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FULL PAPER

Histogram analysis derived from apparent diffusion coefficient (ADC) is more sensitive to reflect serological parameters in myositis than conventional ADC analysis

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Objective: Diffusion-weighted imaging (DWI) has the potential of being able to reflect histopathology architecture. A novel imaging approach, namely histogram analysis, is used to further characterize tissues on MRI. The aim of this study was to correlate histogram parameters derived from apparent diffusion coefficient (ADC) maps with serological parameters in myositis.

Methods: 16 patients with autoimmune myositis were included in this retrospective study. DWI was obtained on a 1.5 T scanner by using the *b*-values of 0 and 1000 s mm⁻². Histogram analysis was performed as a whole muscle measurement by using a custom-made Matlab-based application. The following ADC histogram parameters were estimated: ADCmean, ADCmax, ADCmin, ADCmedian, ADCmode, and the following percentiles ADCp10, ADCp25, ADCp75, ADCp90, as well as histogram parameters kurtosis, skewness, and entropy. In all patients, the blood sample was acquired within

3 days to the MRI. The following serological parameters were estimated: alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase, C-reactive protein (CRP) and myoglobin. All patients were screened for Jo1-autobodies.

Results: Kurtosis correlated inversely with CRP ($p = -0.55$ and 0.03). Furthermore, ADCp10 and ADCp90 values tended to correlate with creatine kinase ($p = -0.43$, 0.11 , and $p = -0.42$, $= 0.12$ respectively). In addition, ADCmean, p10, p25, median, mode, and entropy were different between Jo1-positive and Jo1-negative patients.

Conclusion: ADC histogram parameters are sensitive for detection of muscle alterations in myositis patients.

Advances in knowledge: This study identified that kurtosis derived from ADC maps is associated with CRP in myositis patients. Furthermore, several ADC histogram parameters are statistically different between Jo1-positive and Jo1-negative patients.

INTRODUCTION

Autoimmune myositis is a heterogeneous group of muscle disorders. They comprise different entities, namely polymyositis, dermatomyositis, inclusion body myositis, necrotizing autoimmune myositis and overlap myositis associated with other autoimmune disorders like collagenoses. The diagnostic work-up is multimodal, consisting of anamnestic features, clinical examination, serological parameters, imaging studies, and the diagnostic gold standard of muscle biopsy.

MRI is the most important modality for screening and follow up in these patients due to its excellent soft tissue contrast.^{1,2} MRI cannot only provide information regarding morphology but also physiological information about random water movement in tissue derived from diffusion-weighted imaging

(DWI). This can be quantified by apparent diffusion coefficient (ADC).^{3,4} In oncologic imaging, there is increasing evidence that ADC correlates with several histopathology parameters in different tumors.^{4,5}

Several serological parameters are used in clinical practice for muscle disorders. These indirectly reflect muscle cell lysis like lactate dehydrogenase (LDH), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), creatine kinase (CK), and myoglobin. CK is the most sensitive one with an important role in myositis. Moreover, c-reactive protein (CRP) is an inflammatory parameter, which may reflect muscle inflammation in part of the myositis patients.⁶

Recently, an emergent imaging analysis, namely histogram analysis, has been proposed to further characterize

Table 1. Summary about published studies regarding ADC values in myositis

Author, Year, Reference	Tesla strength, DWI protocol	Number of patients	Results
Qi et al, 2008 ¹¹	1.5 T, IVIM protocol with 24 <i>b</i> -values, ranging from 0 to 1000 s mm ⁻²	8	Inflamed muscles had higher ADC values than normal muscles (1.89 ± 0.17 vs $1.62 \pm 0.14 \times 10^{-3}$ mm ² s ⁻¹ , $p < 0.0005$)
Ai et al, 2014 ¹²	3 T, DTI protocol, <i>b</i> -value of 500 s mm ⁻²	12	Edematous muscles had higher ADC values than the control group (1.97 ± 0.19 vs $1.71 \pm 0.12 \times 10^{-3}$ mm ² s ⁻¹ , $p < 0.001$)
Barsotti et al, 2016 ¹³	1.5 T, DWI protocol, <i>b</i> -value of 500 s mm ⁻²	51	ADC values correlated with edema score and physician global assessment
Ran et al, 2016 ¹⁴	3 T, IVIM protocol, <i>b</i> -values ranging from 0 to 1200 s mm ⁻²	46 myopathy patients, 27 with poly/dermatomyositis, 7 with glycogen storage diseases and 12 with muscular dystrophies	No difference between oedematous muscles and the control group, (mean ADC values, 1.66 vs 1.68×10^{-3} mm ² s ⁻¹ .) There were significant differences between the myositis group and glycogen storage disease and muscular dystrophy
Meyer et al, 2018 ¹⁰	1.5 T, DWI protocol, <i>b</i> -values 0 and 1000 s mm ⁻²	17 patients with myositis and 8 with non-inflammatory myopathies	Inflamed muscles had higher ADC values than normal muscles (1.89 vs 1.15×10^{-3} mm ² s ⁻¹ , $p = 0.0002$)

ADC, apparent diffusion coefficient; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; IVIM, intravoxel incoherent motion.

radiological images and to gain imaging data.⁷ Numerous studies emphasize the increasing value of this technique, especially in oncologic imaging.⁷⁻⁹ For this analysis, every voxel of a region of interest (ROI) is issued for a histogram and therefore, more new parameters can be obtained, which can be used as a biomarker. It has been shown, that this approach can better reflect tumor microstructure than conventional DWI analysis. Presumably, this approach might also be further able to reflect muscle alterations in myositis patients. Therefore, it also might correlate with serological parameters in myositis patients. Yet, in one recent study there was no significant correlation between ADC values reflecting the random water movement in tissues and serological parameters, mainly reflecting muscle cell lysis in myositis.¹⁰ Table 1 gives an overview about previous studies regarding ADC values in myositis.

However, no previous study investigated affected muscles in myositis with histogram based imaging and therefore, there is no evidence, whether this approach might be able to reflect muscle microstructure better than conventional imaging analysis.

Therefore, the aim of this study was to correlate histogram parameters derived from ADC maps with serological parameters in myositis.

METHODS AND MATERIALS

This retrospective study was approved by the local institutional ethics board and informed consent was waived.

Inclusion criteria were histopathology-confirmed autoimmune myositis with an available MRI including DWI as well as a blood sample within 3 days to the MRI.

Altogether 16 patients met the inclusion criteria and were included in the present study. The mean age was 54.6 years with a standard deviation of 16, range 27–75 years. There were 8 female (50%) and eight male (50%) patients.

MRI

In all cases, MRI of the thigh and lower leg was performed using a 1.5 T scanner (Magnetom Vision Sonata Upgrade, Siemens, Erlangen, Germany). MRI sequences included turbo spin echo images, *T*₂ weighted (*T*₂W) fat-suppressed short tau inversion recovery images, half-Fourier acquisition single-shot turbo spin echo images, *T*₁ weighted (*T*₁W) spin echo (SE) images prior and after intravenous contrast medium. Diffusion-weighted (DW) images were obtained with a multishot spin echo-echo-planar imaging sequence (repetition time/echo time: 5800/68 ms; flip angle: 90°, thickness: 5 mm). DWI parameters included in all cases *b*-values of 0 and 1000 s mm⁻².

Histogram analysis

DWI data was processed with a custom-made Matlab-based application (The Mathworks, Natick, MA). On the ADC maps, a volume of interest was drawn at the most affected muscle's boundary using all slices (whole muscle measure). All measures were performed by one experienced author (AS, 15 years of radiological experience). The following parameters were calculated: mean (ADC_{mean}), maximum (ADC_{max}), minimum (ADC_{min}), median (ADC_{median}), mode (ADC_{mode}), as well ADC percentiles: 10th (ADC_{p10}), 25th (ADC_{p25}), 75th (ADC_{p75}), and 90th (ADC_{p90}). Furthermore, histogram-based parameters kurtosis, skewness, and entropy—were calculated. Figure 1 exemplarily displays a patient with the region of interest measurement.

Serological parameters

In all patients, the blood sample was taken within 3 days to the MRI. The following serological parameters were measured: ALAT, ASAT, CRP, LDH, CK, and myoglobin. The SI units were used for these parameters. Additionally, the patients were screened for the Jo-1 autoantibody.

Statistical analysis

Statistical analysis and graphics creation was performed using GraphPad Prism (GraphPad Software; La Jolla, CA). Collected

Figure 1. A 48-year-old female patient with Jo1-syndrome. On T_2 weighted images, an affection of the quadriceps femoris muscle can be diagnosed. (b) On T_1 weighted images, after contrast media application there is enhancement of the affected muscles. (c) On the ADC map, the muscle is slightly hyperintense, resulting in a higher ADC value than the surrounding muscles. (d) The resulting ADC histogram of this affected muscle. ADC, apparent diffusion coefficient.

data were evaluated by means of descriptive statistics (absolute and relative frequencies). All values are presented as mean $\pm$ standard deviation. Spearman's correlation coefficient was used to analyze associations between investigated parameters. ADC and clinical subgroups were analyzed by Mann–Whitney test. In all instances, p -values < 0.05 were taken to indicate statistical significance.

RESULTS

The different included myositis entities are displayed in Table 2. The estimated histogram parameters are summarized in Table 3.

Table 2. Summary of ADC values of the patient collective

Parameter	M $\pm$ SD	Median	Range
Mean	1.74 $\pm$ 0.32	1.81	1.14–2.30
Min	0.49 $\pm$ 0.32	0.53	0.10–1.10
Max	2.82 $\pm$ 0.48	2.94	1.89–3.69
P10	1.38 $\pm$ 0.35	1.40	0.74–1.91
P25	1.55 $\pm$ 0.33	1.59	0.96–2.08
P75	1.94 $\pm$ 0.32	2.01	1.36–2.52
P90	2.11 $\pm$ 0.34	2.21	1.52–2.70
Median	1.74 $\pm$ 0.32	1.80	1.15–2.31
Mode	1.71 $\pm$ 0.37	1.79	1.05–2.22
Kurtosis	4.17 $\pm$ 1.24	3.77	2.43–6.51
Skewness	–0.18 $\pm$ 0.41	–0.14	–0.89–0.50
Entropy	4.50 $\pm$ 0.43	4.53	3.78–5.45

ADC, apparent diffusion coefficient; SD, standard deviation.

There were no significant differences between different myositis entities ($p > 0.05$, Mann–Whitney test). Spearman's correlation analysis revealed only one significant correlation, namely between CRP and kurtosis with a correlation coefficient of $p = -0.55$ and 0.03 (Table 4) (Figure 2). However, there was a trend for an inverse correlation between CK and ADC values, especially between p10 as well as p90 and CK ($p = -0.43$, 0.11 and $p = -0.42$, 0.12 respectively).

After division between Jo1-positive and Jo1-negative patients, there were statistically significant differences between these groups (Table 5). Namely, ADCmean, p10, p25, median, mode and entropy were different between these groups (Figure 3a and b).

DISCUSSION

To the best of our knowledge, this is the first study, which to elucidated possible benefit of histogram analysis derived from ADC maps in autoimmune myositis and, whether this imaging technique shows associations with serological parameters in this group of disorders.

Table 3. Included myositis entities

Myositis	n (%)
Overlap myositis	6 (37.5)
Polymyositis	4 (25.0)
Jo1-syndrome	3 (18.75)
Dermatomyositis	2 (12.25)
Inclusion body myositis	1 (6.25)
Total	16 (100)

Table 4. Spearman's correlation analysis between the ADC parameters and serological parameters

Parameter	CK	Myoglobin	CRP	LDH	ASAT	ALAT
Mean	$r = -0.38$ and $p = 0.16$	$r = -0.32$ and $p = 0.37$	$r = -0.38$ and $p = 0.15$	$r = -0.07$ and $p = 0.83$	$r = -0.35$ and $p = 0.23$	$r = 0.37$ and $p = 0.20$
Min	$r = -0.10$ and $p = 0.73$	$r = -0.20$ and $p = 0.57$	$r = -0.05$ and $p = 0.86$	$r = -0.45$ and $p = 0.13$	$r = -0.28$ and $p = 0.33$	$r = -0.19$ and $p = 0.50$
Max	$r = -0.43$ and $p = 0.11$	$r = -0.31$ and $p = 0.38$	$r = -0.03$ and $p = 0.91$	$r = -0.03$ and $p = 0.93$	$r = -0.31$ and $p = 0.29$	$r = 0.38$ and $p = 0.19$
P10	$r = -0.29$ and $p = 0.30$	$r = -0.30$ and $p = 0.40$	$r = -0.41$ and $p = 0.11$	$r = -0.03$ and $p = 0.94$	$r = -0.32$ and $p = 0.27$	$r = 0.31$ and $p = 0.28$
P25	$r = -0.32$ and $p = 0.25$	$r = -0.28$ and $p = 0.43$	$r = -0.35$ and $p = 0.18$	$r = -0.10$ and $p = 0.73$	$r = -0.32$ and $p = 0.26$	$r = 0.35$ and $p = 0.21$
P75	$r = -0.40$ and $p = 0.14$	$r = -0.32$ and $p = 0.37$	$r = -0.23$ and $p = 0.39$	$r = -0.12$ and $p = 0.69$	$r = -0.37$ and $p = 0.20$	$r = 0.37$ and $p = 0.20$
P90	$r = -0.42$ and $p = 0.12$	$r = -0.30$ and $p = 0.40$	$r = -0.18$ and $p = 0.50$	$r = -0.18$ and $p = 0.57$	$r = -0.41$ and $p = 0.15$	$r = 0.36$ and $p = 0.21$
Median	$r = -0.38$ and $p = 0.16$	$r = -0.38$ and $p = 0.16$	$r = -0.38$ and $p = 0.16$	$r = -0.38$ and $p = 0.84$	$r = -0.33$ and $p = 0.25$	$r = 0.38$ and $p = 0.18$
Mode	$r = -0.36$ and $p = 0.19$	$r = -0.20$ and $p = 0.58$	$r = -0.26$ and $p = 0.34$	$r = -0.26$ and $p = 0.38$	$r = -0.42$ and $p = 0.13$	$r = 0.40$ and $p = 0.16$
Kurtosis	$r = -0.19$ and $p = 0.50$	$r = -0.04$ and $p = 0.91$	$r = -0.55$ and $p = 0.03$	$r = 0.10$ and $p = 0.75$	$r = -0.26$ and $p = 0.37$	$r = -0.35$ and $p = 0.23$
Skewness	$r = -0.15$ and $p = 0.60$	$r = -0.24$ and $p = 0.51$	$r = 0.10$ and $p = 0.75$	$r = -0.20$ and $p = 0.52$	$r = -0.14$ and $p = 0.64$	$r = 0.38$ and $p = 0.18$
Entropy	$r = -0.30$ and $p = 0.28$	$r = -0.32$ and $p = 0.37$	$r = 0.20$ and $p = 0.45$	$r = 0.28$ and $p = 0.35$	$r = -0.15$ and $p = 0.62$	$r = -0.21$ and $p = 0.46$

ADC, apparent diffusion coefficient; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Contrary to the present study, previous studies investigating ADC values of affected muscles in myositis used mean ADC values only.^{10-12,14} However, in oncologic imaging, there is increasing evidence that histogram analysis can obtain further information regarding tissue microstructure and might be a promising biomarker for prognosis and treatment prediction with better results than conventional ADC measurement in several

different tumors.⁷ It has been shown that it better correlates with cellularity and with other histopathological parameters in several tumors.^{7,15,16} Furthermore, second order statistics,

Figure 2. Correlation analysis between C-reactive protein and ADC kurtosis with a correlation coefficient of $r = -0.55$ and $p = 0.03$. ADC, apparent diffusion coefficient; CRP, C-reactive protein.

Table 5. Comparison between Jo1-positive and Jo1-negative myositis patients

Parameter	Jo1-positive (M ± SD)	Jo1-negative (M ± SD)	p-value Mann-Whitney
Mean	1.33 ± 0.18	1.86 ± 0.27	0.03
Min	0.23 ± 0.23	0.55 ± 0.32	0.10
Max	2.49 ± 0.66	2.94 ± 0.41	0.35
P10	0.87 ± 0.18	1.52 ± 0.25	0.01
P25	1.09 ± 0.13	1.68 ± 0.25	0.01
P75	1.59 ± 0.28	2.04 ± 0.28	0.051
P90	1.79 ± 0.36	2.21 ± 0.30	0.07
Median	1.33 ± 0.17	1.85 ± 0.27	0.03
Mode	1.17 ± 0.11	1.84 ± 0.30	0.02
Kurtosis	3.49 ± 1.35	4.38 ± 1.26	0.17
Skewness	-0.30 ± 0.30	-0.11 ± 0.43	0.35
Entropy	5.02 ± 0.42	4.37 ± 0.35	0.04

ADC, apparent diffusion coefficient; SD, standard deviation.

Figure 3. Scatter plot displaying the difference between Jo1-positive and Jo1-negative myositis patients regarding ADC p10, $p = 0.01$. (b) Scatter plot displaying the difference regarding entropy, $p = 0.04$. ADC, apparent diffusion coefficient.

namely skewness, kurtosis and entropy can be estimated, which might further reflect microstructure.⁷ Presumably, due to better reflection of microstructure features in tissues, this technique hypothetically might also better be able to reflect muscle tissue affection in myositis.

Previously, Qi et al¹¹ investigated eight patients with myositis and identified a mean ADC value of $1.89 \pm 0.17 \text{ mm}^2 \text{ s}^{-1}$, which was significantly higher than normal muscles with a mean of $1.62 \pm 0.14 \text{ mm}^2 \text{ s}^{-1}$. In another recent study by Ran et al,¹⁴ the mean ADC value was $1.66 \text{ mm}^2 \text{ s}^{-1}$ with a range of $1.54\text{--}1.82 \text{ mm}^2 \text{ s}^{-1}$. This was interestingly lower than non-diseased muscles and significantly greater than in muscle dystrophy and glycogen storage disease.¹⁴ Furthermore, in another study, the mean ADC of affected myositis muscles was $1.87 \pm 0.37 \text{ mm}^2 \text{ s}^{-1}$, which was significantly higher than those of unaffected muscles.¹⁰ These promising results showed that ADC values are able to reflect pathological tissue alterations in myositis patients.

Contrary to these findings, there were no significant correlations between mean ADC values and serological parameters in a recent study.¹⁰ This finding is not easy to ascertain because serological parameters also reflect cell lysis and therefore, both modalities might correlate with each other.

As mentioned above, previous studies investigated mean ADC values only.^{10–12,14} Regarding neurogenic or myogenic disorders, only a study of texture analysis derived from ultrasonography showed promising first results to discriminate between these entities.¹⁷ However, there is still paucity of histogram analysis derived from ADC maps in myogenic disorders.

Serological parameters are important in clinically diagnostic routine.⁶ Most of them indicate unspecific cell lysis and thus, are associated with clinical presentation in myositis.^{18,19} The muscle enzymes are elevated before treatment and are significantly lowered with treatment response.²⁰ Especially, CK levels are associated with clinical presentation.⁶ Pathophysiologically, the underlying tissue alterations are complex in myositis.²¹ Firstly, inflammatory T-cells, located in the endomysium, surround the muscle fibers.²¹ In a further step, the muscle fibers are degraded by this inflammatory reaction, e.g. due to lymphocyte attack or phagocytosis and necrosis.²¹

In the present study, a statistically significant inverse correlation between kurtosis and CRP was identified. Kurtosis

represents the peakedness of the histogram.⁷ A histogram with a lower peak and with a flat raise was associated with a higher CRP level. This ADC histogram is caused by diseased muscles with various different ADC values reflecting heterogeneous tissue areas with different amounts of inflammation cells and cell lysis. This seems to be moderately correlated with the CRP serum level, which indicates unspecific inflammation in patients. This association is in good agreement with another inflammatory disease of unknown etiology, namely Crohn's disease in which also an inverse correlation between ADC values and CRP serum level was identified.²² Notably, ADC values only reflect a small part of the body, whereas serological parameter represent the complex interactions within the whole body.

Presumably, cell lysis indicated by serological markers might be associated with ADC values. Hypothetically, due to cell lysis the muscle microstructure is altered in such a way that the free extracellular diffusion is elevated and thus, the ADC values might be higher as compared to non-diseased muscles, as was shown previously.^{10,11} This finding could not be shown with mean ADC values¹¹ but in the present study, even with the histogram-based approach, no statistically significant correlation between serological markers, mainly representing cell lysis and ADC values could be obtained. However, there was a trend for an inverse correlation. Further studies with a greater study sample might show significant correlations.

Moreover, this study identified significant differences between Jo1-positive and Jo1-negative myositis patients. Jo1-autoantibodies can be found in about 15–30% of patients with polymyositis.²³ Furthermore, the presence of antiJo1 antibody results in more severe myositis, increased risk of tumors and joint impairment.²⁴ Therefore, it is an interesting finding that ADC histogram analysis shows significant differences between these groups. In a recent study, no significant differences between Jo1-positive and Jo1-negative myositis could be identified by using only a mean ADC value.¹¹

The results of the present study should not indicate that MRI might be able to replace serological evaluation of myositis patients. There is still little evidence, whether functional MRI is able to reflect the disease state and to be used as a possible biomarker in myositis. In a first retrospective study, Barsotti et al¹³ could identify that ADC are correlated with edema score and even with a validated clinical score (PGA). Based upon previous results that ADC values are to discriminate between diseased and non-diseased muscles and therefore, it might aid as a diagnostic tool, there might be a possible role for a predictive biomarker. As an example, Qi et al¹¹ reported one patient, which ADC values lowered significantly under therapy. Clearly, further prospective studies are needed to elucidate ADC values as a new promising biomarker of myositis.

There are several limitations of the present study to address. Firstly, it is a retrospective study with possible known bias. Secondly, and surely, the most important limitation, is the small size of the patient sample, mainly caused by low incidence of

this disorder. Furthermore, similar studies also suffered from this limitation. Thirdly, the study sample comprised mainly of overlap and polymyositis, other types of myositis may show other associations between serological parameters and ADC values.

In conclusion, this study identified associations between serological parameters and histogram parameters derived from ADC maps indicating that these parameters are more sensitive for muscle alterations than conventional ADC values in myositis patients.

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