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Original paper

An observational pilot study comparing diffusion tensor neurography findings of the median nerve in carpal tunnel syndrome patients and healthy controls

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Abstract

Purpose: To determine normative fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values of the median nerve in the healthy population across various age groups and genders and to derive cut-off FA and ADC values for diagnosing carpal tunnel syndrome (CTS).

Material and methods: After ethics board approval and written informed consent were obtained, 60 healthy volunteers (42 women, 18 men) and 20 patients (14 women, 6 men) were studied. Magnetic resonance (MR) neurography with diffusion-tensor imaging (DTI) was performed in all study participants at 3.0 T by using a single-shot echo-planar imaging sequence (repetition time msec/echo time msec, 10,123/40; *b*-value, 1000 sec/mm^2). FA and ADC of the median nerve were determined at 3 locations: the levels of the distal radioulnar joint, pisiform bone, and hamate bone.

Results: Normative FA and ADC values were calculated at different anatomic locations. FA and ADC did not differ between men and women ($p = 0.46$ and $p = 0.41$, respectively) or age dependence. There was significant difference between healthy volunteers and patients with carpal tunnel syndrome ($p = 0.001$ for both FA and ADC). An FA threshold of 0.545 and an ADC threshold of 0.822×10^{-3} mm^2/sec might be used in the diagnosis of carpal tunnel syndrome. Cross sectional area threshold of 10.8 mm^2 at the carpal tunnel (inlet) was also noted for diagnosis of carpal tunnel syndrome.

Conclusions: DTI is a valuable tool in diagnosing CTS. Patients with CTS demonstrate lower FA and higher ADC values. FA and ADC threshold values might be used to diagnose carpal tunnel syndrome.

Key words: DTI, neurography, median nerve, FA, ADC, MR neurography.

Introduction

Magnetic resonance (MR) neurography for peripheral neuropathies in current practice uses the assessment of nerve calibre and intraneural T2-weighted contrast for the anatomical localisation and diagnosis. As a new technique in MR neurography, diffusion-tensor imaging (DTI) is increasingly being investigated to assess its ability to diagnose nerve injuries, reinnervation, and for accurate visualisation [1]. MR neurography has not been explored adequately for the evaluation of carpal tunnel syndrome (CTS). In the present study the median nerve is taken for DTI studies because it is superficial and has a large diameter for DTI measurements. The nerve is also easily accessible for standardised clinical examinations, such as electrodiagnostic tests (nerve conduction study).

Along with the evolution and developments of magnetic resonance imaging (MRI) methods in the last few years, it has become evident that diffusion properties and their measurements in neural tissues provides distinctive information of clinical and biological relevance. It gives details regarding the microstructures and architectural

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A Study design · **B** Data collection · **C** Statistical analysis · **D** Data interpretation · **E** Manuscript preparation · **F** Literature search · **G** Funds collection

organisation. This information can be obtained noninvasively, by measuring the mobility of water in tissues. Mathematical models describing the Brownian motion of water molecules are the basis of diffusion imaging [2].

Diffusion-weighted images (DWIs) are MRIs acquired by incorporating diffusion gradient pulses within a conventional MRI pulse sequence. Diffusion-weighted MRI is a one-dimensional technique, which measures the projection of all molecular displacements along one direction only. Hence, it is largely dependent on the orientation of the tissue. In isotropic tissue like brain grey matter, acquiring a single apparent diffusion coefficient (ADC) is sufficient. However, in anisotropic media like skeletal muscle, white matter of the central nervous system, spinal cord, cardiac muscle, etc., the single ADC value obtained will depend on the orientation of the tissue. Hence, in anisotropic media, a single ADC value cannot characterise the orientation-dependent water mobility. It is not possible to determine whether the ADC and DWI intensity changes are of physiological origin or due to the relative orientation of tracts. Such anisotropic orientation-biased diffusion can be better illustrated by a symmetric or apparent diffusion tensor of water. The solution to this problem was provided by DTI. The NMR measurement of apparent diffusion tensor of water and the analysis and display of the information it contains in each voxel is called DTI or diffusion tensor MRI [3].

Diffusion tensor imaging helps to measure quantifiable values such as fractional anisotropy (FA) and apparent diffusion coefficient, which may help to diagnose CTS and assess median nerve integrity [4]. FA approximates the coherence of oriented structures such as myelinated nerve fibres. It is a measure of the extent to which water within a voxel diffuses preferentially along one axis rather than showing isotropic diffusion (i.e. diffusion of water equally along all axes) [5,6]. Both these measures supplement and augment each other to attain a highly sensitive three-dimensional diffusion ellipsoid tensor model called DTI [7]. Hence, this observational pilot study was undertaken to determine normative diffusion values of the median nerve in healthy controls and compare these normative values with those found in patients with CTS.

Material and methods

Study participants

The study participants included healthy human controls and CTS patients as 2 groups. The study was started after due approval of the Institute Research Committee and Institute Ethics Committee (Human Studies). The study included 20 cases and 20 controls; the mean age of the cases was 48.8 years (SD 8.6) and that of controls was 36.1years (SD 8.7). The study enrolled 13 females (68.4%) and 6 males (31.2%) in controls and 17 females (85%) and 3 males (15%) in cases.

Inclusion criteria for patients were as follows: 1) all clinically diagnosed cases of carpel tunnel syndrome, 2) aged 18 to 60 years. Nerve conduction studies will be done as standard management of the patient on all selected patients. Exclusion criteria were as follows: 1) general contraindications of MRI, e.g. pacemaker, claustrophobia, 2) requirement of general anaesthesia, 3) severe contractures, which do not allow proper positioning and image acquisition, 4) prior surgery at the wrist, and 5) severe inflammatory disease. Healthy controls were sought from the general population. The sampling technique used was convenience sampling.

MR imaging

Written informed consent was obtained from all participants. No preparation was required for the MRI exam.

Magnetic resonance neurography was performed with a 3.0 T MRI machine (GE DISCOVERY 750 W) using a flex coil (GEM flex medium array coil). MR imaging was performed with participants in the superman position (prone position with their hands extended over the head). The following MR sequences would be acquired in both CTS and control groups:

1. T1-weighted image (T1WI) – axial T1-weighted fast spin-echo (FSE-XL) anatomic reference MR images (repetition time msec/echo time msec, 580/15.5, matrix size, 288 × 256 mm; NEX 4, field of view, 12 × 12; number of sections, 25; acquisition time, 5 minutes 17 seconds).
2. IT2-weighted image (T2WI) – axial T2-weighted fast recovery fast spin-echo (FRFSE-XL) anatomic reference MR images (repetition time msec/echo time msec, 5366/85, matrix size, 288 × 256 mm; NEX 4, field of view, 12 × 12; number of sections, 25; one signal acquired; acquisition time, 5 minutes 49 seconds).
3. IDTI and neurography: consisted of a single-shot echo-planar imaging sequence (10123/40; *b*-value, 1000 sec/mm^2; matrix size, 128 × 128 mm; Nex 4; field of view, 20 × 14 cm; section thickness, 2 mm; spacing zero; relative SNR 70%; number of gradient directions, 8; two signals acquired; fat suppression, spectral presaturation attenuated inversion recovery; acquisition time, 3 minutes 31 seconds).

DTI postprocessing

MR images were postprocessed and FA and ADC maps were calculated semiautomatically from the raw DTI data by using dedicated vendor-specific software (Figures 2 and 3). Regions of interest (ROIs) that exactly encircled the median nerve were drawn at 3 different anatomic locations within the carpal tunnel: at the levels of the distal radioulnar joint, pisiform bone, and hook of hamate bone, resembling locations proximal, at (inlet), and distal to carpal tunnel. T1-weighted images served as the anatomic reference (Figure 1).

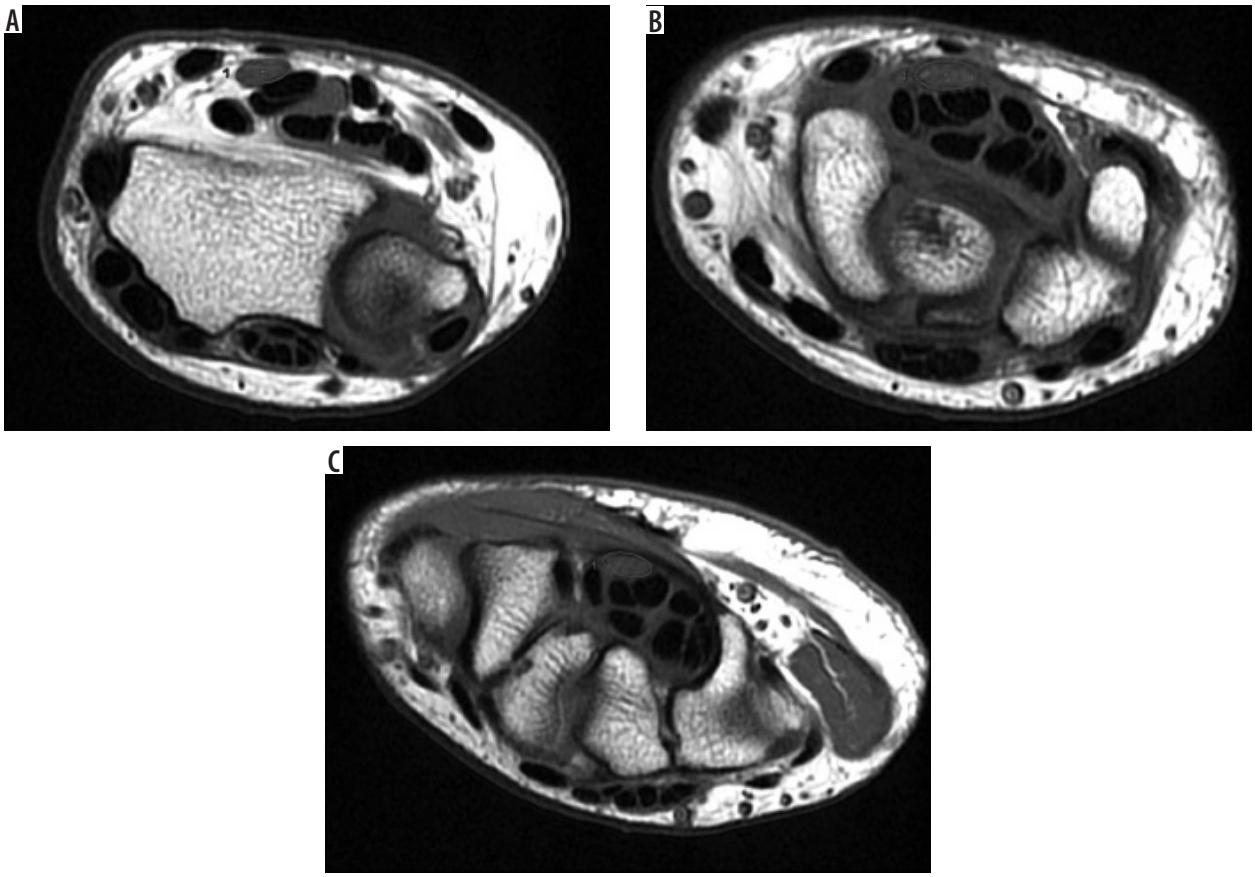

Figure 1. Fractional anisotropy and apparent diffusion coefficient and cross-sectional areas values of the median nerve was determined at three anatomical locations along the median nerve, one just prior to carpel tunnel, one within and another just after, drawing region of interest (ROI) to cover the entire visible cross section of the nerve at that particular level. **A**, **B** and **C**) Axial T1 weighted FSE MR image of left wrist showing sections at each anatomical location. **A**) The region prior to the carpal tunnel (at the distal radioulnar joint), **B** – within the carpal tunnel (pisiform bone) and **C** – just after the carpal tunnel (hook of hamate). The blue ROI denotes the median nerve

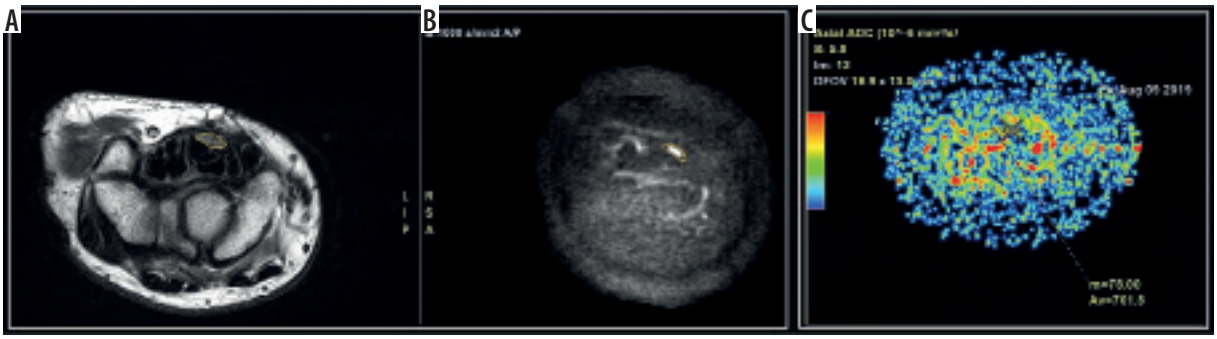

Figure 2. Apparent diffusion coefficient (ADC) maps from the diffusion tensor imaging. The median nerve is identified in T2 weighted image (anatomical reference – **A**) and egion of interest is placed over it, and superimposed to neurography images. **B** and **C**) ADC maps, showing the ADC value in mm^2/sec

Statistical analysis

Statistical analysis was done by using IBM SPSS Statistics (release 20.0; IBM, Somers, NY). First, data were used to calculate mean FA and mean ADC values for subsequent statistical analysis. Normal distribution of these means was tested using the Shapiro-Wilk test.

An independent-samples *t*-test was run to determine if there were differences in mean FA and mean ADC between the cases and controls. A *p*-value of less than 0.05 was considered to indicate a significant difference statistically.

Further analysis was done in the control population on dependence of FA and ADC on age and sex. Comparison of mean values of FA and ADC (mm^2/sec) with respect to gender categories was done to see the dependence on sex in the control population. An independent-samples *t*-test was run to determine if there were differences in mean FA and ADC values between the two groups. A *p*-value of less than 0.05 was considered to indicate a significant difference.

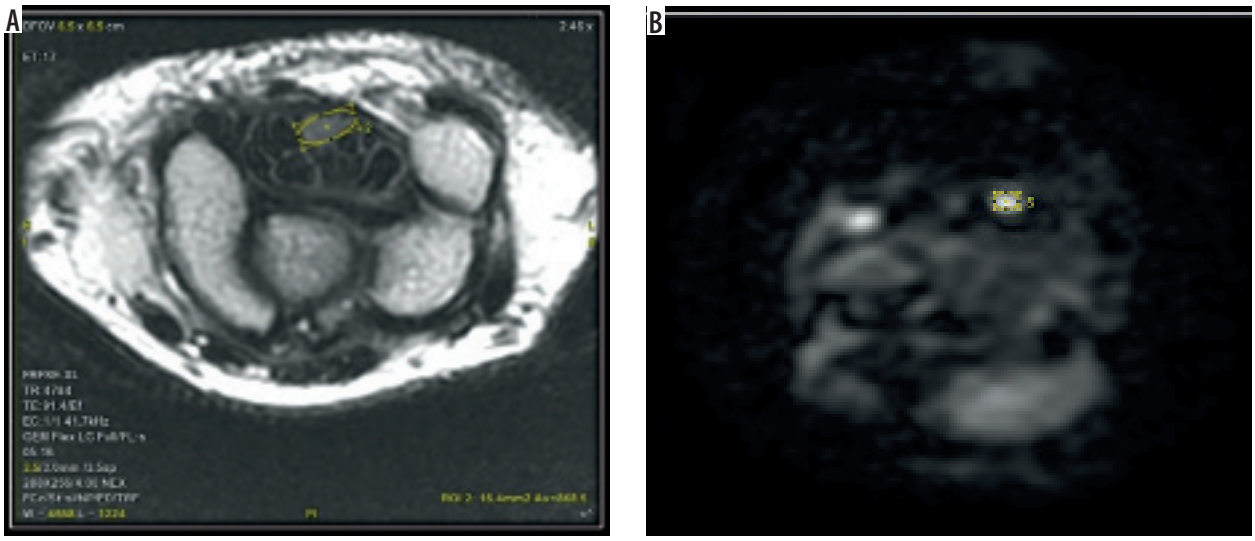

Figure 3. T2-weighted MR image shows median nerve (yellow region of interest [ROI] – **A**) as oval structure with high signal intensity under transverse carpal ligament. There is enlarged cross-sectional areas with loss of fasciculations. **B**) Fractional anisotropy (FA) maps from diffusion tensor imaging with superimposed ROI (anatomic reference – **B**) to obtain FA values of median nerves

Correlation of mean FA and mean ADC values with age was analysed by using the Pearson correlation coefficient (R). A Pearson product-moment correlation was run to assess the relationship between age and FA and ADC values in controls

Receiver operating characteristics (ROC) analysis was used to calculate the FA and ADC cutoff values for diagnosis of CTS. The maximum sensitivity and specificity values within a 95% confidence interval were considered as the cutoff values. A p-value < 0.05 was considered as significant.

Results

Healthy volunteers (control) versus patients with carpal tunnel syndrome (cases) – FA and ADC

Mean FA, and ADC values significantly differed between healthy volunteers and patients with carpal tunnel syndrome in different anatomical locations ($p < 0.05$ for all) (Table 1).

Box plots show increase in ADC from proximal (distal radioulnar joint) to distal (hamate bone) locations in cases and controls (Figure 4). Each box plot shows minimum, first quartile, median, third quartile, and maximum values. Outliers are defined as cases of more than 1.5 times the interquartile range (equivalent to box length) away from the box ends.

Dependence of FA and ADC on age and sex

Comparison of mean values of FA and ADC (mm^2/sec) with respect to gender categories was done to see the dependence on sex in the control population. There were 17 females and 3 males (Table 2).

Correlation of mean FA and mean ADC values with age was calculated by using the Pearson correlation coefficient (R). There was a statistically insignificant/small

Table 1. Mean fractional anisotropy (FA) and apparent diffusion coefficient (ADC) between healthy volunteers (control) and patients with carpal tunnel syndrome (cases) by independent samples t-test

	Control ($n = 20$), mean	Standard deviation	Case ($n = 20$), mean	Standard deviation	p-value (independent samples t-test)
FA(prx)	0.666	0.108	0.47	0.111	< 0.001*
FA(at)	0.654	0.112	0.456	0.06	< 0.001*
FA(distal)	0.653	0.132	0.523	0.094	< 0.002*
ADC(prx)	0.609	0.170	0.864	0.238	< 0.001*
ADC(at)	0.656	0.128	0.989	0.249	< 0.001*
ADC(distal)	0.699	0.168	0.920	0.316	< 0.001*

*$p < 0.05$ is significant.
prx – at level of distal radio-ulnar joint, at – at the level of pisiform bone (inlet), distal – at the level of hook of hamate

Table 2. Mean fractional anisotropy (FA) and apparent diffusion coefficient (ADC) distribution across genders in the control population – independent samples *t*-test

	Female ($n = 14$), mean	Standard deviation	Male ($n = 6$), mean	Standard deviation	*p*-value (independent *t*-test)
FA(at)	0.635	0.095	0.695	0.144	0.396
ADC(at)	0.660	0.102	0.648	0.183	0.452

*$p < 0.05$ is significant.
at – at the level of pisiform bone (inlet)

correlation between age and FA and ADC values, $r < 0.1$, $p > 0.05$ (Figure 5).

ROC analysis of FA and ADC for cases and controls

The mean FA and ADC area under the curve between controls and patients with CTS were 0.794 and 0.853, respectively. A mean FA cut-off value of 0.545 showed a sensitivity of 84.2% and a specificity of 63%, whereas a mean ADC of 0.882 (10-3 mm^2/s) showed a sensitivity of 75% and a specificity of 90%.

Thus, the corresponding overall threshold mean FA and mean ADC values were 0.524 and 0.882 × 10^{-3} mm^2/sec, respectively; hence, the participants with an FA lower than 0.524 and ADC higher than 0.882 × 10^{-3} mm^2/sec would be classified as having carpal tunnel syndrome (Figure 6).

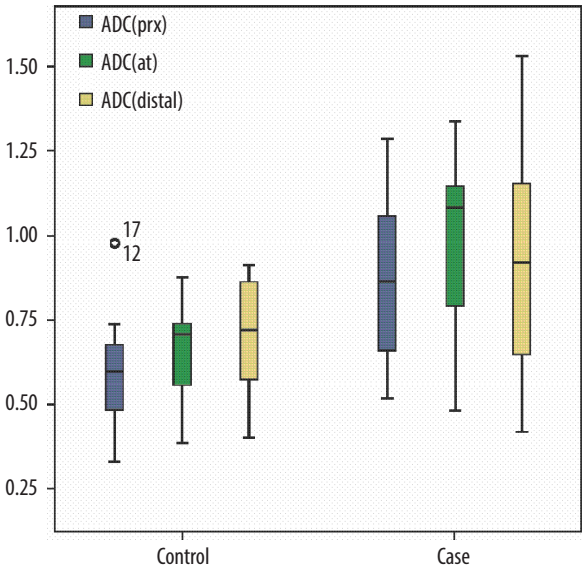

Figure 4. Boxplots showing apparent diffusion coefficient (ADC) at different anatomical levels

Discussion

DTI is a relatively novel MR technique that has been used mainly in neuroradiology, and most high field-strength systems with strong gradients are also used to perform diffusion imaging [8]. Diagnosis of nerve pathologies is usually based on electrophysiology and ultrasound examinations. Although EPS is highly specific

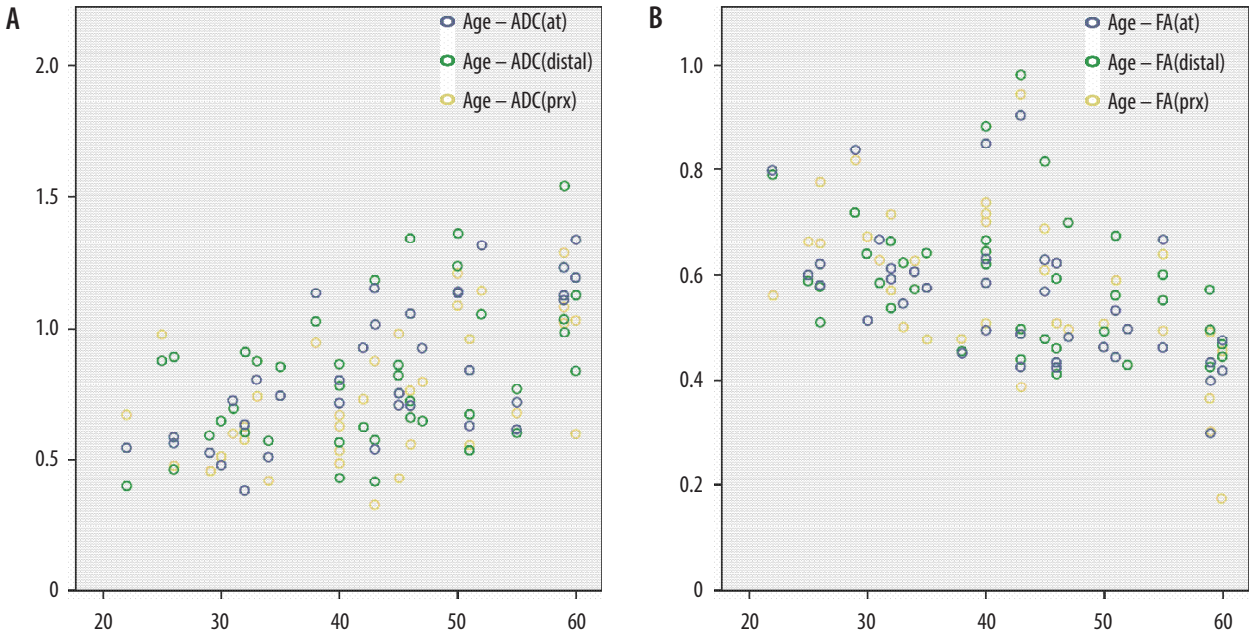

Figure 5. Scatter plot: Pearson correlation coefficient of fractional anisotropy (FA) and apparent diffusion coefficient (ADC) versus age, showing no correlation

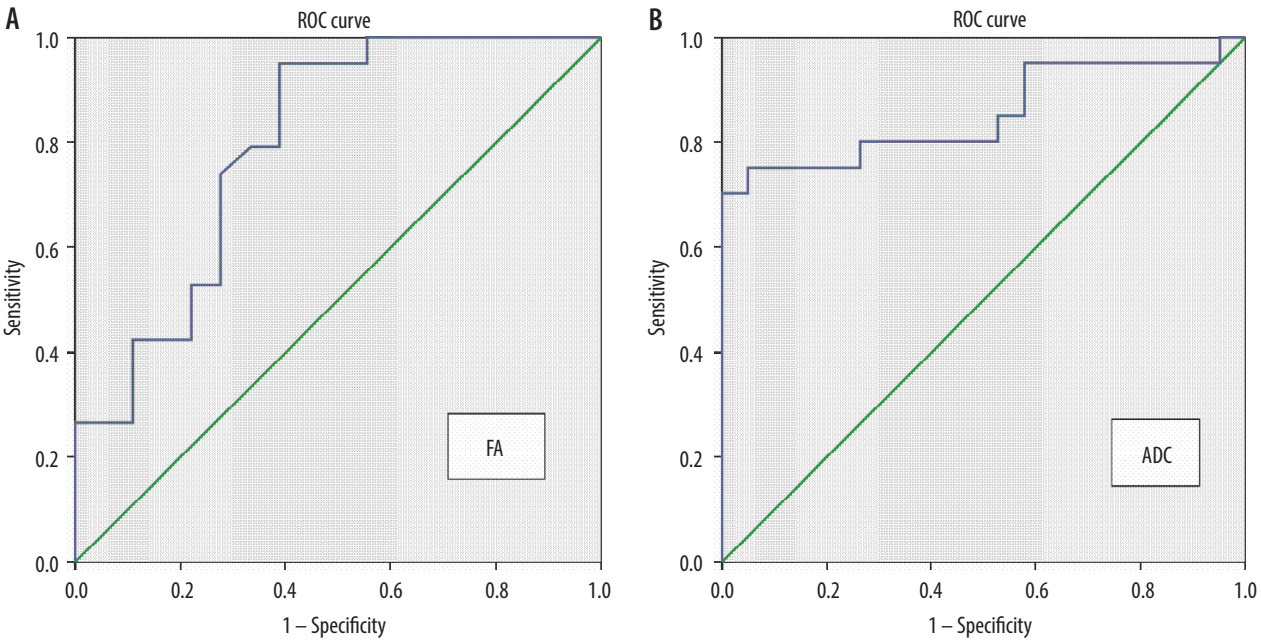

Figure 6. Graphs show results for receiver operating characteristic (ROC) curves analysis of fractional anisotropy (FA) and apparent diffusion coefficient (ADC)

for CTS diagnosis (80-90% accurate), it also has limitations – false-negative results occur in 10-20% of cases [9]. It also does not provide the anatomical cause of CTS. Another problem is the diagnosis in the early stages because of discrepancies in the measured clinical and/or EPS parameters [10,11]. Imaging methods, such as US and conventional MRI, can resolve these discrepancies between them [8,12]. Nerve conduction study is a cumbersome method that may lead some patients to prefer imaging methodologies. However, conventional MRI provides only a qualitative assessment, while DTI, a sophisticated MRI technique, can provide more accurate results because of better visualisation of median nerve fibres and quantitative analysis [13,14].

Age dependency and sex dependency of FA and ADC values in the normal population were also assessed. Our study shows no dependence of FA and ADC values on sex and age. Both males and females showed no significant difference across all the anatomical locations. The mean FA values within the carpal tunnel were 0.635 in females and 0.695 in males. The ADC values were 0.660×10^{-3} mm^2/sec in females and 0.648×10^{-3} mm^2/sec in males. The study by Guggenberger *et al.* [15] also showed similar conclusions in the case of gender; however, contrary to our study, they showed age dependence, stating a decrease in FA and a increase in ADC with an increase in age.

The main goal of the study was to compare the FA and ADC values in healthy volunteers versus patients with CTS. In our study, we found a significant difference between mean FA and mean ADC of cases and controls. Different authors have measured FA and ADC at different anatomical locations. The findings in our study were in agreement with many similar studies done at various institutes across the world. Guggenberger *et al.* [15], Koh *et al.* [16], and Paniandi *et al.* [17] used similar anatomical landmarks for measurements as in our study. All these studies recommend measurement at the level of the pisiform bone (within the carpal tunnel) to be the best location for diagnosis of CTS. Many authors consider this level to be the inlet of the carpal tunnel [15,16,18]. This

Table 3. Sensitivities and specificities of diffusion-tensor imaging fractional anisotropy (FA) in diagnosing carpal tunnel syndrome (CTS) observed in different studies in comparison with our study

Author [Ref.], year of publication	Cut-off	Sensitivity	Specificity
Our study	0.545	84.2 %	63.0%
Guggenberger *et al.* [15], 2012	0.470	83.0%	67.0%
Tasdelen *et al.* [23], 2012	0.554	80.7%	80.0%
Koh *et al.* [16], 2014	0.536	73.8%	76.2%
Bulut *et al.* [24], 2014	0.532	94.4%	70.8%
Kwon *et al.* [25], 2014	0.440	72.0%	82.0%

Cut-off values are FA values for diagnosis of CTS.

is also helped by the fact that carpal tunnel measurement at the level of the pisiform bone is the most frequent site of severe compression of the median nerve in CTS and thus has the most remarkable morphologic and pathologic changes [19-21].

Based on this evidence and ROC curve analysis at proximal and distal locations, we found that the highest sensitivity and specificity for a threshold value, which can help in diagnosing CTS, was in the inlet (pisiform bone). Hence, in our study also, we took the ROC curve analysis at this level to calculate the cutoff value. The area under the curve (AUC) for FA in our study was 0.794, and ADC was 0.853, which are similar to the AUC values in the study by Koh *et al.*, which were 0.824 for FA and 0.742 for ADC. The sensitivity seems to be higher for the FA value whereas the ADC value shows more specificity in the current study for the given thresholds. The comparison with other studies is shown in Table 3 [15,16,23-25]. Hence, our study also concluded that FA values are lower in patients in comparison to healthy volunteers. Guggenberger *et al.* [22], in another study comparing 3.0 T MR scanners from different vendors to evaluate the agreement of FA and ADC values of the median nerve, found significant differences between the vendors. So, this can be a reason for different cutoffs in different studies for FA and ADC.

Conclusions

DTI is a valuable tool in diagnosing CTS. Mean FA was lower in patients with CTS than in healthy volunteers. Mean ADC was higher in patients with CTS than in healthy volunteers. FA and ADC threshold values might be used to diagnose carpal tunnel syndrome. Patients with CTS demonstrate lower FA and higher ADC values.

Disclosures

1. IInstitutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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