Can Diffusion Tensor Imaging Apparent Diffusion Coefficient Diagnose Carpal Tunnel Syndrome? A Systematic Review and Meta-Analysis

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Abstract

Magnetic resonance diffusion tensor imaging (DTI) can detect microstructural changes in peripheral nerves. Studies have reported that the median nerve apparent diffusion coefficient (ADC), a quantification of water molecule diffusion direction, is sensitive in diagnosing carpal tunnel syndrome (CTS). Five databases were searched for studies using ADC to investigate CTS. Apparent diffusion coefficient (measured in mm^2/s) were pooled in random-effects meta-analyses. Twenty-two studies met criteria yielding 592 patients with CTS and 414 controls. Median nerve ADC were measured at the level of the distal radioulnar joint (CTS ADC: 1.11, 95% CI: 1.07-1.15, $I^2 = 54\%$; control ADC: 1.04, 95% CI: 1.01-1.07, $I^2 = 57\%$), pisiform (CTS ADC: 1.39, 95% CI: 1.37-1.42, $I^2 = 0\%$; control ADC: 1.27, 95% CI: 1.23-1.31, $I^2 = 59\%$), hamate (CTS ADC: 1.40, 95% CI: 1.36-1.43, $I^2 = 58\%$; control ADC: 1.27, 95% CI: 1.25-1.28, $I^2 = 47\%$), and as an combination of several measurements (CTS ADC: 1.40, 95% CI: 1.37-1.47, $I^2 = 100\%$; control ADC: 1.39, 95% CI: 1.24-1.53, $I^2 = 100\%$). Median nerve ADC is decreased in individuals with CTS compared to controls at the levels of the hamate and pisiform. ADC cut-offs to diagnose CTS should be established according to these anatomic levels and can be improved through additional studies that include use of a wrist coil.

Keywords: carpal tunnel syndrome, nerve, diagnosis, median nerve, diffusion tensor imaging, apparent diffusion coefficient, nerve compression

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy and affects 7.8% to 14.4% of individuals.[1,2] Symptoms may include paresthesias, numbness, pain in the hand, thenar atrophy, and motor loss.[3] The carpal tunnel contains the median nerve and digital flexor tendons, and extends from the pisiform to the hamate attachments of the overlying transverse carpal ligament (or flexor retinaculum).[4]

Magnetic resonance (MR) diffusion tensor imaging (DTI) has grown in use over the past 15 years as a method of investigating the median nerve changes in carpal tunnel syndrome.[5-26] Traditionally utilized to study the white matter tracts of the brain, DTI can also track water diffusion to create a 3-dimensional (3D) map of the peripheral nervous system.[27] Regions of interest (ROIs) may be specified to examine only a nerve segment while excluding surrounding vessels, tendons, and connective tissue. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) are indices that describe water diffusion in neural tracts and allow a more sensitive investigation of the DTI map. FA describes the symmetry, or isotropic environment, of the water diffusion. Apparent diffusion coefficient is often synonymously referred to as mean diffusivity (MD), although ADC was originally derived from the diffusion weighted imaging data, whereas MD was derived from the tensor fitted data.[28] ADC is comprised of 3 eigenvalues, 2 of which are radial diffusivity (RD) and 1 is axial diffusivity (AD).

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RD describes the magnitude of water diffusion perpendicular to the plane of the ROI chosen, whereas AD quantifies the magnitude of water diffusion parallel to the plane of the ROI, which in a nerve is traditionally chosen to be parallel to the course of the nerve.[29] Increased ADC values, and increased water diffusion, may be explained by several pathophysiologic changes of a compressive neuropathy, such as edema or demyelination.[21]

A 3-D, colored map may be created using these eigenvalues to visualize the nerve, and the FA values are used to provide a color scheme. Additionally, the individual values of FA and ADC have been investigated as means of understanding pathology of the nervous system.[28] While median nerve ADC measurements at the carpal tunnel have been reported to be able to diagnose CTS, a consensus on how to obtain and use ADC measurements to diagnose CTS does not exist. The present study is a systematic review and meta-analysis that establishes a pooled mean ADC value in carpal tunnel syndrome and evaluates the use of this value in diagnosing CTS.

Methods

This study is compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30] and was registered under the PROSPERO ID: CRD42020199996.

Search Strategy

Independent literature searches were performed by 2 reviewers (B.A. and M.M.) of the databases Cochrane Library, Ovid EMBASE, Ovid MEDLINE, ClinicalTrials.gov, and Web of Science. Databases were searched in June, 2020 from database inception through June 8, 2020 for text word and Medical Subheading (MeSH) terms such as "nerve pain," "neuropathy," "nerve compression," "diffusion tensor imaging," "DTI," "diffusion tensor weighted imaging," "carpal tunnel," "median nerve," as well as word variations and similar words combined using the Boolean operators "OR" and "AND." The full search strategy is included in Supplementary Information. Bibliographies of included studies were also searched. Disagreements about study inclusion were resolved by involving a third author (A.E.) in the discussion. Two reviewers (B.A. and M.M.) extracted data into preformed excel template with another reviewer (A.E.) checking over 90% of the extracted data. Experts in diffusion tensor imaging, hand surgery, and neurology were involved in the study.

Inclusion and Exclusion Criteria

Included studies were: (1) peer-reviewed research; (2) in English; (3) including a minimum of 8 patients with carpal tunnel syndrome; (4) applying DTI at the wrist; and (5) reporting on ADC or MD.

Excluded studies were: (1) reviews, meta-analyses, case reports; (2) animal studies, letters, opinion pieces, editorials, non-peer-reviewed literature, gray literature, conference proceedings, abstracts, and book chapters; and (3) duplicates of studies or cohorts.

Outcomes

The primary outcome was the measured ADC or MD of the median nerve at the wrist in patients with CTS and in controls. The secondary outcome was the investigation of DTI protocol variations that contribute to heterogeneity in ADC across studies.

Statistical Analysis

Statistical analyses were performed via the RStudio meta package (version 4.15-1). Meta-analyses were performed with inverse variance method of weighting. Standard errors were derived from standard deviations.[31] To incorporate heterogeneity between studies, I^2 was calculated with an $I^2 \geq 75\%$ indicating high heterogeneity and warranting investigation.[32] Meta-analyses were performed for patients and controls at regions of the: (1) distal radioulnar joint (DRUJ); (2) pisiform; (3) hamate; and (4) multiple or averaged ROIs of the median nerve at the wrist.

Results

Literature Search

In all, 3477 records were identified from the search strategy, and after de-duplication, 2744 records underwent a title and abstract screen. In all, 131 studies were eligible for full-text screen, of which 109 were excluded for reasons. Therefore, 22 studies were included in the qualitative synthesis, and 16 studies were included in quantitative analysis. The full article selection process is shown in Figure 1.

Study Design and Patient Demographics

Included studies enrolled a total of 1006 persons (592 patients with CTS and 414 controls), including 260 males and 664 females for the studies that reported gender. A diagnosis of CTS was initially made clinically alone[17,18,23] or clinically with electrodiagnostic support.[6-16,19-22] Of the 3 studies relying on a clinical diagnosis, 1 study utilized a 6-question validated carpal tunnel syndrome symptom questionnaire.[33] Studies reported mean ages of enrolled individuals that ranged from 23 to 58 years. Ten studies were conducted in Asia,[6,9,12,15,16,19,21,22,24,25] 8 in Europe,[7,8,10,11,13,14,17,26] 3 in Africa,[5,20,23] and 1 in North Amer-
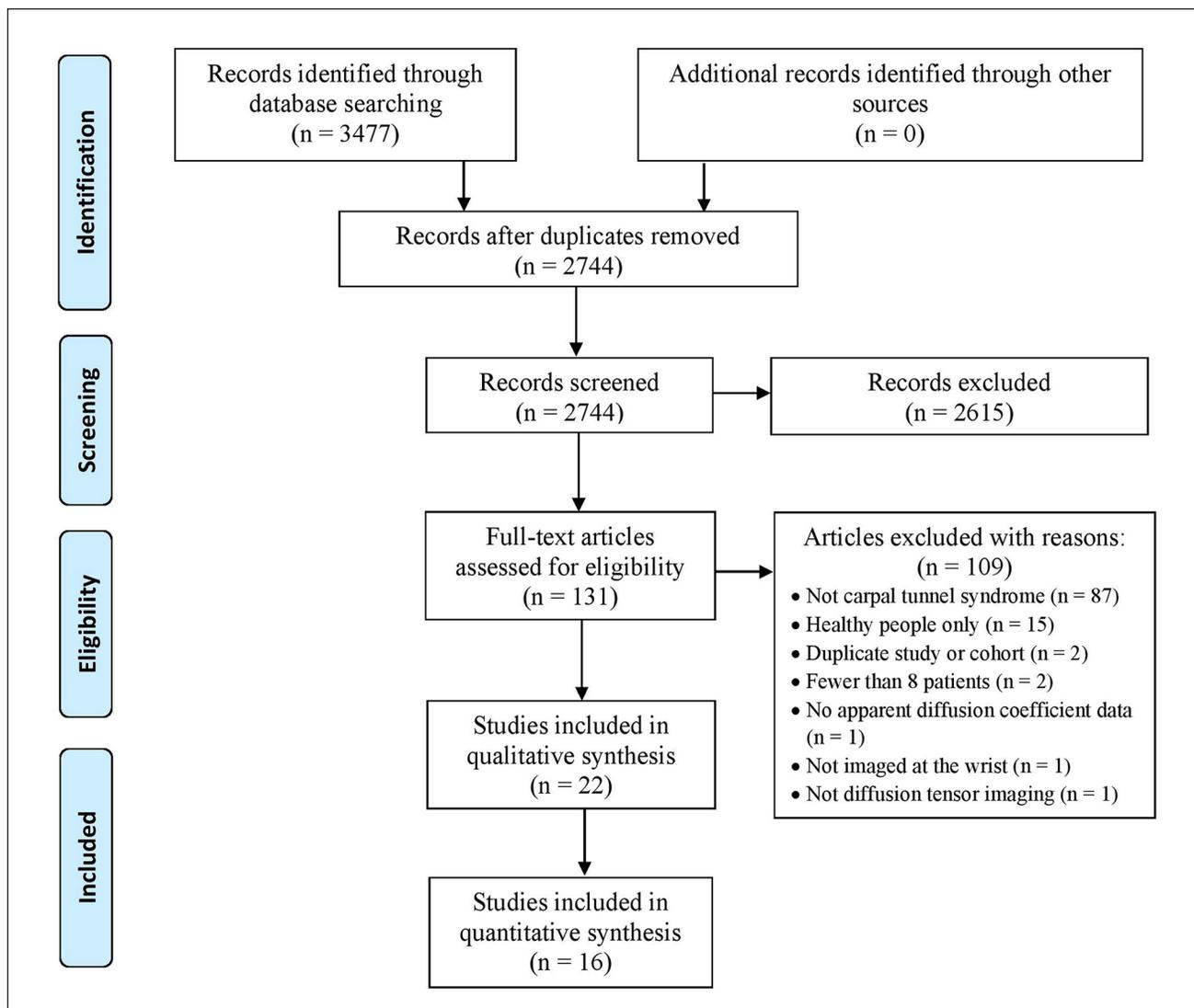
Figure 1. Application of the search strategy identified 3477 records, of which 131 met criteria for full-text screen. 109 articles were excluded for reasons, resulting in 22 articles being included in the systematic review, of which 16 were included in the meta-analyses.

ica.[18] Study diffusion imaging protocols are summarized in Supplemental Information 2.

Meta-Analyses

Median nerve ADC values were assessed at the levels of the DRUJ, pisiform, hamate, or as a combination of several values to represent the entire carpal tunnel. The values assessed at the DRUJ may be thought to represent a location proximal to the carpal tunnel and the expected area of nerve compression. The values assessed at the pisiform may be thought to represent a location within the carpal tunnel where high anatomic complexity is present, whereas the values assessed at the hamate may be thought of as being toward the distal end of the carpal tunnel where less

anatomic complexity is present.[26] The method of combining several values varied across studies, but often included averaging all values obtained as well as the combination of the DRUJ, pisiform, and hamate measurements. Investigation of data from studies with outlier data revealed that the outliers did not use a coil to amplify the signal-to-noise ratio or used a coil designed for a non-wrist body part. Accordingly, studies without the use of a wrist coil were removed from the meta-analyses.

Ten studies were included in the meta-analyses of median nerve ADC values obtained by combining several carpal tunnel ROIs. The pooled mean ADC for patients with carpal tunnel syndrome was 1.40 mm^2/s (95% CI: 1.37-1.47, I^2 = 100%) and in controls was 1.39 mm^2/s (95% CI: 1.24-1.53, I^2 = 100%), shown in Figure 2.
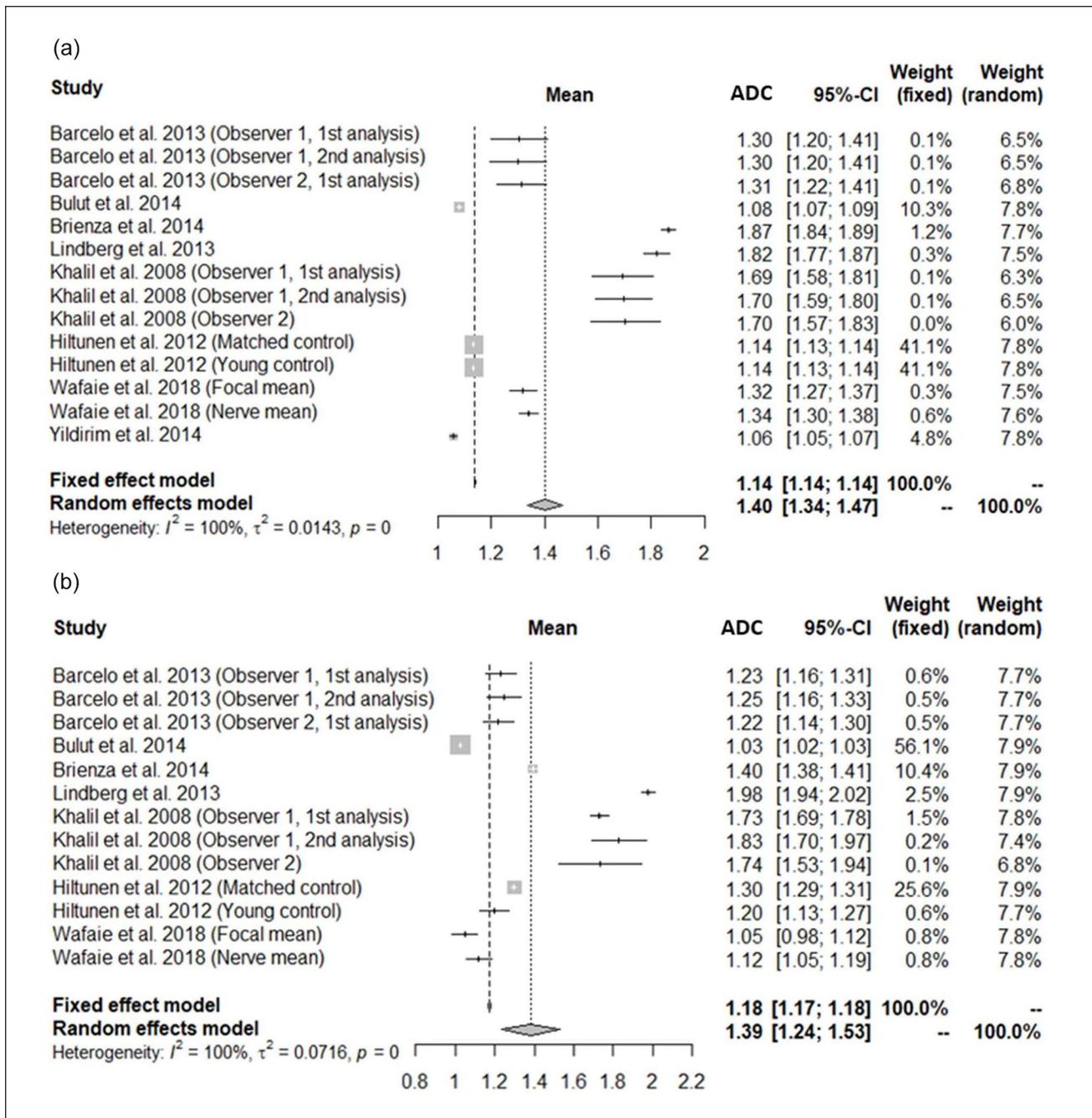
Figure 2. Median nerve apparent diffusion coefficients of several combined regions of interest resulted in a pooled mean apparent diffusion coefficient for patients with carpal tunnel syndrome of 1.40 mm2/s (95% CI: 1.37-1.47) and for controls of 1.39 mm2/s (95% CI: 1.24-1.53). (a) Patients with carpal tunnel syndrome. (b) Controls.
Note. Significant heterogeneity was present in both analyses, 100% and 100%, respectively. CI = confidence interval; ADC = apparent diffusion coefficient.

Eight studies were included in the meta-analyses of median nerve ADC values measured at the level of the DRUJ. The pooled mean ADC for patients with carpal tunnel syndrome was 1.11 mm²/s (95% CI: 1.07-1.15, I^2 = 54%) and in controls was 1.04 mm²/s (95% CI: 1.01-1.07, I^2 = 57%), shown in Figure 3.

Five studies were included in the meta-analyses of median nerve ADC values measured at the level of the pisi-form. The pooled mean ADC for patients with carpal tunnel syndrome was 1.39 mm²/s (95% CI: 1.37-1.42, I^2 = 0%) and in controls was 1.27 mm²/s (95% CI: 1.23-1.31, I^2 = 59%), shown in Figure 4.
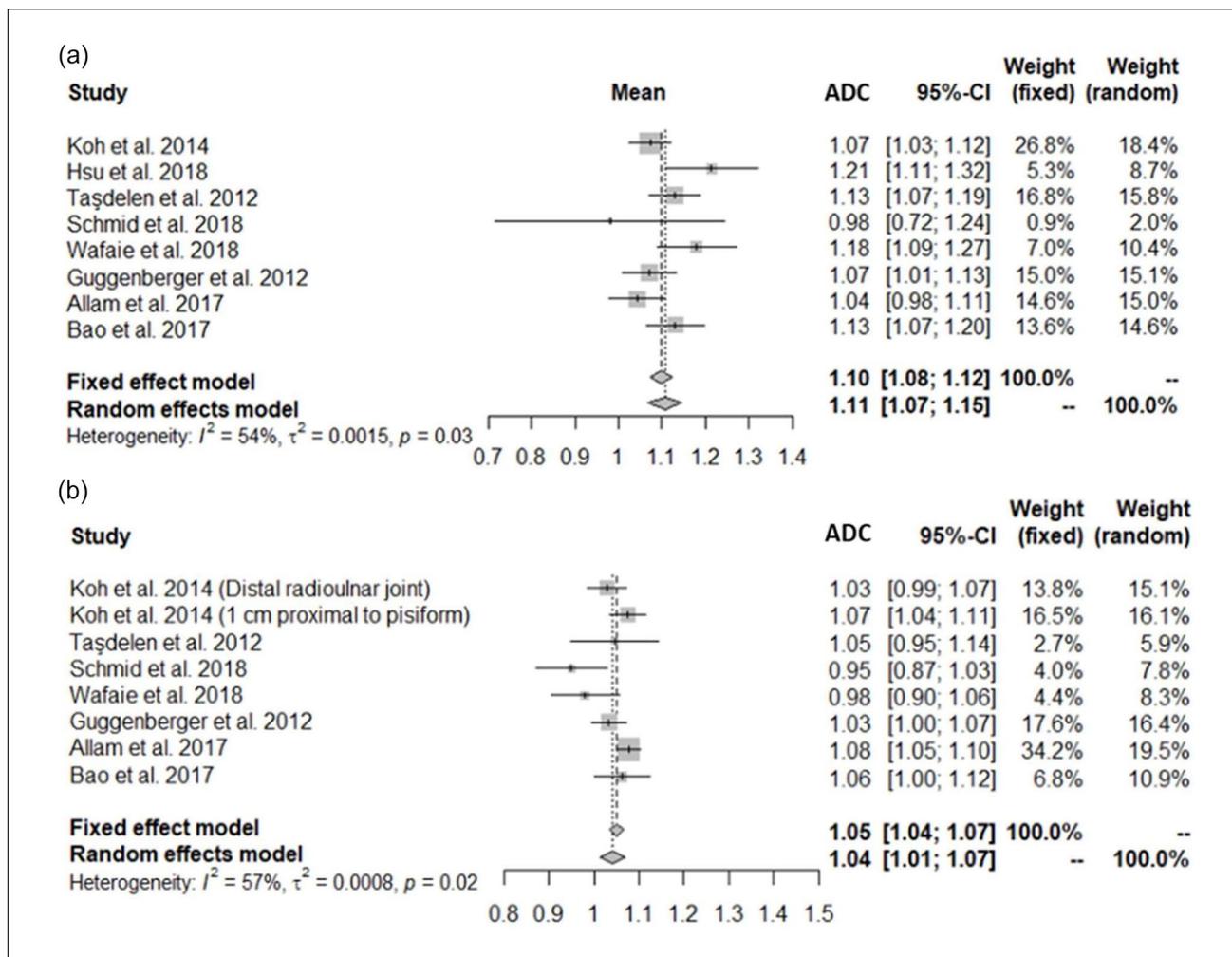
Figure 3. Median nerve apparent diffusion coefficients measured proximally at the level of the distal radioulnar joint provided a pooled mean apparent diffusion coefficient for patients with carpal tunnel syndrome of 1.11 mm2/s (95% CI: 1.07-1.15) and for controls of 1.04 mm2/s (95% CI: 1.01-1.07). (a) Patients with carpal tunnel syndrome. (b) Control.
Note. CI = confidence interval; ADC = apparent diffusion coefficient.

Five studies were included in the meta-analyses of median nerve ADC values measured at the level of the hamate. The pooled mean ADC for patients with carpal tunnel syndrome was 1.40 mm^2/s (95% CI: 1.36-1.43, I^2 = 58%) and in controls was 1.27 mm^2/s (95% CI: 1.25-1.28, I^2 = 47%), shown in Figure 5.

Discussion

Our meta-analyses indicate individuals with CTS have increased median nerve ADC within the carpal tunnel at specific ROIs. This study reveals that focusing on individual ROIs improves the utility of ADC values as a diagnostic parameter for CTS. ADC values at the DRUJ, pisiform, and hamate, in patients with CTS and controls had acceptable heterogeneity for pooled meta-analyses. Conversely, averaging or combining ROIs led to greater heterogeneity and

yielded similar ADC values between CTS patients and controls. The lack of overlap in the confidence intervals of the meta-analyses at the pisiform and hamate demonstrates a statistically significant difference between patients and controls, suggesting that these locations are superior to the DRUJ in diagnosing CTS.

Diagnostic Cut-Offs

Several ADC cut-off point values have been proposed to diagnose CTS, ranging from 1.05 to 1.35 mm^2/s.[5,6,9,11,20,23] The broad range of cut-off values is related to different anatomic levels requiring separate cut-offs. One study, by Klauser et al in 2017, did not detect a statistically significant difference between CTS patients and controls by assessing ADC values of a 3 to 4 cm nerve segment just distal to the pronator quadratus. This lends support to the
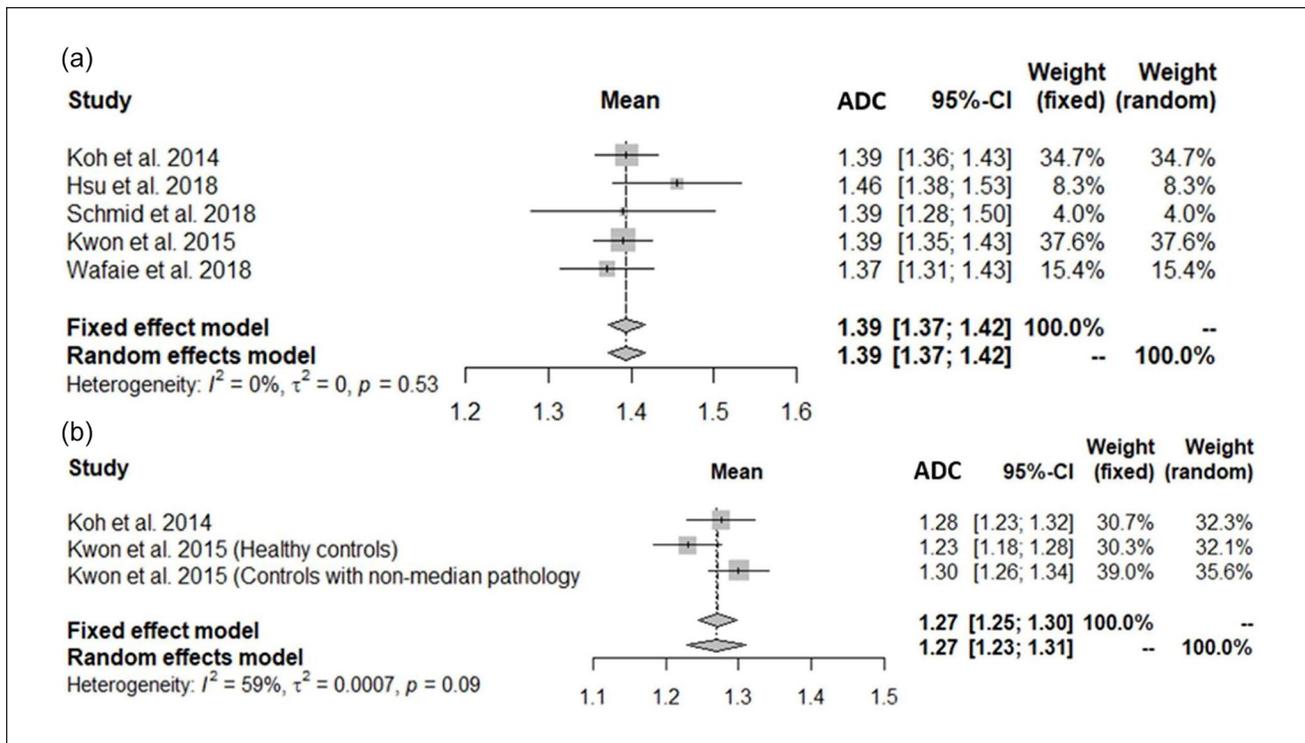
Figure 4. Median nerve apparent diffusion coefficients measured at the level of the pisiform provided a pooled mean apparent diffusion coefficient for patients with carpal tunnel syndrome of 1.39 mm2/s (95% CI: 1.37-1.42) and for controls of 1.27 mm2/s (95% CI: 1.23-1.31). (a) Patients with carpal tunnel syndrome. (b) Controls.
Note. CI = confidence interval; ADC = apparent diffusion coefficient.

limited diagnostic utility of proximal measurements, such as in the region of the DRUJ. Another study, by Khalil et al[13] in 2008, averaged ADC values over the carpal tunnel and similarly did not detect a difference between patients and controls, further suggesting that combining ADC values over the carpal tunnel is not useful in diagnosing CTS. Instead, ADC cut-off's appear to be of the greatest diagnostic utility when evaluated at a specific ROI such as the pisiform and hamate.

The pooled mean ADC confidence intervals for patients and controls in this study can provide boundaries for a diagnostic cut-off. While ADC values at the DRUJ overlapped between patients and controls, at the pisiform a cut-off could fall within the range of 1.27 to 1.39 mm^2/s and at the hamate between 1.27 and 1.40 mm^2/s. This range should be further refined through additional studies that investigate age-specific cut-offs[11,17,22] and CTS severity specific cut-offs.[9,20]

Effect of Treatments on ADC

Studies have investigated whether median nerve ADC values are altered by treatments such as corticosteroid injection, carpal tunnel release, or therapeutic ultrasound with a wrist orthosis. Hsu and Cohen[34] in 2018 found that after corticosteroid injection, a statistically significant decrease in the ADC values at the pisiform correlated with symptomatic improvement. Naraghi et al in 2013 found that ADC values 6 months after carpal tunnel release decreased significantly at the DRUJ. Similarly, Yildirim et al in 2014 reported a statistically significant decrease in the ADC values after 4 weeks of wrist orthoses with 3 weeks of therapeutic ultrasound.

Nerve Study Correlates With Apparent Diffusion Coefficient

Nerve conduction studies (NCS) are the current gold-standard for grading CTS severity. Several studies included in this analysis found that conduction velocity and distal latency of both motor and sensory nerves correlated with ADC values.[9,17,20,23,24] The compound motor unit action potential (CMAP) is a component of an electrodiagnostic study which has been recently shown to best predict ulnar nerve injury severity in cubital tunnel syndrome, and both CMAP as well as the amplitude of the sensory nerves (SNAP) showed the strongest association with ADC of NCS parameters.[16,35]
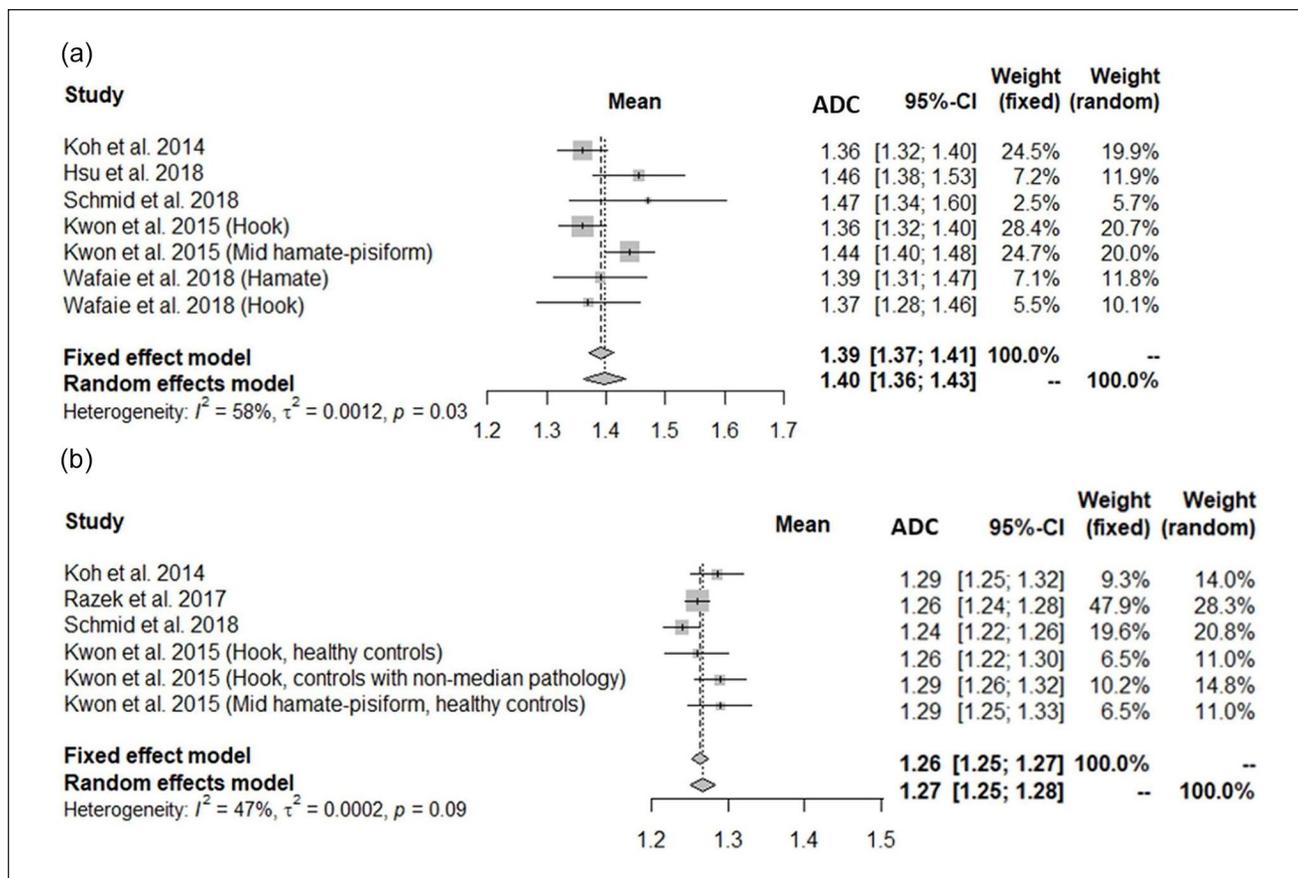
Figure 5. Median nerve apparent diffusion coefficients measured at the level of the hamate provided a pooled mean apparent diffusion coefficient for patients with carpal tunnel syndrome of 1.40 mm2/s (95% CI: 1.36-1.43) and for controls of 1.27 mm^2/s (95% CI: 1.25-1.28). (a) Patients with carpal tunnel syndrome. (b) Controls.
Note. CI = confidence interval; ADC = apparent diffusion coefficient.

The cross-sectional area of the median nerve in the carpal tunnel may be increased or decreased in CTS.[6,10,14,20] Despite this discrepancy, ADC values appear consistently increased in CTS irrespective of whether edema or compression have altered the size of the nerve. This suggests ADC values may be superior in reliability to diagnostic ultrasound of the carpal tunnel.

Axial and Radial Diffusivity

The ADC is comprised of axial and radial diffusivity (AD and RD) which provide directionality to water diffusion magnitudes. The increase in ADC that occurs with age has accordingly been shown to also increase both AD and RD.[17]

In 2009, a study by Stein et al[21] found that of ADC, AD, and RD, only RD was statistically different in patients with CTS than controls. Studies have similarly found that RD correlated with CTS severity when MD and AD did not, suggesting that RD may be superior at investigating CTS severity.[19,26] Radial diffusivity was also the most effective DTI

parameter at differentiating patients from controls.[16,26] This is supported by Lindberg et al,[17] who found that RD exhibited the greatest increase at the distal carpal tunnel, 33%, whereas ADC and AD were 16% and 6% higher, respectively, at the distal carpal tunnel than at the proximal carpal tunnel. Additionally, Lindberg et al found that patients with endoneurial fibrosis had a statistically significant reduction in ADC and RD at a level 2 cm proximal to the wrist.

AD, on the other hand, has been found to have significant correlation with NCS parameters in CTS.[17] Future studies are needed to investigate the correlation of AD with conduction velocity and CMAP as the parallel diffusion may provide prognostic information related to the quantity or structural integrity of axons.[36]

Reliability of Apparent Diffusion Coefficient Measurements

Five studies assessed intra-reader reliability of DTI, with reports of excellent to perfect reliability.[7,13-15,34] 6 studies

assessed inter-reader reliability of DTI, and while most found excellent to perfect reliability, Koh et al reported fair to moderate inter-reader reliability.[7,9,11,13,15,34]

Limitations

Patient populations varied in CTS severity across the included studies. While CTS is a clinical diagnosis that is often easy for experienced clinicians to diagnose, variability in the use of validated questionnaires or electrodiagnostic studies to confirm the diagnosis was present across the included studies and may limit the homogeneity of patient populations. Additionally, no standard DTI protocol exists, lending increases in heterogeneity according to specifications determined at each institution, as well as whether the institution used a wrist coil to amplify their signal-to-noise ratio. Studies also varied in their ROIs, although a strength of our study is that we analyzed ADC by grouping similar ROI data in the same analysis.

Conclusions

This analysis confirms that median nerve ADC values are generally increased in individuals with CTS compared to controls and providing separate ADC cut-off values for the pisiform and hamate regions will improve diagnostic reliability. Standardization of DTI methodology and specifically utilizing a wrist coil will allow for more comparable studies on ADC values in the future.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

This article does not include any individuals to have an informed consent.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors A.G.E. and T.K. have declared multiple affiliations. The other authors declare that there is no conflict of interest.

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