be especially useful in the pediatric age group. As DWI does not need IV contrast, its benefits may be more accentuated in patients with renal impairment.

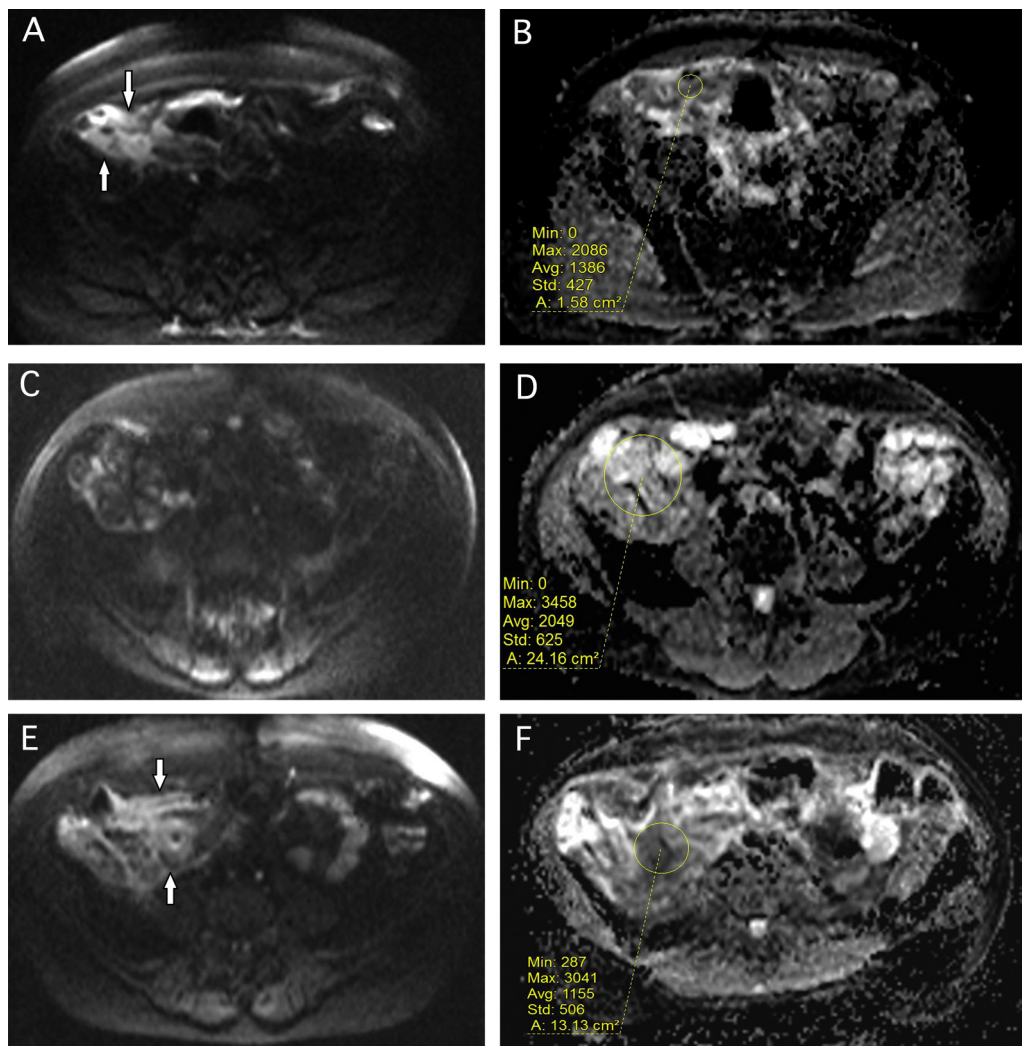


Fig. 6. A 37-year-old female with right lower quadrant (RLQ) pain for last 3 days. Clinical, laboratory and imaging findings were suggestive of IAM at presentation. At the sixth month of follow-up the patient came over with RLQ pain suggestive of relapse of appendicitis. Imaging findings were compatible with IAM. (a, b) DWI and ADC map reveal a RLQ mass with diffusion restriction at the time of first presentation (arrows). (c, d) Control DWI and ADC map show complete regression of IAM with antibiotic therapy. (e, f) Six months following the first presentation there was recurrence of IAM depicted on DWI and ADC map (arrows).

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