SEMMELWEIS EGYETEM
DOKTORI ISKOLA

Ph.D. értekezések

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HERGÁR LUCA

A támasztó és mozgató szervrendszer működésének fiziológiája
című program

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TRANSLATIONAL KEY POINTS BETWEEN RADIOLOGY, PHYSICAL EXAMINATION AND HAND SURGERY

Ph.D. Thesis

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“A goal without a plan is just a wish.”

Antoine de Saint-Exupéry

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1. LIST OF ABBREVATIONS

1.5T	1.5 Tesla
2 PD	Two-point discrimination
3D	Three dimensional
3T	3 Tesla
ASSH	American Society for Surgery of the Hand
AUC	Area Under the Curve
CI	Confidence Interval
CSA	Cross sectional area
CTS	Carpal Tunnel Syndrome
DASH	Disabilities of the Arm, Shoulder and Hand
EMG	Electromyography
ENG	Electroneurography
FN	False negative
FP	False positive
FSE	Fast spin echo
FSS	Functional status scale
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
LR+	Positive likelihood ratio
LR-	Negative likelihood ratio
LT	Lunotriquetral
mm	millimetre
MRI	Magnetic Resonance Imaging
NPV	Negative predictive value
PD	Proton density

PERSiST	Prisma in Exercise, Rehabilitation, Sport medicine and SporTs science
PICO	Population, Intervention, Comparison, Outcomes
PPV	Positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies
ROC	Receiver operating characteristic
SD	Standard Deviation
se	Sensitivity
SNR	Signal-to-noise ratio
SL	Scapholunate
sp	Specificity
SSS	Symptom severity scale
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TFCC	Triangular Fibrocartilage Complex
TN	True negative
TP	True positive
UT	Ulnotriquetral

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to improve diagnostic efficiency in hand surgery by enhancing the accuracy of assessments at the initial patient encounter. My mission is to assess the reliability of imaging techniques and physical examination in hand surgery. My specific goals are to evaluate the diagnostic accuracy of wrist MRI and the clinical application of two-point discrimination measurement.

2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	15.7
Av IF/publication:	2.62
Ranking (SCImago):	D1: 2, Q1: 2, Q2: 1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.4
Av IF/publication:	3.7
Ranking (Sci Mago):	D1: 1, Q1: 1
Number of citations on Google Scholar:	5
Number of citations on MTMT (independent):	3
H-index:	1

The detailed bibliography of the student can be found on pages 73.-74.

2.3. Future plans

My future plans include exploring the difference between the rate of incidental findings of 1.5 T and 3 T MRI for wrist pathologies, and to find out in which cases is it strongly advised to aim for higher field strength imaging. I would also like to investigate the hand function and presence of sarcopenia in elderly patients and to work on preventive guidelines. These efforts align with my broader goal of investigating meaningful outcome measures in hand surgery to support evidence-based clinical decision-making.

3. SUMMARY OF THE THESIS

Imaging modalities as well as the findings of a physical examination are crucial contributors of the diagnostic process in hand surgery. Though widely applied, the accuracy of these resources, and factors influencing reliability have not yet been completely identified.

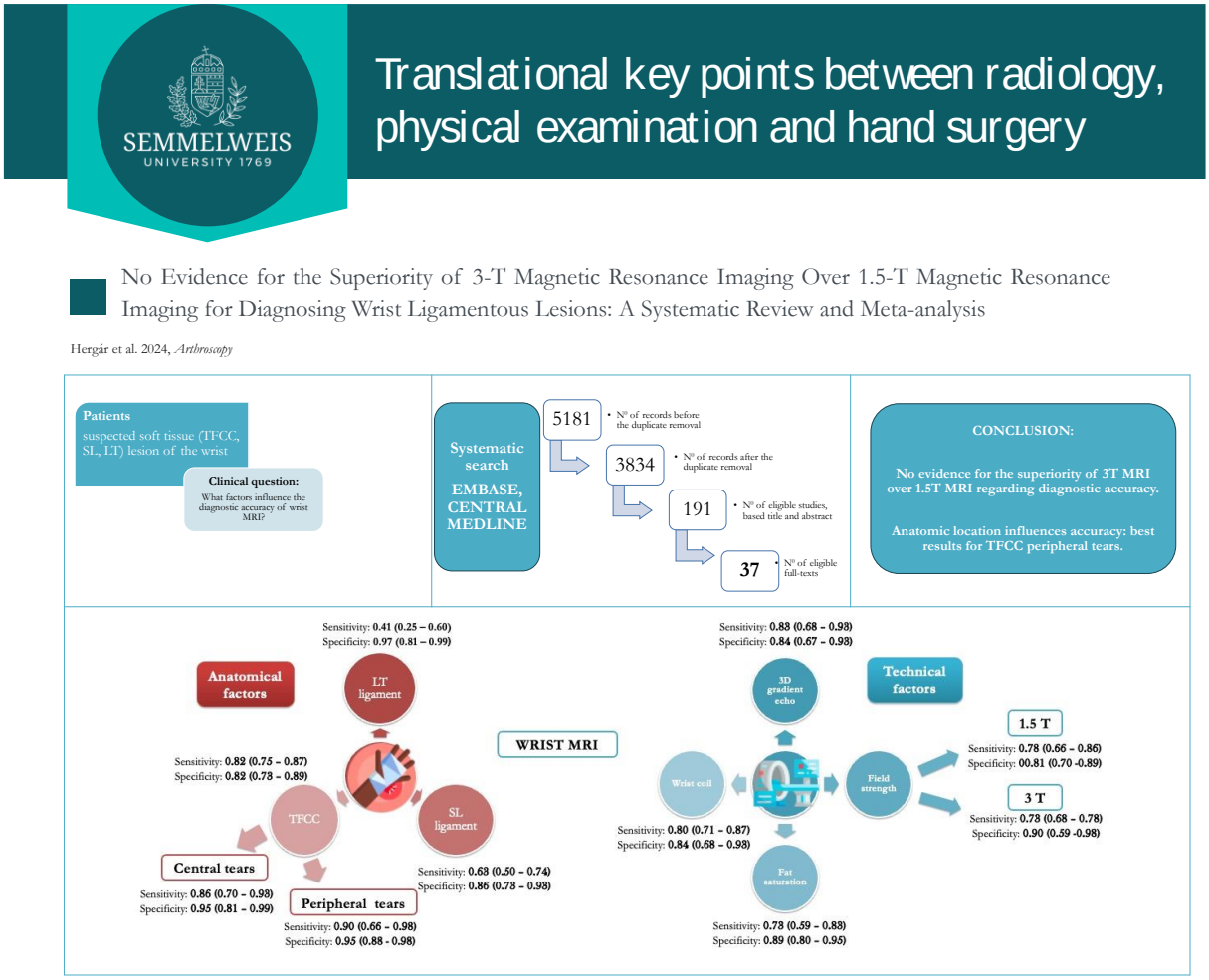
The aim of my research work was twofold. Firstly, to assess the reliability of wrist magnetic resonance imaging (MRI) depending on different technical factors and the anatomic location of the suspected ligamentous injury of the wrist. Secondly, the assessment of the role of two-point discrimination (2PD) measurement in the diagnosis of carpal tunnel syndrome (CTS) severity. The studies aimed to enhance clinical decision-making process and to present both the potential and the limits of MRI and two-point discrimination measurement.

A systematic review and meta-analysis was conducted to assess the sensitivity and specificity of wrist MRI for suspected ligamentous lesions. Prospective and retrospective cohort studies, case-control and cross-sectional studies reporting about adult patients who underwent MRI and wrist arthroscopy were included to the analysis. Contrary to expectations, our results showed no significant difference between the accuracy of 1.5 T and 3 T MRI. Observed tendencies did suggest however, the potential superiority of 3T MRI in the diagnosis of scapholunate (SL) ligamentous injury, even if final results were inconclusive. Differences in accuracy based on anatomic location proved that most accurate results can be expected for central and peripheral tears of the triangular fibrocartilage complex (TFCC).

To assess the relationship between 2PD measurements and the severity of CTS, a cross-sectional study was conducted including 81 patients who were operated for CTS. Patient characteristics, results of CTS questionnaires, findings of electrophysiological studies and if available, results of peripheral nerve ultrasound examination were assessed. Correlation between these variables and 2PD values were calculated. Predefined electrophysiological severity categories had a significant positive correlation with 2PD values, determining a 9.5 mm cut-off value as the most effective threshold to differentiate between severe and non-severe CTS.

Being informed about the diagnostic capacity of wrist MRI and the potential use of 2PD measurements as a screening method for severe CTS would contribute to hand surgeons' diagnostic assessment, and to the more effective counselling of patients about the expected outcomes and their planned care.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

Wrist ligamentous injuries and carpal tunnel syndrome are common pathologies in hand surgery. The focus of this research is finding key points in the diagnostic process of these conditions, where efficacy could be improved.

5.1.2. What is the problem to solve?

Diagnostic accuracy of wrist MRI is spread on a large scale. Some studies reported a sensitivity of 60% for TFCC injuries (1), while others estimated accuracy up to 98.3% (2). The reason behind these differences remained unsolved thus far. Currently, the gold standard diagnostic method for ligamentous injuries is wrist arthroscopy (3). However, the invasiveness and the 1.2% – 7.94% complication rate (4) of this method, as well as its limited availability justify the demand for precise non-invasive imaging for these lesions.

Carpal tunnel syndrome occurs at 10% of the patients presenting at a hand surgeon's clinic (5). The large number of patients calls for an objective screening method, to distinguish between severe and non-severe cases.

5.1.3. What is the importance of the topic?

Effective diagnosis of these conditions is of great importance for physicians and patients alike.

For wrist ligamentous injuries, beside the findings of the physical examination, the result of the MRI is also a potential indicator for surgery. Accurate imaging can prevent unnecessary interventions and help both patients and physicians to prepare for the surgery and the recovery period, manage expectations and treatment planning (6).

Following carpal tunnel release, the recovery of the median nerve is correlated to the severity of the disease (7). An objective screening method for severe carpal tunnel syndrome can accelerate the diagnosis and surgical treatment of the selected patients, contributing to better long-term results.

5.1.4. What would be the impact of our research results?

Adequate information about the limits of wrist MRI, both in regard of technical conditions and the anatomic location of the suspected injury, would contribute to a more cautious diagnostic approach, and awareness of the potential error-rate of this imaging modality.

The application of 2PD measurement as a screening method during physical examination would form and objective basis to advance the necessary preoperative examinations and the date of the planned surgery for patients with potentially severe CTS, to reduce the chance of irreversible changes.

5.2. Ligamentous injuries of the wrist

Traumatic injuries of the TFCC are associated to wrist compression in ulnar deviated position (8) and might occur in 34 - 84% of distal radius fractures (9, 10). The leading symptom of TFCC lesions is ulnar sided wrist pain, limited axial loadbearing, as well as painful pronation and supination of the wrist (11). If initial conservative treatment proves to be ineffective after 2 – 6 months (12) or in case of unambiguous distal radioulnar joint instability (13), surgical therapy is indicated. According to the study by Park et al. (14), 43% of patients needed arthroscopic intervention following failed conservative treatment.

Scapholunate (SL) and lunotriquetral (LT) ligaments play a crucial role in maintaining the alignment of the proximal carpal bones, as intrinsic stabilizers of the wrist joint (15). In case of partial tears and mild symptoms, initial treatment of these injuries is also conservative (16), while for young and active patients with higher grade SL ligament injury, surgical repair is often advised (17). Delayed diagnosis and treatment of these injuries lead to progressive carpal instability, chronic wrist pain and early arthritic changes (18), therefore timely, accurate diagnosis has pivotal importance.

Numerous treatment options are available for wrist ligamentous injuries (13, 19), varying in invasiveness, operation time, complication rate, length of immobilizations and time needed for recovery. Considering the complexity of decision making, our study our research aimed to contribute to the precise and reliable preoperative diagnosis of these injuries.

5.3. MRI imaging for the wrist

Technical improvement of MRI has been accelerating in the past two decades. Higher field strength, application of wrist coils, 3D gradient echo sequences and fat saturation were some of the recent advances. Increased field strength contributes to higher resolution of the examined structures, enabling the detection of more subtle changes of small anatomical structures (20). Fat suppression reduces the signal from the fatty tissue, while ensuring the high intensity of fluids, facilitating the delineation between the two on MRI and the diagnosis of oedema after a ligamentous injury (21). 3D sequences create thin image slices and limit the gap between them, permitting improved spatial resolution, and the decrease of noise and artifacts (22). Wrist coils also contribute to adequate spatial resolution, as their application reduces the signal-to-noise ratio (21). The question arises, do these advances make a quantifiable difference in the diagnostic accuracy of wrist ligamentous injuries? Is there an optimal MRI setting to achieve the best results?

5.4. Carpal tunnel syndrome

Carpal tunnel syndrome is the most common peripheral neuropathy, arising from the compression of the median nerve (23). The prevalence of the disease is 1-5% in the general population (24, 25), predominantly occurring in middle-aged and elderly, female patients (26, 27). Symptoms consist of pain, especially during night, tingling and loss of hand function. Diagnosis is established based on patient history, physical examination and the results of electrophysiological studies, containing electromyography (EMG) and electroneurography (ENG) (28). Conservative measures, such as activity modification, nighttime splinting, analgesic medication or glucocorticoid injection might reduce symptoms for patient with mild symptoms, while for patients with a severe, long-standing disease, surgical release is recommended. (7).

5.5. Two-point discrimination

Two-point discrimination measurement is a quantitative tool to assess the sensory function of the nerves (29). Depending on the anatomic location, the density of sensory receptors differs in the skin. Two-point discrimination is the smallest distance between two points that we are able to distinguish as separates (30). Hands and fingers are one of

the most sensitive areas of the human body, where normal two-point discrimination values vary between 2-6 mm (31, 32). Several studies have proved the utility of 2PD measurements in the diagnosis of CTS (33-35), however most of them concentrated on establishing a threshold to diagnose the disease. The large number of affected patients indicate an objective, easily applicable screening method for the severity of CTS. According to our hypothesis, 2PD measurement has the capacity to act as a screening modality in orienting physicians regarding the severity of the disease.

6. OBJECTIVES

6.1. Study I. – Investigating the diagnostic accuracy of MRI for wrist ligamentous lesions

The aim of our study was to determine the diagnostic accuracy of native MRI for ligamentous lesions of the wrist, such as TFCC, SL and LT ligament injuries and to analyse the underlying influence of technical characteristics, namely field strength, application of fat saturation, 3D sequences, and wrist coils.

6.2. Study II. – Assessing the role of two-point discrimination measurements as a screening method for severe CTS

The objective of our second study was to find out whether 2PD measurement could be used as a screening method to assess the severity of carpal tunnel syndrome.

7. METHODS

7.1. Study I. – Investigating the diagnostic accuracy of MRI for wrist ligamentous lesions

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (36). It also followed the Prisma in Exercise, Rehabilitation, Sport medicine and SporTs science (PERSiST) (37) guidelines.

Before completing the systematic search, our study was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database (registration number: CRD42021282031). The only deviation from the protocol, beside the final title, was that the experience of the radiologist and hand surgeon could not be assessed, as in most studies it was not mentioned, and we lacked sufficient data for a subgroup analysis.

7.1.1. Literature search and eligibility criteria

The systematic search was executed on the 22nd of October 2022 and was updated on the 12th of February 2024, using MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials databases. We have used the following search key for all three databases: ((TFCC OR SL OR LT OR "triangular fibrocartilage complex" OR scapholuna* OR lunotriquetr* OR ligament* OR cartilag*) AND (hand OR wrist OR radiocarpal OR radioulnar) AND (MRI OR "magnetic resonance imaging")). Filters or any kind of restrictions were not applied. The reference list of all eligible articles and citing articles were screened through Google Scholar search engine to capture all possibly relevant studies.

7.1.2. Study selection and data extraction

Our review included prospective and retrospective observational studies and experimental studies. Non-peer-reviewed literature and publications with different study design were excluded.

Eligibility criteria were set up according to the predetermined Population, Intervention, Comparison, Outcomes (PICO) framework. We have included studies reporting about the diagnostic accuracy of wrist MRI compared to arthroscopy for ligamentous injury of the wrist in adults. Both MRI (I) and wrist arthroscopy (C) needed to be carried out. The sensitivity and specificity (O) of MRI was determined based on the results of the

arthroscopy, what we have considered gold standard. Studies presenting patients with suspected TCC, SL, LT or ulnotriquetral (UT) ligament injuries were eligible. Exclusion criteria were the use of intravenous contrast material or arthrography, the inclusion of skeletally immature patients, cadaver and animal studies.

All articles corresponding the eligibility criteria were included, regardless the date and language of the publication.

The selection process was completed by two independent authors. Studies were selected first by title and abstract, the based on the full text of the articles. Cohen's Kappa coefficients were calculated to assess interrater reliability. Disagreements were resolved by a third independent author.

The following data were extracted from each eligible publication: name of the first author, year of publication, information about study design and population, inclusion and exclusion criteria, MRI settings (e.g., field strength, the use of fat saturation, application of wrist coils or 3D sequences, slice thickness and gap), experience of the radiologist and of the hand surgeon, information regarding potential risk of bias, and outcomes. Main outcomes were sensitivity and specificity of the MRI compared to arthroscopy. When available, positive and negative predictive values, diagnostic accuracy, and the number of true positive, true negative, false positive and false negative patients were also extracted. Outcomes were extracted based on anatomic location of the suspected injury (TFCC – not specified, central or peripheral location, SL ligament, LT ligament, UT ligament). The unit of measurements was the ligament tear, meaning that if a patient had two or more different injuries, these were calculated as separate outcomes. The study did not distinguish between partial and full thickness tears, both types of injury were counted as ligament tears.

7.1.3. Quality assessment

Risk of bias and applicability of the included articles was assessed by two independent author with the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) assessment tool (38). Disagreements were resolved by the senior author.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence for each of our outcomes.

7.1.4. Data synthesis and analysis

Primary data collection was carried out using a predefined data collection sheet in Microsoft Excel (Microsoft, Redmond, WA). True positive, true negative, false positive and false negative values were whether directly extracted from the articles or calculated from the available data.

Publications with inconsistent results were excluded from the analysis.

When two or more experts evaluated the MRI images, the results reported by the more experienced one was included to the main analysis. When there was no difference in the experience between radiologists, the evaluation performed by one of them was chosen randomly, by selecting the number of the expert from a closed envelope.

Subgroup analyses were performed according to different technical settings of the MRI and anatomic location of the ligamentous injury. These technical settings were field strengths (low field (<1.5 T), 1.5 T, or 3 T), the use of wrist coils, fat saturation and 3D sequences. The subgroups created by anatomic location were for TFCC, SL ligament and LT ligament injuries. For TFCC lesions, if the reported data allowed it, sensitivity and specificity was calculated separately for central and peripheral tears, as well as the overall sensitivity and specificity.

To compare the effect of the experience for the radiologists, additional analysis was conducted where the results reported by the less experienced radiologist were included. Two additional aspects were also considered to perform comparative subgroup analyses. One of these was the exclusion of the evaluations of radiologists who were not blinded to the results of the physical examination, and the other was the exclusion of studies where not all patients underwent arthroscopy, introducing potential bias. Combining these possibilities, five additional analyses were conducted.

Statistical analysis was carried out in R (39).

A joint analysis of specificity (sp) and sensitivity (se) was performed using the bivariate model of Reitsma et al (40) and Chu and Cole (41), respecting their independency. Receiver operating characteristic (ROC) plots were created based on the online tool described by Freeman et al. (42). The plots show the study level sensitivity and specificity values, and the corresponding 95% prediction region. The summary estimate of specificity and sensitivity yielded by the fitted bivariate model and the corresponding confidence region were also represented. Study-level values in this plot are represented

by ellipses. The lengths of the axis reflects the weights calculated according to Burke et al. (43).

The sensitivity and specificity of included studies with their 95% confidence intervals were displayed on coupled forest plots. The summary estimate was calculated using the bivariate model. To assess the significance of difference regarding the sensitivity and specificity of the different subgroups, two-tailed z tests were carried.

Positive and negative predictive values (PPV and NPV), as well as positive and negative likelihood ratios (LR+ and LR−), were calculated using the pooled sensitivity, specificity, their standard errors, and the correlation coefficient between them. To reflect the uncertainty and correlation between these parameters, we used the variance–covariance matrix of the model to generate 10,000 simulated pairs of logit-transformed sensitivity and specificity via Cholesky decomposition. These simulated values were back-transformed to the probability scale and used to calculate LR+ and LR−. PPV and NPV were subsequently computed using each simulated sensitivity–specificity pair in combination with the fixed median prevalence across studies, as predictive values depend on disease prevalence. The median prevalence was calculated for all studies and for each subgroup. The resulting distributions of LR+, LR−, PPV, and NPV were summarized by reporting the mean and 95% confidence intervals. Results were evaluated according to the article of Denegar and Cordova (44).

Heterogeneity of included studies was assessed visually based on the area of the aforementioned prediction region and on the coupled forest plot as recommended by Lee et al. (45). If a subgroup consisted of at least 10 studies, publication bias was assessed according to the methods of Deeks et al. (46). The analysis corresponds to the advice of Harrer et al. (47).

7.2. Study II. – Assessing the severity of carpal tunnel syndrome by measuring two-point discrimination

7.2.1. Study design

This study is a post-hoc cross sectional analysis of prospectively collected data on patients presenting with CTS. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (48).

7.2.2. Setting

Data collection was organized between September 2015 and June 2019 at the Department of Orthopaedics at Semmelweis University. Eligible patients were re-examined on the day of their surgery, and the results of the physical examination were recorded alongside the findings of preoperative auxiliary examinations, including the results of electrophysiological assessments.

7.2.3. Ethics and patient consent

Our study was approved by the Hungarian Scientific and Research Ethics Committee of the Medical Research Council (30/2023). Patients who were treated at our institute consented the use of their clinical data for research purposes at the beginning of their care. Personal patient data were anonymized; individual patients cannot be recognized in this study. Research was conducted in accordance with the Helsinki Declaration.

7.2.4. Participants

Adult patients who underwent nerve release surgery for CTS at the Department of Orthopaedics at Semmelweis University were included in this study. Those who did not undergo electrophysiological (EMG-ENG) or nerve ultrasound examination preoperatively and did not undergo detailed physical examination with 2PD measurements were excluded. Patients under 18 years old were also excluded.

7.2.5. Variables and data sources

Collected data consisted of detailed patient history focusing on the duration and quality of symptoms, such as numbness or paraesthesia of fingers and pain. For duration of the symptoms, we distinguished three categories: symptoms started maximum 6 months ago, between 6 and 12 months ago and over 12 months ago. During physical examination positivity of Tinel- and Phalen-signs (49) were recorded, as well as the presence of thenar muscle atrophy. Motor function of the hand was assessed by measuring grip strength and the strength of key pinch. Sensory function was evaluated by examining the hand for hypesthesia and by measuring 2PD.

For 2PD measurements, we have used the validated Two-Point Discriminator (Baseline®) tool. Measurements were carried out for a uniform and standardized way for all patients. In the beginning of the examination, the measurement procedure was demonstrated for patients by pressing one and then two points (10 mm apart from each other) on one of

their fingers under their visual control. Afterwards we have asked patients to close their eyes and state if they have felt one or two pressing points on the examined side of the finger. Distance between points were increased by 1 mm at a time from 2 mm until the patient was able to distinguish the two points based on tactile stimulus or until we have reached the measuring maximum of the device at 15 mm. Examination was performed once for each digital nerve, on the volar, lateral side of the fingertips. Severity categories of 2PD values were also recorded. Based on the classification of the American Society for Surgery of the Hand (32) 2PD was considered normal below 6 mm, elongated between 6-11 mm and pathological over 11 mm.

Results of the ENG, such as the conduction velocity of the sensory fibres, amplitude and distal sensory latency and the severity of the disease according to the evaluating neurologist were also recorded. There were six possible evaluation categories: very mild, mild, moderate, medium, severe and very severe. Severity was also classified according to the categories described by El Miedany et al. (50), where mild, moderate and severe categories were distinguished. As there is no severity classification of individual variables (conduction velocity, amplitude and distal sensory latency) of the ENG, categories were defined as normal and pathological for these variables.

If patients underwent peripheral nerve ultrasound, cross sectional area (CSA) of the median nerve at the entrance of the carpal tunnel and severity of the disease according to the examinator were noted. CSA was considered abnormal above the 10 mm^2 cut-off value (51, 52).

Patient complaints and preoperative functional status were assessed by the Hungarian version of the DASH (Disabilities of the Arm, Shoulder and Hand) questionnaire (53) and the Boston CTS questionnaires (54).

7.2.6. Bias and evidence synthesis

Despite the prospective design of our study, the use of validated tools and standardized questionnaires during the examination, potential bias might have arisen during patient selection, as only patients who were scheduled for operation were included, limiting the number of patients with mild disease severity. The standardized protocol for physical examination was designed to reduce potential measurement bias, however as the 2PD

measurement was performed only one time and the evaluator was aware of patients' history and complaints, it could not be eliminated completely.

Evidence synthesis was based on descriptive and inferential statistics. 2PD values and severity categories were correlated to the findings of the ENG and the nerve ultrasound, as well as the results of patient questionnaires and demographic parameters. Data imputation was not performed; only available data was used for the analysis for each variable.

7.2.7. Statistical methods

Statistical analysis was carried out using R (39).

Descriptive analysis was performed for each variable. Ratios were calculated for categoric outcomes, while mean and median values together with standard deviation (SD) and interquartile range (IQR) were determined for continuous variables.

Normal distribution of 2PD values was checked using Shapiro-Wilk tests. Although the values did not follow normal distribution, our sample with over 80 observations was considered robust to the absence of normal distribution, according to the Central Limit Theorem (55). Paired Student's t-tests were conducted to assess the difference in 2PD according to different digital nerves.

Relationship between 2PD and the results of ENG, of nerve ultrasound, age and sex of patients, the duration of their symptoms and the results of patient questionnaires was examined using Pearson correlation. The level of significance was 0.05. Pearson correlation coefficients and their confidence intervals were displayed on "CI Thermometer" plots (56).

Diagnostic efficacy, sensitivity, specificity, diagnostic odds ratio and positive and negative likelihood ratios were calculated at different 2PD thresholds for severe CTS. A ROC plot was constructed to show the relation between sensitivity and specificity. Confidence band was calculated using the {pCOR} R package, version 1.18.0 (57). The Area Under the Curve (AUC) was determined using the DeLong method (58).

8. RESULTS

8.1. Study I: Investigating the diagnostic accuracy of MRI for wrist ligamentous lesions

8.1.1. Study selection

The systematic search captured 5 181 articles, 1 665 articles from the MEDLINE, 91 from the Cochrane Central Register of Controlled Trials, and 3 425 from the Embase databases. The Cohen's Kappa coefficient for the two authors was 0.66 for the title and abstract selection and 0.71 for the full-text selection. Following the selection protocol, 36 articles were found eligible for inclusion to our study. Studies were mostly excluded due to differences in PICO, or in the execution of the diagnostic process (e.g., the use of contrast material during MRI, or no surgical verification of the diagnosis). Another important reason for exclusion was the lack of appropriate data or inconsistency in the reported numbers. Cross-checking the reference list of the selected articles, we have found one additional eligible article that was not among the results of the systematic search, leading to 37 articles (2, 59-93) that were included to the analysis. The summary of the selection process is shown on the PRISMA flowchart (Fig. 1).

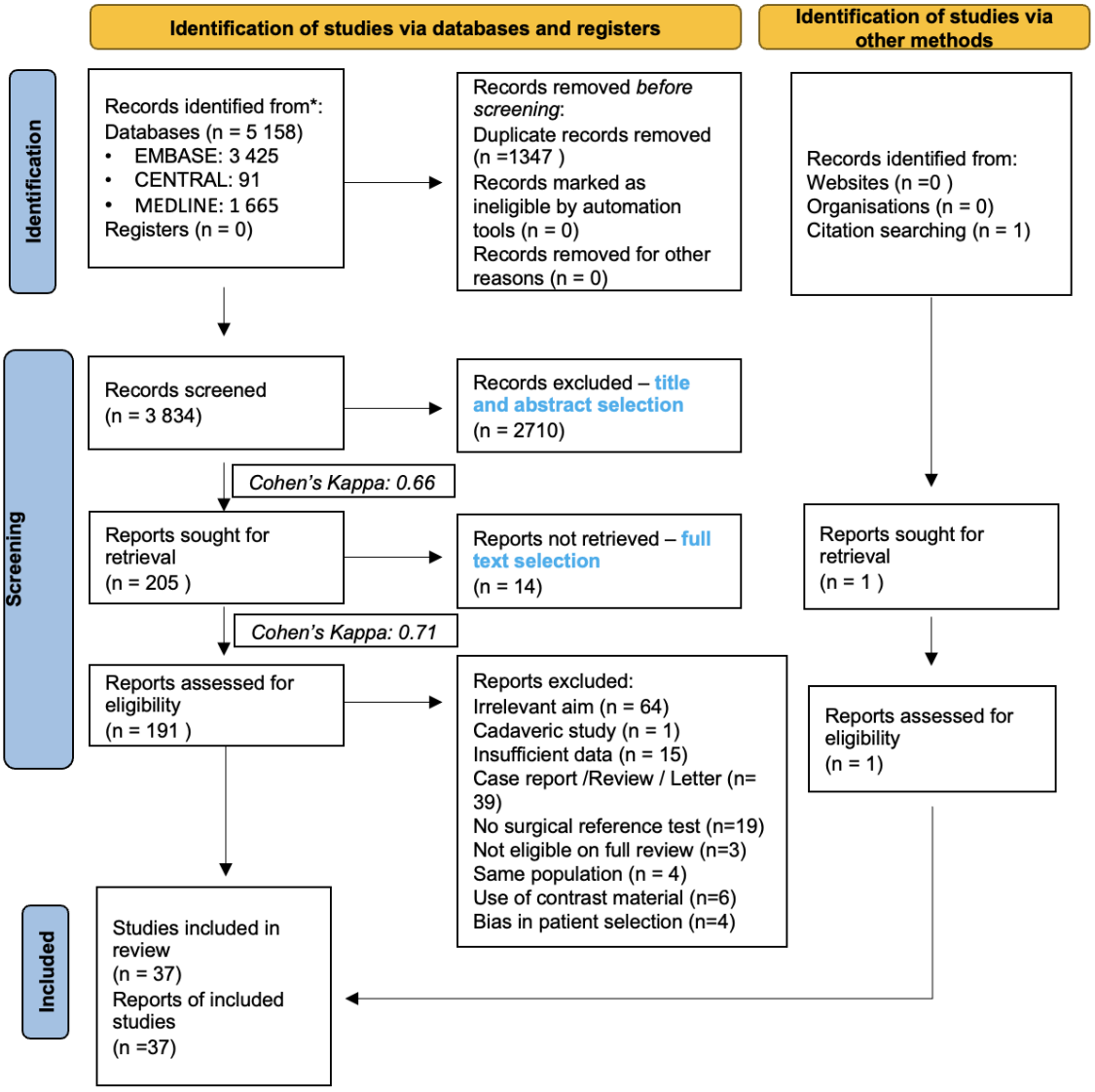


Figure 1. *PRISMA 2020 flowchart representing the study selection process. Cohen's Kappa values show the interrater agreement between co-investigators during title and abstract and full text selection. (94)*

8.1.2. Study characteristics

Characteristics of the included studies are shown in Table 1. Of the 37 eligible studies, 18 were prospective and 19 were retrospective cohort studies. Thirty studies reported about TFCC examination, 24 on SL ligament and 14 on LT ligament imaging. UT ligament injury was examined in only one of the included studies, therefore separate analysis for these types of lesions was not possible.

Table 1. Characteristics of included studies. (94)

Author	Year	Country	Study design	No. of patients	Age (mean)	Examined condition	Sensitivity	Specificity	TP	TN	FP	FN	Radiologist blinded	Hand surgeon blinded	Field strength	3D sequence	Fat suppression	wrist coil	LOE
Abdelsattar (60)	2012	Egypt	prospective clinical trial	44	38	TFCC	0.89	1.00	31	9	0	4	?	?	1.5	no	no	no	III
Anderson (61)	2008	USA	retrospective study	102	32	TFCC, SL, LT, UT	0.90	0.91	45	42	4	5	?	?	1.5 / 3	no	yes	no	II
Boer (62)	2018	Netherlands	retrospective study	120	38	TFCC	0.73	0.69	57	29	13	21	?	?	1.5 / 3	no	no	yes	II
Brennan (63)	2021	UK	retrospective study	79	?	TFCC (ce)	0.57	0.79	26	26	7	20	?	?	1.5	no	yes	no	II
Daunt (2)	2021	Australia	retrospective study	89	?	TFCC (ce/pe), SL, LT	0.90	0.80	112	78	19	13	?	?	1.5 / 3	yes	yes	yes	II
De Santis (64)	2021	Italy	retrospective study	146	38	TFCC, SL, LT	0.53	0.49	59	17	18	52	yes	?	1.5	no	no	no	II
De Smet (65)	2005	Belgium	retrospective study	35	33	TFCC	0.61	0.88	11	15	2	7	yes	?	?	no	no	no	III
Gabl (66)	1996	Austria	prospective clinical trial	32	27	TFCC (ce)	0.97	1.00	31	32	0	1	yes	?	?	no	no	no	II
Greditzer (67)	2016	USA	retrospective study	26	38	SL	0.82	0.47	9	7	8	2	?	?	1.5	yes	yes	yes	II
Haims (59)	2003	USA	retrospective study	45	38.5	TFCC (ce), SL, LT	0.43	0.95	15	95	5	20	?	?	1.5	yes	yes	yes	II
Johnstone (68)	1997	UK	prospective clinical trial	43	30	TFCC, SL, LT	0.56	0.92	19	87	8	15	yes	?	0.5	no	no	no	III
Kaddah (69)	2016	Egypt	prospective clinical trial	57	34.3	TFCC (ce/pe), SL, LT	0.68	1.00	46	40	0	22	yes	no	?	no	no	yes	III
Kader (70)	2022	UK	retrospective study	61	37.9	SL	0.19	0.914	5	32	3	21	yes	?	?	?	?	?	III

Kamal (71)	2014	Egypt	prospective clinical trial	51	38	SL, LT	0.32	0.94	12	47	3	26	yes	?	1.5	yes	yes	no	III
Kato (72)	2000	Japan	retrospective study	33	35	TFCC	1.00	0.33	18	5	10	0	yes	?	1.5	no	no	no	II
Katschnig (73)	2006	Austria	retrospective study	58	40	TFCC, SL	0.76	0.00	32	0	3	10	yes	?	1	no	no	no	II
Kovanlikaya (74)	1997	Turkey	prospective clinical trial	25	?	TFCC, SL, LT	0.78	0.87	29	33	5	8	yes	?	1	yes	no	no	III
Lee (95)	2013	Republic of Korea	retrospective clinical trial	48	34,2	TFCC (ce/pe), SL, LT	0.66	1.00	56	107	0	29	yes	?	3	yes	yes	yes	II
Morley (75)	2001	UK	prospective clinical trial	54	31	TFCC, SL	0.38	0.92	18	55	5	30	yes	yes	1.5	no	no	no	II
Nevalainen (76)	2023	USA	retrospective case-control study	133	44	TFCC (pe)	0.91	0.93	48	74	6	5	yes	no	1.5	no	yes	yes	II
Ochman (77)	2017	Germany	retrospective study	18	34,8	TFCC, SL	0.80	0.73	8	19	7	2	yes	yes	3	no	yes	yes	III
Oneson (78)	1997	USA	prospective clinical trial	56	35	TFCC (ce/pe)	0.75	0.95	9	148	8	3	yes	?	1.5	no	no	no	III
Potter (79)	1997	USA	prospective clinical trial	77	35.7	TFCC (ce/pe), SL, LT	0.94	0.97	74	84	3	5	yes	?	1.5	no	no	yes	II
Prosser (80)	2011	Australia	cross-sectional study	105	37	TFCC, SL, LT	0.65	0.91	39	96	9	21	yes	no	?	no	yes	no	III
Ruston (81)	2013	UK	retrospective study	66	35	TFCC, SL, LT	0.47	0.94	23	61	4	26	yes	?	?	?	?	?	III
Schädel-Höpfner (82)	2001	Germany	prospective clinical trial	103	?	SL	0.64	0.85	21	33	6	12	yes	?	1	no	no	no	III
Scheck (83)	1997	Germany	prospective clinical trial	41	34	SL	0.52	0.34	15	32	62	14	yes	?	1.5	no	no	yes	II

Scheck (84)	1999	Germany	prospective clinical trial	35	34.7	TFCC, SL, LT	0.85	0.56	22	19	15	4	yes	?	1.5	yes	no	yes	III
Shionova (85)	1998	Japan	retrospective study	102	32	TFCC	0.73	0.72	30	44	17	11	yes	?	1.5	no	no	no	II
Spaans (86)	2013	Netherlands	retrospective study	37	?	SL	0.70	1.00	26	1	0	11	?	?	3	no	no	yes	II
Spies (87)	2022	Germany	retrospective study	689	43.1	TFCC	0.77	0.44	322	120	150	97	yes	?	?	?	?	?	II
Stouracova (88)	2016	Czech Republic	prospective clinical trial	47	30.7	SL	1.00	0.67	14	4	2	0	yes	?	1.5	yes	no	yes	III
Tanaka (89)	2006	Japan	prospective clinical trial	11	31	TFCC	1.00	1.00	10	1	0	0	yes	?	1.5	no	yes	yes	III
Thomsen (90)	2018	Sweden	retrospective study	51	38.3	TFCC, SL	0.76	0.53	45	25	22	14	yes	no	3	no	no	yes	II
Totterman (91)	1996	USA	prospective clinical trial	31	42	TFCC	0.92	0.83	12	15	3	1	yes	?	1.5	yes	no	yes	II
Valeri (92)	1999	Italy	prospective clinical trial	35	35	TFCC, SL, LT	0.63	0.25	12	7	21	7	yes	?	1	no	no	no	III
Zlatkin (93)	1989	USA	prospective clinical trial	43	?	TFCC	0.95	0.00	19	0	1	1	yes	?	1.5	no	no	no	II

Abbreviations: ?: not data, ce: central tear, FN: false negative, FP: false positive, LOE: level of evidence, pe: peripheral tear, LT: lunotriquetral ligament, SL: scapholunate ligament, TFCC: triangular fibrocartilage complex, TN: true negative, TP: true positive, UT: ulnotriquetral

8.1.3. Risk of bias and applicability

The results of risk of bias and applicability assessment are displayed on Figure 2. We detected high risk of selection bias in 11 studies, high risk of bias related to the index test in one study, related to the reference standard in one study and in 14 cases, related to the flow and timing of the study. This consisted mostly of partial verification bias and disease progression bias, as in some studies not all originally included patients underwent arthroscopy, and in some cases more than 6 months have passed between MRI and wrist arthroscopy. In some studies hand surgeons were aware of the results of the MRI before performing the operation, potentially introducing diagnostic review bias.

We have considered that the seven studies (60, 71, 78, 84, 88, 92, 93) where not all patients underwent arthroscopy might have an important influence on the overall outcomes, therefore we have performed a subgroup analysis without the inclusion of these articles. In three studies (2, 77, 93) radiologists were aware of the clinical findings when evaluating the MRI. A separate subgroup analysis was performed with the exclusion of these studies to reduce diagnostic review bias.

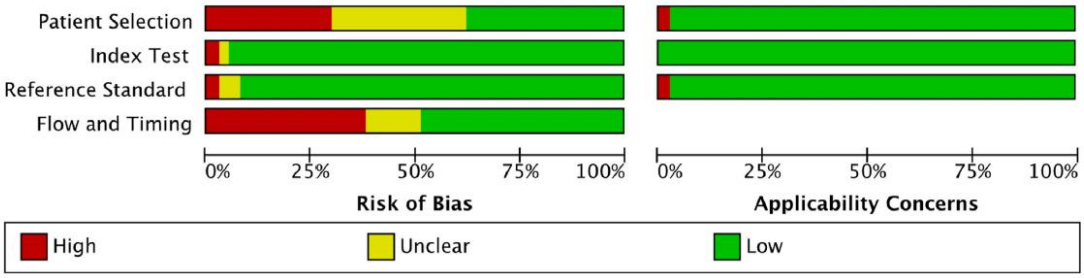


Figure 2. *Risk of bias and applicability concerns graph of the included studies. Review of authors' judgments about each domain presented as percentages across included studies. (94)*

8.1.4. Heterogeneity and publication bias

The studies displayed heterogeneity in terms of study design, technical conditions of the MRI and classification systems used to describe ligamentous injuries.

Based on the funnel plots and asymmetry tests, no significant publication bias was detectable.

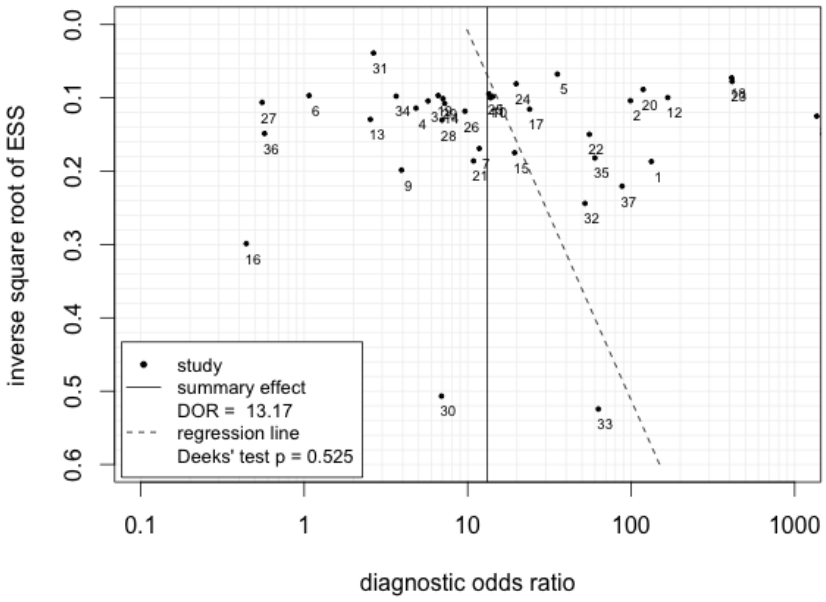


Figure 3. *Funnel plot and asymmetry test of all included studies. Numbers represent studies in alphabetical order. No significant bias was detected (p=0.525).*

8.1.5. Synthesis of results

The main analysis, containing all included studies found that MRI had an overall sensitivity of 0.74 (0.66 – 0.80) and an overall specificity of 0.84 (0.75 – 0.90) for diagnosing wrist ligamentous injuries. (Figure 4.)

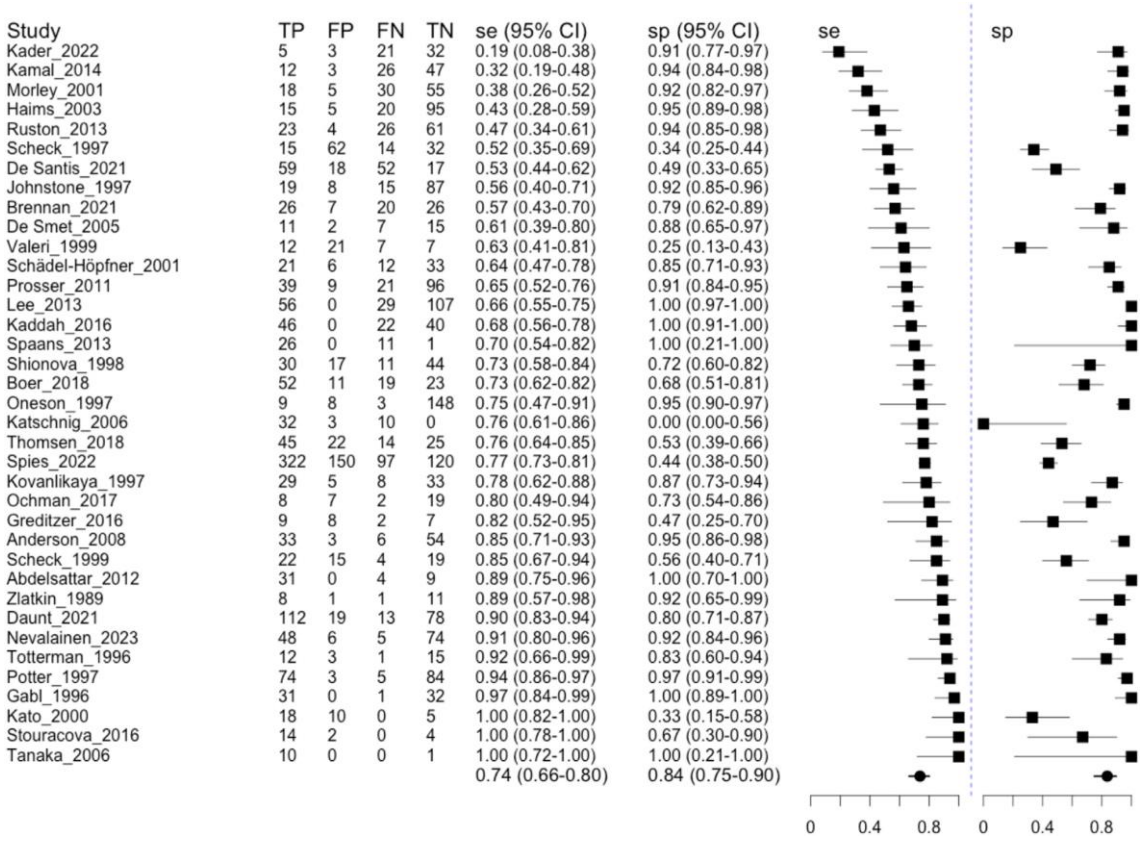


Figure 4. *Forest plot representing the overall sensitivity and specificity of magnetic resonance imaging of the wrist for ligamentous lesions (triangular fibrocartilage complex, scapholunate ligament, and the lunotriquetral ligament).*

Abbreviations: CI: confidence interval, FN: false negative, FP: false positive, se: sensitivity, sp: specificity, TN: true negative, TP: true positive. (94)

Sensitivity and specificity values were also determined for different subgroups based on technical conditions of the MRI and anatomic location of the suspected injury. The pooled values can be found in Table 2.

Table 2. Sensitivity and specificity of MRI based on different technical aspects and types of ligamentous injury of the wrist.

		Sensitivity	Specificity
ALL (3T)*		0.74 (0.66 – 0.80)	0.84 (0.75 – 0.90)
Field strength	Low field (< 1.5 T)	0.69 (0.60 – 0.76)	0.66 (0.26 – 0.91)
	1.5 T	0.78 (0.66 – 0.86)	0.81 (0.70 -0.89)
	3 T	0.73 (0.68 – 0.78)	0.90 (0.59 -0.98)
Wrist coil	yes	0.80 (0.71 – 0.87)	0.84 (0.68 – 0.93)
	no	0.71 (0.61 – 0.79)	0.84 (0.73 – 0.92)
3D sequence	yes	0.83 (0.68 – 0.93)	0.84 (0.67 – 0.93)
	no	0.73 (0.65 -0.79)	0.84 (0.72 – 0.91)
Fat saturation	yes	0.73 (0.59 – 0.83)	0.89 (0.80 – 0.95)
	no	0.78 (0.69 – 0.84)	0.81 (0.67 – 0.90)
TFCC	ALL	0.82 (0.75 – 0.87)	0.82 (0.73 – 0.89)
	Low field (<1.5 T)	0.83 (0.72 -0.90)	0.67 (0.17 – 0.95)
	1.5 T	0.83 (0.73 - 0.90)	0.81 (0.70 - 0.88)
	3 T	0.74 (0.67 - 0.80)	0.82 (0.50 -0.95)
	Central tear	0.85 (0.70 – 0.93)	0.95 (0.81 – 0.99)
	Peripheral tear	0.90 (0.66 – 0.98)	0.95 (0.88 - 0.98)
SL ligament	ALL	0.63 (0.50 - 0.74)	0.86 (0.73 - 0.93)
	Low field (<1.5 T)	0.63 (0.45 - 0.78)	0.83 (0.30 - 0.98)
	1.5T	0.61 (0.39 – 0.80)	0.82 (0.60 – 0.93)
	3T	0.76 (0.64 – 0.85)	0.97 (0.57 – 1.00)
LT ligament	ALL	0.41 (0.25 – 0.60)	0.93 (0.81 – 0.98)
	Low field (<1.5 T)	0.45 (0.06 - 0.92)	0.77 (0.18 - 0.98)
	1.5T	0.32 (0.13 – 0.60)	0.93 (0.81-0.98)

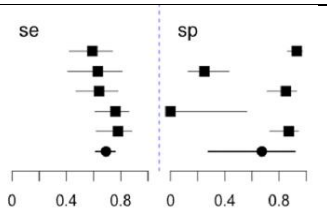
Pooled sensitivity and specificity point estimates, and their 95% confidence intervals are reported in this table.

* If within one study patients were examined with both 1.5T and 3T machines, the results of the 3T MRI were used to calculate overall sensitivity and specificity. (94)

Regarding the field strength of MRI, we found that higher field strength resulted in increased specificity. For low-field, MRI the specificity was 0.66 (0.26-0.91); for 1.5T machines, it was 0.81 (0.70-0.89); and for 3T machines, it was 0.90 (0.59-0.98). Sensitivity values were similar for 1.5T and 3T MRI, 0.78 (0.66-0.86) compared to 0.73 (0.68-0.78). (Figure 5.) The application of wrist coils seemed to increase sensitivity (from 0.71 (0.61 – 0.79) to 0.80 (0.71 – 0.87)), while specificity remained mainly unchanged (Figure 6.). The use of 3D sequences showed a similar tendency, raising sensitivity from 0.73 (0.65 - 0.79) to 0.83 (0.68 – 0.93), while specificity was unaffected (Figure 7.). The use of fat saturation on the other hand was associated with a decreased sensitivity (0.73 (0.59 – 0.83) compared to 0.78 (0.69 – 0.84)), and an increased specificity (0.89 (0.80 – 0.95) compared to 0.81 (0.67 – 0.90)) (Figure 8.). Results of two-tailed z tests showed however, that these differences between subgroups were not significant (Table 3.).

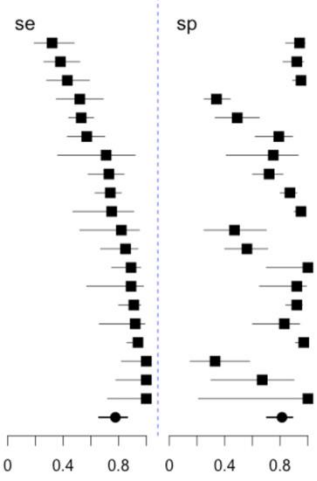
A

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Johnstone_1997	20	7	14	89	0.59 (0.42-0.74)	0.93 (0.86-0.97)
Valeri_1999	12	21	7	7	0.63 (0.41-0.81)	0.25 (0.13-0.43)
Schädel-Höpfner_2001	21	6	12	33	0.64 (0.47-0.78)	0.85 (0.71-0.93)
Katschnig_2006	32	3	10	0	0.76 (0.61-0.86)	0.00 (0.00-0.56)
Kovanlikaya_1997	29	5	8	33	0.78 (0.62-0.88)	0.87 (0.73-0.94)
					0.69 (0.62-0.76)	0.67 (0.28-0.92)



B

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Kamal_2014	12	3	26	47	0.32 (0.19-0.48)	0.94 (0.84-0.98)
Morley_2001	18	5	30	55	0.38 (0.26-0.52)	0.92 (0.82-0.97)
Haims_2003	15	5	20	95	0.43 (0.28-0.59)	0.95 (0.89-0.98)
Scheck_1997	15	62	14	32	0.52 (0.35-0.69)	0.34 (0.25-0.44)
De Santis_2021	59	18	52	17	0.53 (0.44-0.62)	0.49 (0.33-0.65)
Brennan_2021	26	7	20	26	0.57 (0.43-0.70)	0.79 (0.62-0.89)
Boer_2018	5	2	2	6	0.71 (0.36-0.92)	0.75 (0.41-0.93)
Shionova_1998	30	17	11	44	0.73 (0.58-0.84)	0.72 (0.60-0.82)
Anderson_2008	59	17	21	113	0.74 (0.63-0.82)	0.87 (0.80-0.92)
Oneson_1997	9	8	3	148	0.75 (0.47-0.91)	0.95 (0.90-0.97)
Greditzer_2016	9	8	2	7	0.82 (0.52-0.95)	0.47 (0.25-0.70)
Scheck_1999	22	15	4	19	0.85 (0.67-0.94)	0.56 (0.40-0.71)
Abdelsattar_2012	31	0	4	9	0.89 (0.75-0.96)	1.00 (0.70-1.00)
Zlatkin_1989	8	1	1	11	0.89 (0.57-0.98)	0.92 (0.65-0.99)
Nevalainen_2023	48	6	5	74	0.91 (0.80-0.96)	0.92 (0.84-0.96)
Totterman_1996	12	3	1	15	0.92 (0.66-0.99)	0.83 (0.60-0.94)
Potter_1997	74	3	5	84	0.94 (0.86-0.97)	0.97 (0.91-0.99)
Kato_2000	18	10	0	5	1.00 (0.82-1.00)	0.33 (0.15-0.58)
Stouracova_2016	14	2	0	4	1.00 (0.78-1.00)	0.67 (0.30-0.90)
Tanaka_2006	10	0	0	1	1.00 (0.72-1.00)	1.00 (0.21-1.00)
					0.78 (0.66-0.86)	0.81 (0.70-0.89)



C

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Lee_2013	56	0	29	107	0.66 (0.55-0.75)	1.00 (0.97-1.00)
Spaans_2013	26	0	11	1	0.70 (0.54-0.82)	1.00 (0.21-1.00)
Boer_2018	52	11	19	23	0.73 (0.62-0.82)	0.68 (0.51-0.81)
Thomsen_2018	45	22	14	25	0.76 (0.64-0.85)	0.53 (0.39-0.66)
Ochman_2017	8	7	2	19	0.80 (0.49-0.94)	0.73 (0.54-0.86)
Anderson_2008	33	3	6	54	0.85 (0.71-0.93)	0.95 (0.86-0.98)
					0.73 (0.68-0.78)	0.90 (0.59-0.98)

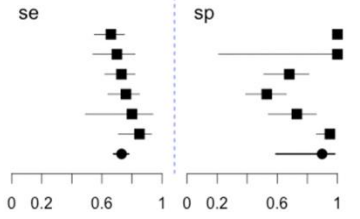
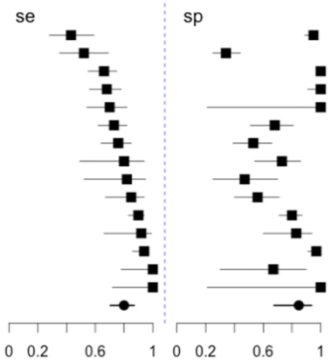


Figure 5. *Forest plot representing sensitivity and specificity of MRI for wrist ligamentous lesions based on field strength. A. Low field (< 1.5T) MRI, B. 1.5T MRI, C. 3T MRI.*

A

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Haims_2003	15	5	20	95	0.43 (0.28-0.59)	0.95 (0.89-0.98)
Scheck_1997	15	62	14	32	0.52 (0.35-0.69)	0.34 (0.25-0.44)
Lee_2013	56	0	29	107	0.66 (0.55-0.75)	1.00 (0.97-1.00)
Kaddah_2016	46	0	22	40	0.68 (0.56-0.78)	1.00 (0.91-1.00)
Spaans_2013	26	0	11	1	0.70 (0.54-0.82)	1.00 (0.21-1.00)
Boer_2018	52	11	19	23	0.73 (0.62-0.82)	0.68 (0.51-0.81)
Thomsen_2018	45	22	14	25	0.76 (0.64-0.85)	0.53 (0.39-0.66)
Ochman_2017	8	7	2	19	0.80 (0.49-0.94)	0.73 (0.54-0.86)
Greditzer_2016	9	8	2	7	0.82 (0.52-0.95)	0.47 (0.25-0.70)
Scheck_1999	22	15	4	19	0.85 (0.67-0.94)	0.56 (0.40-0.71)
Daunt_2021	112	19	13	78	0.90 (0.83-0.94)	0.80 (0.71-0.87)
Totterman_1996	12	3	1	15	0.92 (0.66-0.99)	0.83 (0.60-0.94)
Potter_1997	74	3	5	84	0.94 (0.86-0.97)	0.97 (0.91-0.99)
Stouracova_2016	14	2	0	4	1.00 (0.78-1.00)	0.67 (0.30-0.90)
Tanaka_2006	10	0	0	1	1.00 (0.72-1.00)	1.00 (0.21-1.00)
					0.80 (0.70-0.87)	0.85 (0.68-0.94)



B

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Kamal_2014	12	3	26	47	0.32 (0.19-0.48)	0.94 (0.84-0.98)
Morley_2001	18	5	30	55	0.38 (0.26-0.52)	0.92 (0.82-0.97)
De Santis_2021	59	18	52	17	0.53 (0.44-0.62)	0.49 (0.33-0.65)
Johnstone_1997	19	8	15	87	0.56 (0.40-0.71)	0.92 (0.85-0.96)
Brennan_2021	26	7	20	26	0.57 (0.43-0.70)	0.79 (0.62-0.89)
De Smet_2005	11	2	7	15	0.61 (0.39-0.80)	0.88 (0.65-0.97)
Valeri_1999	12	21	7	7	0.63 (0.41-0.81)	0.25 (0.13-0.43)
Schädel-Höpfner_2001	21	6	12	33	0.64 (0.47-0.78)	0.85 (0.71-0.93)
Prosser_2011	39	9	21	96	0.65 (0.52-0.76)	0.91 (0.84-0.95)
Shionova_1998	30	17	11	44	0.73 (0.58-0.84)	0.72 (0.60-0.82)
Oneson_1997	9	8	3	148	0.75 (0.47-0.91)	0.95 (0.90-0.97)
Katschnig_2006	32	3	10	0	0.76 (0.61-0.86)	0.00 (0.00-0.56)
Anderson_2008	92	20	27	167	0.77 (0.69-0.84)	0.89 (0.84-0.93)
Kovanlikaya_1997	29	5	8	33	0.78 (0.62-0.88)	0.87 (0.73-0.94)
Abdelsattar_2012	31	0	4	9	0.89 (0.75-0.96)	1.00 (0.70-1.00)
Zlatkin_1989	8	1	1	11	0.89 (0.57-0.98)	0.92 (0.65-0.99)
Gabl_1996	31	0	1	32	0.97 (0.84-0.99)	1.00 (0.89-1.00)
Kato_2000	18	10	0	5	1.00 (0.82-1.00)	0.33 (0.15-0.58)
					0.71 (0.61-0.79)	0.84 (0.72-0.92)

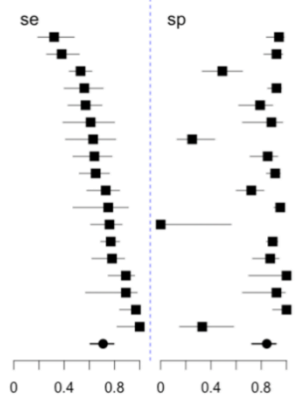


Figure 6*. Forest plot representing sensitivity and specificity of MRI for wrist ligamentous lesions based on the application of dedicated wrist coils. A. Application of dedicated wrist coils. B. Dedicated wrist coils were not applied.*

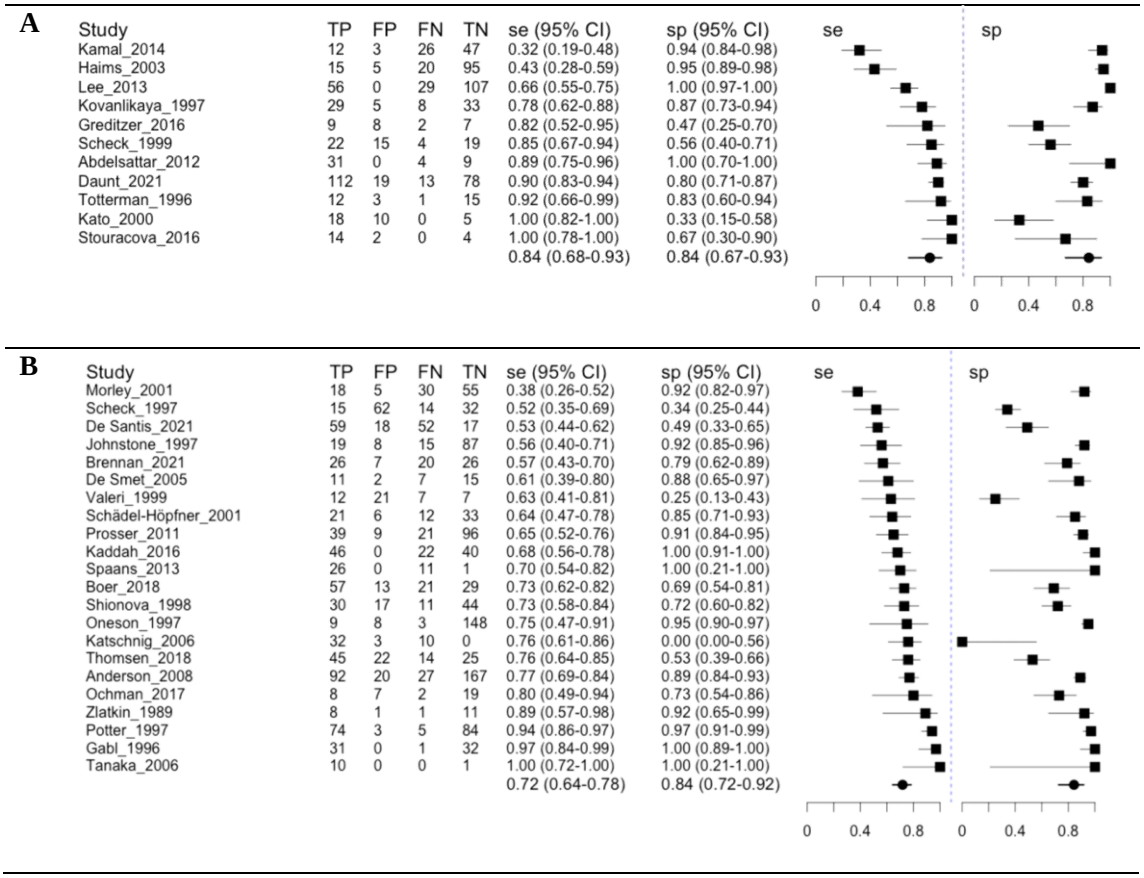
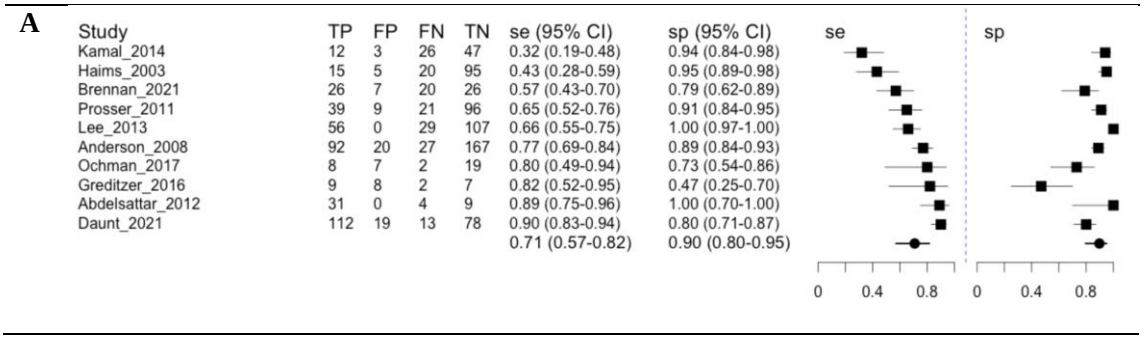


Figure 7. *Forest plot representing sensitivity and specificity of MRI for wrist ligamentous lesions based on the application of 3D sequences. A. Application of 3D sequences. B. 3D sequences were not applied.*



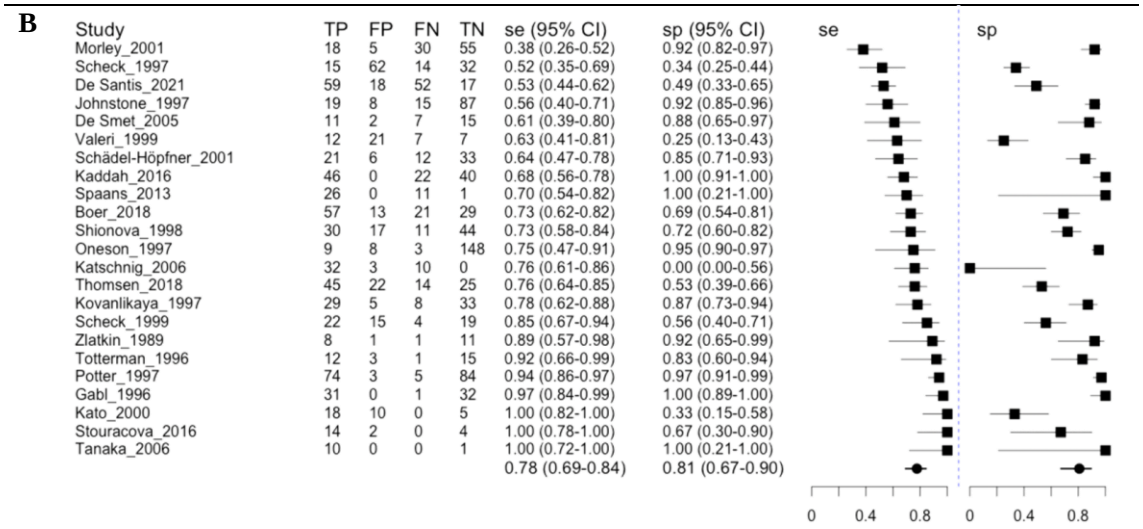
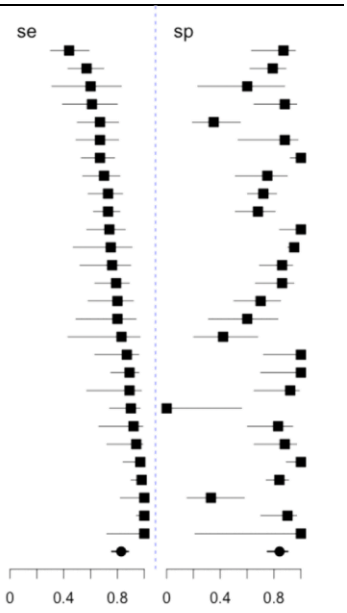


Figure 8. *Forest plot representing sensitivity and specificity of MRI for wrist ligamentous lesions based on the application of fat saturation. A. Application of fat saturation. B. Fat saturation was not applied.*

Based on the location of the suspected injury, MRI was proven to be the most accurate in the diagnosis of TFCC peripheral tears, where sensitivity was 0.90 (0.66-0.98) and a specificity was 0.95 (0.88-0.98). These results were closely followed by the diagnostic accuracy for TFCC central tears, with a sensitivity of 0.85 (0.70-0.93) and a specificity of 0.95 (0.81-0.99). For both SL and LT ligament lesions, sensitivity was lower (0.63 (0.50 - 0.74) and 0.41 (0.25 – 0.60)), while specificity remained high (0.86 (0.73 - 0.93) and 0.93 (0.81 – 0.98)) (Figure 9.). For the SL ligament injury, 3T images had a higher sensitivity (0.76 (0.64 – 0.85)) and specificity 0.97 (0.57 – 1.00)) compared to the 1.5T images (se: 0.61 (0.39 – 0.80) and sp: 0.82 (0.60 – 0.93)), however this difference was nonsignificant. Two-tailed z tests showed no significant difference between the subgroups based on anatomic location of the suspected injury either. (Table 3.)

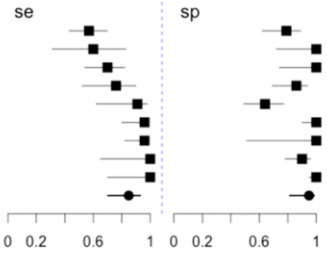
A

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Morley_2001	17	2	22	13	0.44 (0.30-0.59)	0.87 (0.63-0.96)
Brennan_2021	26	7	20	26	0.57 (0.43-0.70)	0.79 (0.62-0.89)
Valeri_1999	6	2	4	3	0.60 (0.31-0.83)	0.60 (0.23-0.88)
De Smet_2005	11	2	7	15	0.61 (0.39-0.80)	0.88 (0.65-0.97)
De Santis_2021	22	15	11	8	0.67 (0.50-0.81)	0.35 (0.19-0.55)
Ruston_2013	20	1	10	7	0.67 (0.49-0.81)	0.88 (0.53-0.98)
Lee_2013	35	0	17	44	0.67 (0.53-0.78)	1.00 (0.92-1.00)
Thomsen_2018	26	4	11	12	0.70 (0.54-0.82)	0.75 (0.51-0.90)
Shionova_1998	30	17	11	44	0.73 (0.58-0.84)	0.72 (0.60-0.82)
Boer_2018	52	11	19	23	0.73 (0.62-0.82)	0.68 (0.51-0.81)
Kaddah_2016	25	0	9	20	0.74 (0.57-0.86)	1.00 (0.84-1.00)
Oneson_1997	9	8	3	148	0.75 (0.47-0.91)	0.95 (0.90-0.97)
Haims_2003	13	4	4	24	0.76 (0.52-0.90)	0.86 (0.69-0.94)
Prosser_2011	27	3	7	18	0.79 (0.63-0.89)	0.86 (0.66-0.95)
Johnstone_1997	16	7	4	16	0.80 (0.58-0.92)	0.70 (0.50-0.85)
Scheck_1999	8	4	2	6	0.80 (0.49-0.94)	0.60 (0.31-0.83)
Ochman_2017	5	7	1	5	0.83 (0.43-0.97)	0.42 (0.20-0.68)
Kovalinkaya_1997	13	0	2	10	0.87 (0.63-0.96)	1.00 (0.72-1.00)
Abdelsattar_2012	31	0	4	9	0.89 (0.75-0.96)	1.00 (0.70-1.00)
Zlatkin_1989	8	1	1	11	0.89 (0.57-0.98)	0.92 (0.65-0.99)
Katschnig_2006	27	3	3	0	0.90 (0.74-0.97)	0.00 (0.00-0.56)
Totterman_1996	12	3	1	15	0.92 (0.66-0.99)	0.83 (0.60-0.94)
Anderson_2008	15	2	1	14	0.94 (0.72-0.99)	0.88 (0.65-0.97)
Gabl_1996	31	0	1	32	0.97 (0.84-0.99)	1.00 (0.89-1.00)
Daunt_2021	50	11	1	58	0.98 (0.90-1.00)	0.84 (0.74-0.91)
Kato_2000	18	10	0	5	1.00 (0.82-1.00)	0.33 (0.15-0.58)
Potter_1997	57	2	0	18	1.00 (0.94-1.00)	0.90 (0.70-0.97)
Tanaka_2006	10	0	0	1	1.00 (0.72-1.00)	1.00 (0.21-1.00)
					0.83 (0.76-0.88)	0.84 (0.75-0.90)



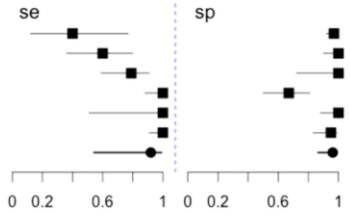
B

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Brennan_2021	26	7	20	26	0.57 (0.43-0.70)	0.79 (0.62-0.89)
Kaddah_2016	6	0	4	10	0.60 (0.31-0.83)	1.00 (0.72-1.00)
Lee_2013	26	0	11	11	0.70 (0.54-0.82)	1.00 (0.74-1.00)
Haims_2003	13	4	4	24	0.76 (0.52-0.90)	0.86 (0.69-0.94)
Thomsen_2018	10	15	1	27	0.91 (0.62-0.98)	0.64 (0.49-0.77)
Daunt_2021	23	0	1	36	0.96 (0.80-0.99)	1.00 (0.90-1.00)
Gabl_1996	27	0	1	4	0.96 (0.82-0.99)	1.00 (0.51-1.00)
Oneson_1997	7	5	0	44	1.00 (0.65-1.00)	0.90 (0.78-0.96)
Potter_1997	9	0	0	68	1.00 (0.70-1.00)	1.00 (0.95-1.00)
					0.85 (0.70-0.93)	0.95 (0.81-0.99)



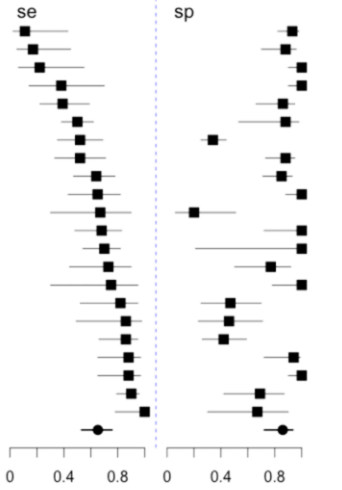
C

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Oneson_1997	2	3	3	104	0.40 (0.12-0.77)	0.97 (0.92-0.99)
Lee_2013	9	0	6	33	0.60 (0.36-0.80)	1.00 (0.90-1.00)
Kaddah_2016	19	0	5	10	0.79 (0.59-0.91)	1.00 (0.72-1.00)
Daunt_2021	27	11	0	22	1.00 (0.88-1.00)	0.67 (0.50-0.81)
Gabl_1996	4	0	0	28	1.00 (0.51-1.00)	1.00 (0.88-1.00)
Potter_1997	37	2	0	38	1.00 (0.91-1.00)	0.95 (0.83-0.99)
					0.92 (0.54-0.99)	0.96 (0.86-0.99)



D

Study	TP	FP	FN	TN	se (95% CI)	sp (95% CI)
Morley_2001	1	3	8	42	0.11 (0.02-0.43)	0.93 (0.82-0.98)
Ruston_2013	2	3	10	23	0.17 (0.05-0.45)	0.88 (0.70-0.96)
Haims_2003	2	0	7	36	0.22 (0.06-0.55)	1.00 (0.90-1.00)
Johnstone_1997	3	0	5	35	0.38 (0.14-0.70)	1.00 (0.90-1.00)
Kamal_2014	9	3	14	18	0.39 (0.22-0.59)	0.86 (0.66-0.95)
De Santis_2021	34	1	34	7	0.50 (0.38-0.62)	0.88 (0.53-0.98)
Scheck_1997	15	62	14	32	0.52 (0.35-0.69)	0.34 (0.25-0.44)
Prosser_2011	12	4	11	28	0.52 (0.33-0.71)	0.88 (0.73-0.95)
Schädel-Höpfner_2001	21	6	12	33	0.64 (0.47-0.78)	0.85 (0.71-0.93)
Lee_2013	13	0	7	28	0.65 (0.43-0.82)	1.00 (0.88-1.00)
Valeri_1999	4	8	2	2	0.67 (0.30-0.90)	0.20 (0.06-0.51)
Kaddah_2016	17	0	8	10	0.68 (0.48-0.83)	1.00 (0.72-1.00)
Spaans_2013	26	0	11	1	0.70 (0.54-0.82)	1.00 (0.21-1.00)
Kovalinkaya_1997	8	3	3	10	0.73 (0.44-0.90)	0.77 (0.50-0.92)
Ochman_2017	3	0	1	14	0.75 (0.30-0.95)	1.00 (0.78-1.00)
Greditzer_2016	9	8	2	7	0.82 (0.52-0.95)	0.47 (0.25-0.70)
Scheck_1999	6	7	1	6	0.86 (0.49-0.98)	0.46 (0.23-0.71)
Thomsen _2018	19	18	3	13	0.86 (0.66-0.95)	0.42 (0.26-0.59)
Anderson_2008	14	1	2	15	0.88 (0.65-0.97)	0.94 (0.72-0.99)
Potter_1997	15	0	2	36	0.88 (0.65-0.97)	1.00 (0.90-1.00)
Daunt_2021	47	4	5	9	0.90 (0.79-0.96)	0.69 (0.42-0.87)
Stouracova_2016	14	2	0	4	1.00 (0.78-1.00)	0.67 (0.30-0.90)
					0.65 (0.53-0.76)	0.86 (0.72-0.94)



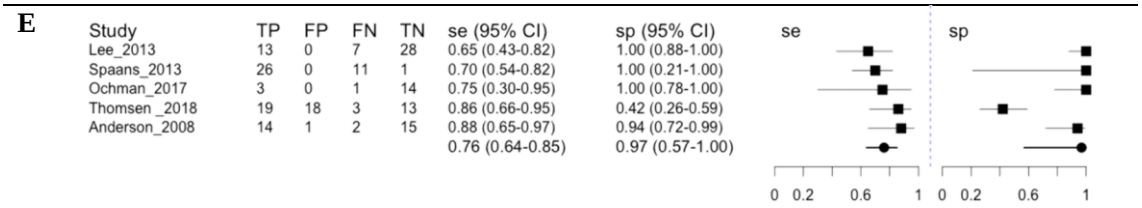


Figure 9. *Forest plot representing sensitivity and specificity of MRI for wrist ligamentous lesions based on anatomic location. A. TFCC, B. TFCC central tear, C. TFCC peripheral tear, D. SL ligament, E. LT ligament*

Table 3. Results of two-tailed z test for the comparison of sensitivity and specificity of MRI for different subgroups (94).

Subset 1	Subset 2	Two-tailed z-test p value for sensitivity	Two-tailed z-test p value for specificity
low field MRI	1.5 T MRI	0,1684	0,3852
1.5 T	3 T MRI	0,3807	0,4248
low field MRI	3T MRI	0,4060	0,2146
TFCC – low field MRI	TFCC – 1.5 T MRI	1,0000	0,4712
TFCC – low field MRI	TFCC – 3 T MRI	0,0763	0,5138
TFCC – 1.5 T MRI	TFCC – 3 T MRI	0,0993	0,9355
SL – low field MRI	SL – 1.5 T MRI	0,8816	0,9586
SL – low field MRI	SL – 3 T MRI	0,1926	0,4757
SL – 1.5 T MRI	SL – 3 T MRI	0,2018	0,2286
LT – low field MRI	LT – 1.5 T MRI	0,6031	0,4432
wrist coil	no wrist coil	0,1429	1,0000
3D sequence	no 3D sequence	0,1713	1,0000
fat saturation	no fat saturation	0,4886	0,2534

Subgroup analyses performed to reduce potential risk of bias have found no significant difference in the overall sensitivity and specificity values compared to the main analysis. Results of these analyses can be found in the Supplementary Table 2. and 3. of the original article (94).

Positive and negative predictive values for calculated using the median prevalence for each subgroup. Results are shown in Table 4. The overall positive predictive value was 0.78 (0.70 - 0.85), while the negative predictive value was 0.80 (0.76 – 0.84). Median

prevalence was the lowest for LT ligament lesions (0.19) and highest for TFCC injuries (0.63). Highest positive and negative predictive values were found for TFCC peripheral (PPV: 0.92 (0.82 – 0.97), NPV: 0.93 (0.81 - 0.98)) and TFCC central tears (PPV: 0.92 (0.75 – 0.98, NPV: 0.90 (0.82 – 0.95)).

Table 4. Positive and negative predictive values of wrist MRI based on different technical aspects and types of ligamentous injury of the wrist.

	Positive Predictive Value (95% CI)	**Negative Predictive Value (95% CI)**	**Median Prevalence**
ALL (3T)*	0.78 (0.70 - 0.85)	0.80 (0.76 – 0.84)	0.44
Low field	0.63 (0.44 – 0.87)	0.71 (0.49 – 0.79)	0.46
1.5 T	0.76 (0.66 – 0.84)	0.83 (0.76 – 0.89)	0.43
3 T	0.88 (0.64 – 0.98)	0.77 (0.68 – 0.81)	0.5
wrist coil	0.81 (0.69 – 0.90)	0.83 (0.77 – 0.88)	0.46
no wrist coil	0.79 (0.68 – 0.87)	0.78 (0.72 – 0.83)	0.45
3D sequences	0.81 (0.66 – 0.91)	0.87 (0.76 – 0.93)	0.44
no 3D sequences	0.79 (0.69 – 0.87)	0.78 (0.73 – 0.82)	0.46
fat saturation	0.83 (0.72 – 0.91)	0.82 (0.75 – 0.88)	0.42
no fat saturation	0.79 (0.70 – 0.88)	0.79 (0.73 – 0.84)	0.49
TFCC (All)	0.85 (0.79 – 0.90)	0.78 (0.72 – 0.83)	0.56
TFCC (Low field)	0.81 (0.63 - 0.97)	0.70 (0.36 – 0.81)	0.63
TFCC (1.5T)	0.82 (0.75 - 0.89)	0.82 (0.73 – 0.89)	0.52
TFCC (3T)	0.83 (0.64 - 0.94)	0.73 (0.61 - 0.78)	0.54
Central (All)	0.92 (0.75 – 0.98)	0.90 (0.82 – 0.95)	0.4
Peripheral (All)	0.92 (0.82 – 0.97)	0.93 (0.81 - 0.98)	0.4
SL (All)	0.77 (0.62 – 0.87)	0.76 (0.70 – 0.82)	0.42
SL (Low field)	0.76 (0.43 – 0.97)	0.72 (0.47 – 0.82)	0.46
SL (1.5T)	0.64 (0.41 – 0.83)	0.81 (0.71 – 0.89)	0.34
SL (3T)	0.95 (0.54 – 1.00)	0.85 (0.75 – 0.90)	0.42
LT (all - 3T)	0.66 (0.37 – 0.87)	0.83 (0.79 – 0.88)	0.24
LT (low field)	0.32 (0.04 – 0.85)	0.86 (0.59 – 0.97)	0.19
LT (1.5T)	0.63 (0.32 – 0.85)	0.79 (0.74 – 0.86)	0.27

The point estimate and 95% confidence interval of positive and negative predictive values (PPV, NPV) are shown in this table. Median prevalence was calculated for each subgroup.

* If within one study patients were examined with both 1.5T and 3T machines, the results of the 3T MRI were used to calculate overall positive and negative predictive values.

Positive and negative likelihood ratios (LR+ and LR-) were also calculated for each subgroup (Table 5.). Overall evaluation showed that LR+ for wrist MRI was 4.51 (2.87 – 7.10) and LR- was 0.31 (0.24 – 0.41). This corresponds to a small to medium increase in probability of the correct diagnosis. Regarding field strength, there was an increasing tendency in LR+ with higher field strengths, however confidence intervals were overlapping, showing that the difference was nonsignificant. The use of 3D sequences, wrist coils and fat saturation technique slightly increased LR+, but these differences were also nonsignificant. LR- slightly decreased when using wrist coils and 3D sequences, increasing the possibility of a negative result being correct. Confidence intervals were overlapping here as well. Based on anatomic location, best results were seen for the diagnosis of TFCC central and peripheral tears, where PPV was over 10 and NPV approached 0.1, the cut-off values for conclusive shift in probability of the correct diagnosis. For SL ligament injuries, 3T MRI had a considerable higher LR+ and substantially lower LR- compared to 1.5T, however differences were nonsignificant. The results for LT ligament injuries showed overall a moderate shift in probability for a correct diagnosis.

Table 5. Positive and negative likelihood ratios wrist MRI based on different technical aspects and types of ligamentous injury of the wrist.

	Positive Likelihood Ratio (95% CI)	**Negative Likelihood Ratio (95% CI)**
ALL (3T)*	4.51 (2.87 - 7.10)	0.31 (0.24 – 0.41)
Low field	1.97 (0.91 – 7.57)	0.48 (0.31 – 1.25)
1.5 T	4.17 (2.51 – 6.91)	0.27 (0.17 – 0.44)
3 T	7.13 (1.76 – 41.30)	0.30 (0.24 – 0.47)
wrist coil	5.02 (2.35 – 10.72)	0.24 (0.16 – 0.36)

no wrist coil	4.52 (2.53 – 8.59)	0.35 (0.24 – 0.48)
3D echo	5.30 (2.45 – 13.56)	0.19 (0.09 – 0.39)
no 3D echo	4.45 (2.44 – 8.12)	0.33 (0.24 – 0.45)
fat saturation	6.89 (3.71 – 12.81)	0.31 (0.20 – 0.46)
no fat saturation	4.02(2.33 – 7.49)	0.28 (0.19 – 0.40)
TFCC (All)	4.57 (2.99 – 7.25)	0.22 (0.16 – 0.31)
TFCC (Low field)	2.51 (0.99 – 18.14)	0.26 (0.13 – 1.06)
TFCC (1.5T)	4.33 (2.62 – 7.15)	0.21 (0.12 – 0.35)
TFCC (3T)	4.56 (2.89 – 7.19)	0.22 (0.16 – 0.31)
Central (All)	16.65 (4.50 – 65.00)	0.16 (0.07 – 0.33)
Peripheral (All)	18.31 (7.69 – 43.62)	0.11 (0.03 – 0.40)
SL (All)	4.50 (2.33 – 8.70)	0.43 (0.31 – 0.59)
SL (Low field)	3.67 (0.86 – 35.73)	0.45 (0.26 – 1.28)
SL (1.5T)	3.41 (1.35 – 9.33)	0.47 (0.24 – 0.82)
SL (3T)	23.78 (1.61 – 629.08)	0.25 (0.16 – 0.49)
LT (all - 3T)	6.18 (1.90 – 21.42)	0.63 (0.43 – 0.84)
LT (low field)	1.97 (0.18 – 27.07)	0.71 (0.13 – 2.97)
LT (1.5T)	4.61 (1.19 – 16.70)	0.73 (0.44 – 0.97)

The point estimate and 95% confidence interval of positive and negative likelihood ratios are shown in this table.

* If within one study patients were examined with both 1.5T and 3T machines, the results of the 3T MRI were used to calculate overall positive and negative predictive values.

8.2. Study II: Assessing the severity of carpal tunnel syndrome by measuring two-point discrimination

8.2.1. Characteristics of the study population

Overall, 81 patients met our inclusion criteria, 59 of them (72.8%) were female. Patients were between 33 and 91 years old, mean age was 60.23 ± 15.51 years. The duration of symptoms varied between 1 and 360 months (mean: 35.78 ± 57.57 months, median: 12 months). Electrophysiological examination was performed for 80 patients and peripheral nerve ultrasound examination was performed for 42 patients. 2PD values varied between 2 mm and >15 mm. Highest values were measured along the second digital nerve, were mean 2PD was 7.5 ± 3.64 mm. Difference between 2PD values was significant compared

to the ones measured on the third digital nerve (mean: 6.38 ± 3.2 mm, p=0.0006) and on the fourth digital nerve (mean: 6.62 ± 4.02 mm, p=0.024). Lowest values were measured along the third digital nerve (mean: 6.38 ± 3.2 mm). These values were significantly lower compared to the ones measured on the first (7.19 ± 3.63 mm, p=0.027), sixth (mean: 7.05 ± 4.01 mm, p = 0.01) and seventh (mean: 7.17 ± 3.75 mm, p = 0.005) digital nerves. Values were also significantly lower on the fourth digital nerve (mean: 6.62 ± 4.02 mm) compared to the sixth (p=0.04) and to the seventh (p=0.02) digital nerve.

8.2.2. Correlation between 2PD and different variables

Electrophysiological severity

2PD values and categories showed significant correlation with the severity of CTS, classified according to the three ENG severity categories (r=0.29, (0.07 – 0.48) and r=0.26 (0.03 – 0.45). When severity was determined according to six categories, significant correlation was found with 2PD values (r=0.25 (0.02 - 0.45). (Figure 10.)

ENG variables

The 2PD severity categories did not correlate significantly with the severity categories of distal sensory latency, amplitude, or conduction velocity. Distal sensory latency and conduction velocity values had a significant correlation with the 2PD categories. However, the correlation coefficients (r = 0.25 (0.02–0.46) and r = 0.24 (- 0.44 - -0.01)) were low. 2PD values showed a similar correlation with the distal sensory latency values (r = 0.25 (0.02–0.45)). (Figure 11.)

Peripheral nerve ultrasound

Severity based on ultrasound examination and CSA measurements did not show significant correlation with 2PD values and categories. (Figures 10. and 11.)

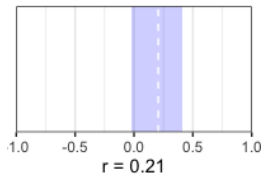
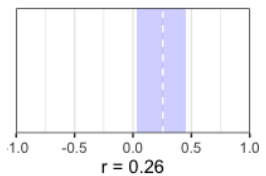
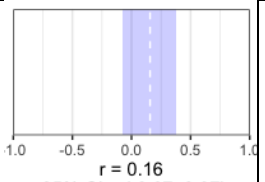
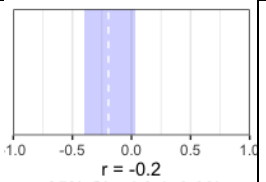
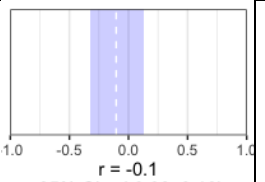
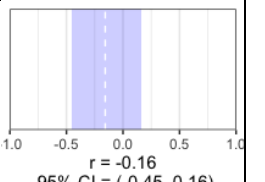
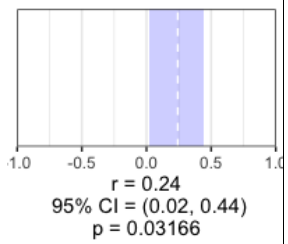
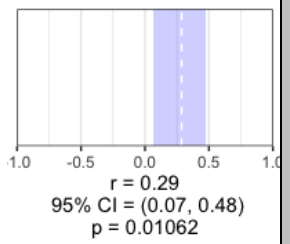
	ENG-EMG					Ultrasound
	NCS severity (6 categories) (n=79)	**NCS severity (3 categories) (n=79)**	**Distal sensory latency category (n=76)**	**Amplitude category (n=79)**	**Nerve conduction velocity category (n=77)**	**US severity category (n=42)**
2 PD severity (3 categories)						
2 PD values (mm)						

Figure 10. *Pearson correlation between 2PD and the severity of carpal tunnel syndrome based on ENG-EMG and peripheral nerve ultrasound examination. (96)*

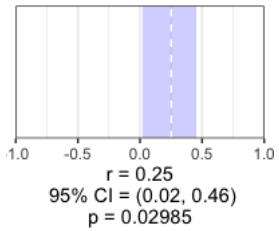
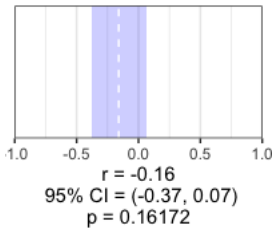
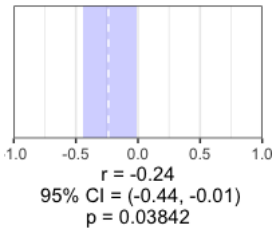
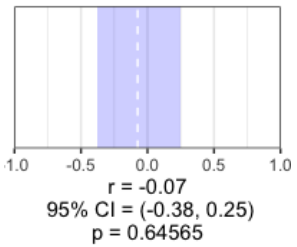
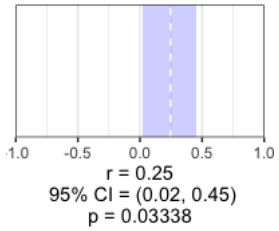
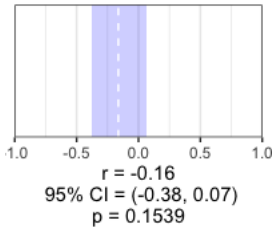
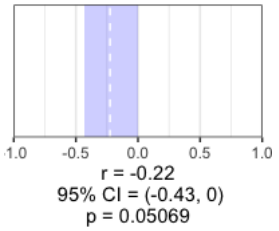
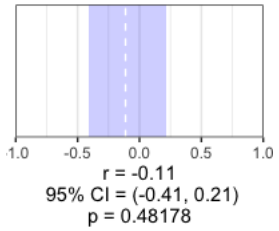
	ENG-EMG			Ultrasound	
	Distal sensory latency values (msec) (n=75)	**Amplitude values (µV) (n=78)**	**Nerve conduction velocity values (m/s) (n=76)**	**CSA values (mm2) (n=41)**	**CSA severity category (threshold: 10 mm2) (n=53)**
2 PD severity					
2 PD values (mm)					

Figure 11. *Correlation between 2 PD and numeric variables measured by ENG-EMG and nerve ultrasound. (96)*

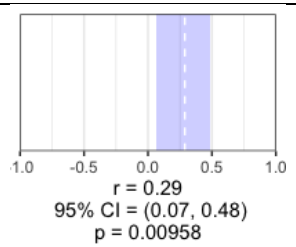
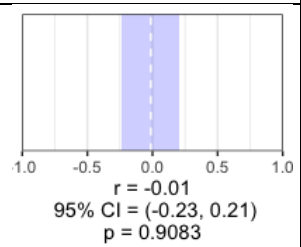
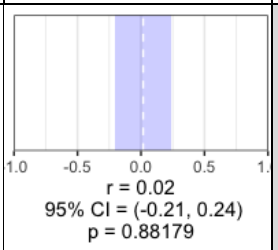
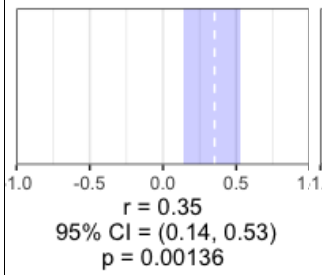
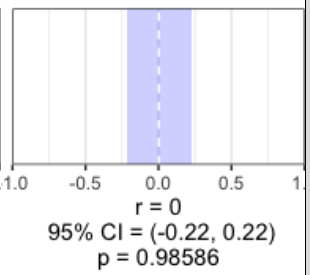
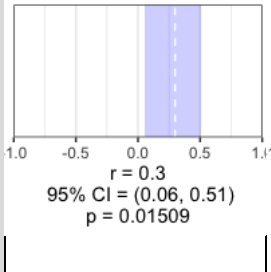
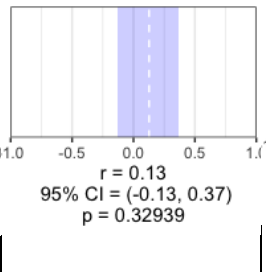
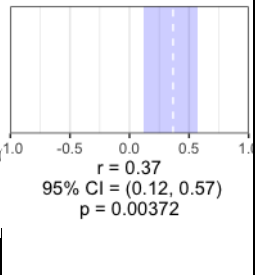
	Age (years) (n=80)	Sex (n=81)	Duration of symptoms (n=79)	DASH value (n=66)	SSS values (n=61)	FSS (n=61)
2 PD severity (3 categories)						
2 PD values (mm)						

Figure 12. *Correlation between 2 PD and patient characteristics, and the severity of symptoms. (96)*

Patient questionnaires and demographic parameters

2PD values had a significant correlation with the results of the DASH questionnaire and the functional status scale (FSS) part of the Boston CTS questionnaire. The symptom severity scale (SSS) of the Boston CTS questionnaire did not have a significant relationship with 2PD. (Fig.12.)

Regarding demographic parameters, age showed significant correlation with 2PD values (r = 0.29 (0.07 – 0.48) and with 2PD severity categories (r = 0.35 (0.14 – 0.53) as well. Sex and duration of symptoms did not have significant correlation with 2PD.

8.2.3. 2PD and the severity of CTS

According to the severity of CTS, distribution of 2PD values were examined (Fig.13.) Patients with 4 mm or less 2PD all had mild CTS, while patients with moderate CTS had 2PD values varying between 5 and 15 mm, with most of them (25.5 %) having a 2PD value of 8 mm. In case of severe CTS, 2PD values had a minimum of 6 mm, and most of them (34.8 %) had 2PDs over the measuring limit (15 mm).

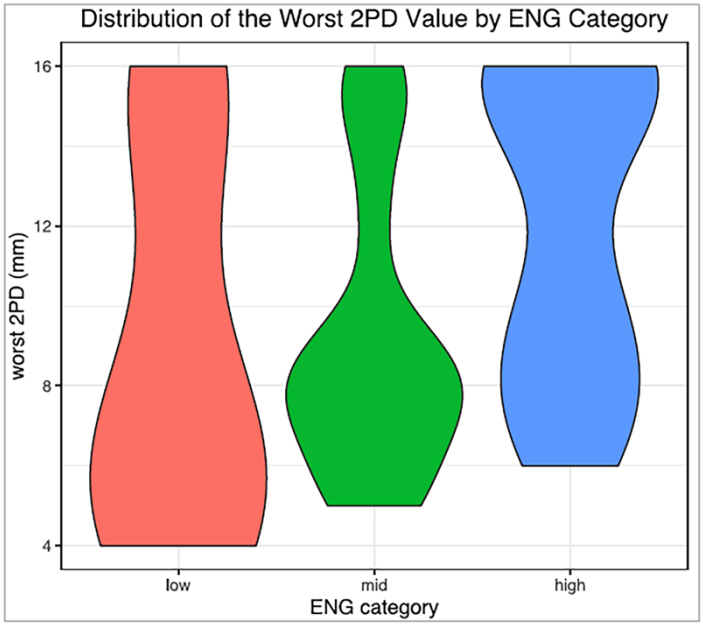


Figure 13. *Distribution of 2PD values according to ENG-EMG severity categories. (96)*

By combining mild and moderate severity groups to a non-severe group, all 2PD values measured in the severe CTS severity group were above the normal (> 6 mm). At the same

time, 2PD values above the measurable maximum (15 mm) occurred both in the non-severe and the severe group. (Fig. 14.)

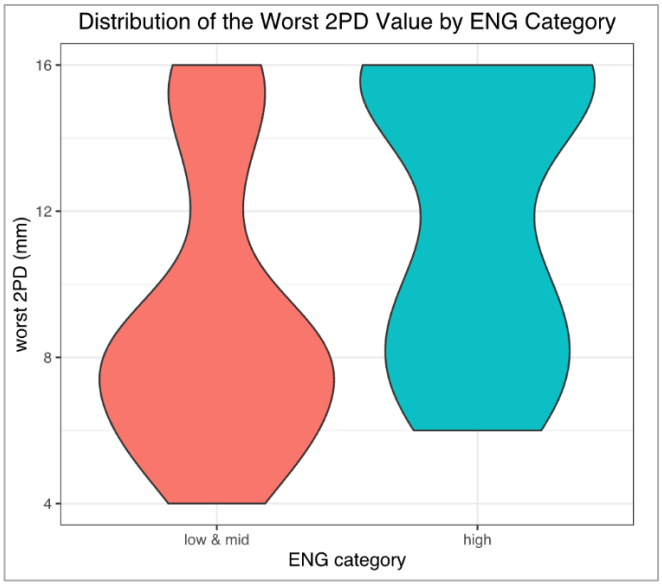


Figure 14. *Distribution of 2PD values according to the severity categories of ENG-EMG severe and non-severe.*

Diagnostic efficacy, sensitivity and specificity of different 2PD cut-off values were tested to screen for severe CTS. Highest sensitivity (0.95 (0.77 - 1.00)) was achieved at 6 mm, but at this level, specificity was only 0.29 (0.18 – 0.41). Optimal diagnostic accuracy (0.69 (0.59 – 0.79)) was found at a threshold of 9.5 mm. This value had a sensitivity of 0.65 (0.45 – 0.81) and a specificity of 0.71 (0.58 – 0.82). (Fig. 15.) At the 9.5 mm threshold, diagnostic odds ratio for severe CTS was 4.688 (1.664 – 13.203). (Fig.16.)

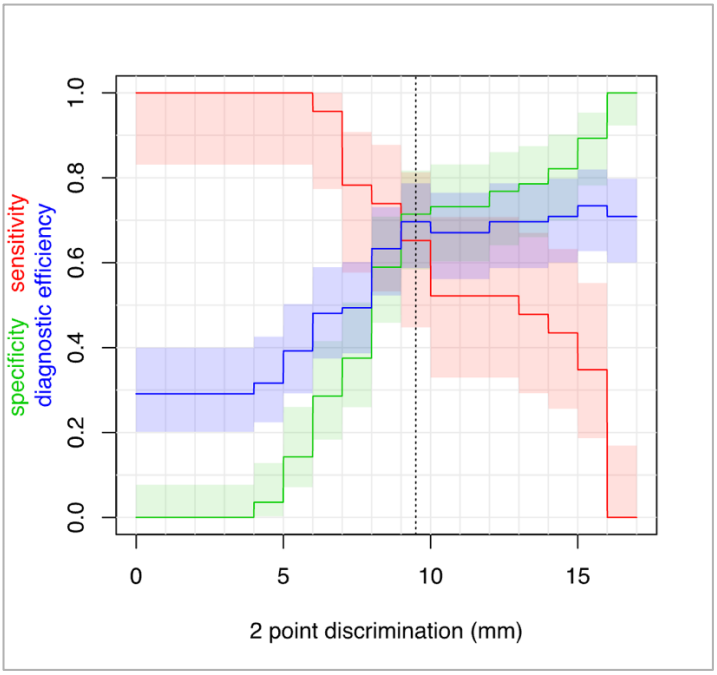


Figure 15. *Sensitivity, specificity and diagnostic efficacy of 2PD values for severe carpal tunnel syndrome.*

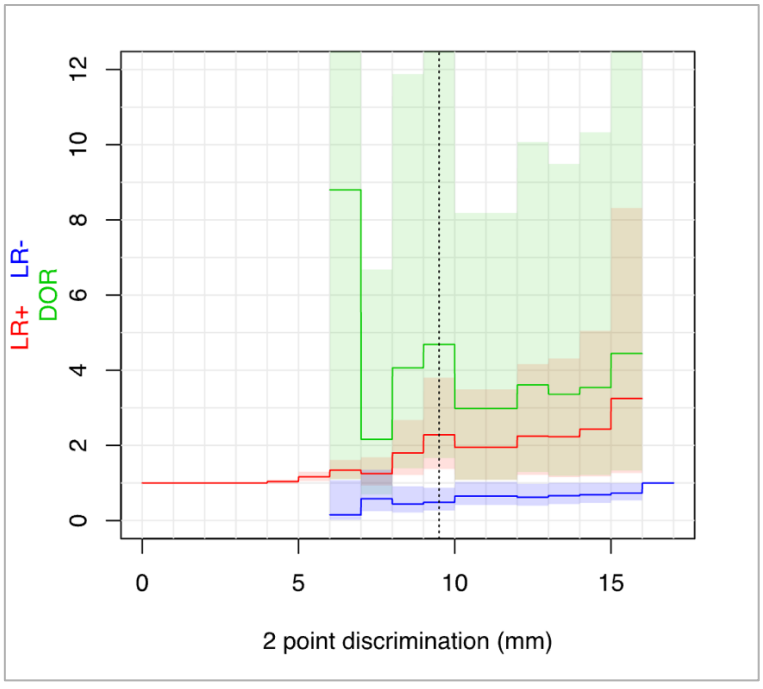


Figure 16. *Odds ratio, positive and negative likelihood ratio of 2PD values for severe carpal tunnel syndrome.*

9. DISCUSSION

9.1. Summary of findings, international comparisons

Our studies showed aimed to bridge a gap in diagnostic procedures in hand surgery.

We examined the diagnostic performance of wrist MRI in the diagnosis of wrist ligamentous injuries, and the application of 2PD measurements in the screening of severe CTS.

Regarding the diagnostic performance of the MRI, our meta-analysis found that technical conditions might play a lesser role than previously thought. Though 1.5T and 3T MRI had superior performance compared to low field strength MRI, differences were below the significance level. Increased field strength and the application of fat saturation contributed to higher specificity, while sensitivity was increased with the use of dedicated wrist coils and 3D sequences, however, these differences were found to be nonsignificant between the examined subgroups. Best diagnostic performance was achieved for TFCC central and peripheral tears, with an estimated sensitivity of 85% and 90% and an estimated specificity of 95%. For SL and LT ligament injuries pooled sensitivity was lower, 63% and 41%, suggesting that these injuries might be underdiagnosed.

9.1.1. Technical conditions of wrist MRI

Field strength

Several authors investigated the effect of field strength on the diagnostic accuracy of wrist MRI. Our study found that the superiority of 3T MRI cannot be declared over 1.5T or low field MRI without further supporting evidence. Two previous meta-analysis, published in 2012 by Smith et al. (97) and in 2016 by Hafezi-Nejad et al. (98) declared the significant superiority of 3T MRI over 1.5T MRI. The most recent previous meta-analysis authored by Krastman et al. (99) in 2020, similarly to our findings, reported that 3T machines were not superior to 1.5T machines regarding ligamentous injuries of the wrist.

Looking for differences across studies, we have concluded that the main reason for divergent results might be the variation in the number of included studies. In earlier studies, when 3T MRI availability was considerably lower, comparison regarding field strength was not balanced. Smith et al. (97) included only one article reporting about the performance of 3T MRI, while Hafezi-Nejad et al. (98) included three. They compared

the results to 20 and 24 studies respectively, reporting about the findings of 1.5T imaging. On the other hand, Krastman et al. (99) worked with a more balanced sample, comparing four publications about 3T MRI to five studies about 1.5T MRI. In our meta-analysis, six publications reported of 3T MRI, 21 studies of 1.5T MRI, and five of low field MRI and in studies. Although numbers were not balanced, with the inclusion of more studies reporting about 3T imaging, the superiority of this technique does not seem evident, as regarding both sensitivity and specificity results were close to the ones of 1.5T imaging. The only case, where 3T MRI might surpass 1.5T MRI is the imaging of suspected SL ligament injuries. In the subgroup analysis, ten studies reported of 1.5T imaging compared to five studies reporting of 3T imaging. Though differences were not significant in the present study, point estimate of the sensitivity and specificity was 15% higher for 3T MRI. From the five studies reporting of 3T imaging, three (1, 77, 86) found a 1.00 specificity, while the other two studies (61, 90) reported a specificity of 0.42 and 0.94. The study by Thomsen et al. gave a summary estimate of the specificity, including partial and full thickness tears of the SL. This was consistent with our methods of calculating outcomes, however it is important to note that for full thickness tears specificity evaluated by two independent observers was 0.95 and 0.98, meaning that for full thickness tears the difference between 1.5T and 3T tears might be greater than estimated. Beside sensitivity and specificity measurements, likelihood ratios also suggest the potential superiority of 3T imaging. Positive likelihood ratio was markedly higher, and negative likelihood ratio was decreased for 3T imaging compared to 1.5T MRI. Although, wide and overlapping confidence intervals prevented us to declare to undoubted superiority of 3T imaging, we cannot discard the possibility that the comparison of more homogenous studies would prove that at least in select cases, 3T MRI might surpass the diagnostic performance of 1.5T imaging.

Wrist coils

Studies with dedicated wrist coils had to a higher range of sensitivity, while specificity remained mainly unchanged. A prior meta-analysis by Hobby et al. (100) advised the use of receive only surface coils, beside the use of 3D gradient echo sequences and higher field strength imaging for satisfactory results. These findings were confirmed by Andersson et al. (6) and suggested that the application of specific wrist coils should be the part of the gold standard for diagnosing TFCC, SL and LT ligament injuries. The MRI

protocol for wrist ligaments by Ringler (101) also mentioned the mandatory use of dedicated surface coils. Following these recommendations, from 2015 most studies reported the use of wrist coils during their imaging protocol. The meta-analysis by Wang et al. (102) defined the use of wrist coils as one of their criteria for high quality imaging of TFCC injuries. Treiser et al. (103) also emphasized the need for dedicated wrist coils in the MRI imaging of TFCC. Our results show similar tendencies as the ones observed by the above-mentioned authors. As included studies differed in terms of technical conditions, other qualities might have contributed to the fact that we have not found significant difference between studies that used wrist coils and the ones that did not.

3D sequences

By increasing spatial resolution and the signal-to-noise ratio (SNR), the use of 3D sequences was expected to increase sensitivity. Our analysis found that 3D sequences did shift the sensitivity to a higher range, and widened the range of specificity as well, but these differences were not significant. The meta-analysis by Hobby et al. (100) also found increased sensitivity values for TFCC, SL and LT ligament injuries as well, but their analysis also found these differences nonsignificant. Saupe et al. (20) compared the use of 3D fast field echo sequences at 1.5T and 3T MRI, without finding significant difference between the two groups. Direct comparison between 3D sequences and the previously generally used 2D fast spin echo pulse sequences was not performed in their study. Tough the superiority of 3D sequences compared to 2D protocols with higher field strength and dedicated wrist coils was not definitively proven (104), in many institutions, the use of 3D sequences became part of the normal imaging protocol (22). Yoshioka et al. (89) justified the use of 3D sequences with the small size of the visualized structured and advised the use of higher field strength machines for better spatial resolution. Naraghi and White (22) also advocated the use of 3D sequences, as according to their study it increases diagnostic confidence in finding subtle changes that might be obscured due to the partial volume averaging effect of 2D protocols.

Fat saturation

Fat saturation increased specificity and narrowed its confidence interval, while sensitivity showed a minimal decrease. PPVs and NPVs were quite similar with or without the application of fat saturation. Positive likelihood ratio showed moderate probability for a

correct diagnosis for an injured patient with the application of fat saturation, and small probability without the use of fat saturation. According to our knowledge, previous meta-analyses have not assessed the role of fat saturation in the diagnostic accuracy of wrist MRI. Yoshioka et al. (21) argues that contrast resolution is increased with the use of fat saturation, leading to higher image quality. The imaging protocol by Ringler (101) also advises the use of fat saturated proton density (PD) or T2-weighted fast spin echo (FSE) sequences. Though we expected positive changes regarding the sensitivity with the application of fat saturation, our analysis did not support our hypothesis.

9.1.2. Diagnostic performance based on anatomic location

Highest sensitivity of MRI was found for the diagnosis of TFCC central and peripheral tears. Overall specificity was high for all locations, 0.95, 0.93 and 0.97 for TFCC, LT ligament and 3T imaging of SL ligaments. High specificity is generally associated to a strong possibility of positive finding for patients having the disease, while high sensitivity is connected to the fact that negative results rule out the disease (105). Meanwhile positive and negative predictive ratios show the chance of the condition to be present or not in case of a positive or negative result (106). A prior systematic review by Andersson et al. (6) had the conclusion, that due to low NPVs, negative MRI results are not sufficient to rule out possible TFCC, SL and LT ligament injuries. They have included seven studies to their review, assessing positive and negative predictive values as primary outcomes for TFCC, SL and LT ligament injuries together. The clinically acceptable limit for NPV was set at 0.95, though it is important to mention: prevalence of the disease, which has a great influence on PPV and NPV values, was not assessed in this study. NPVs are known to decrease in case of higher prevalence (106), which is expected in these studies, as they included patients who were suspected to have ligamentous injuries. Our study calculated with the median prevalence of injuries. Based on anatomic location, point estimates for NPVs varied between 0.70 – 0.93, while point estimates for PPVs were between 0.32 – 0.92. Not only the point estimates, but confidence intervales were also set on a large scale. Significant differences were not shown; however, the observed tendencies related to anatomic location of the suspected injuries still provide useful insights. For central and peripheral TFCC tears both PPVs were 0.92 (0.75-0.98) and 0.92 (0.82-0.95) and NPVs were 0.90 (0.82-0.95) and 0.93 (0.81-0.98), while for SL and LT ligaments these values were lower, PPVs were 0.77 (0.62-0.87) and 0.66 (0.37-0.87) respectively, and NPVs

were 0.76 (0.70-0.82) and 0.83 (0.79-0.88), suggesting that most reliable results are likely to achieved for TFCC central and peripheral lesions.

Likelihood ratios are less reported in general, compared to sensitivity and specificity values in diagnostic accuracy studies. However, their independency of disease prevalence and the fact that they answer the question about the probability of a correct diagnosis makes these outcomes distinctly practical in the clinical decision-making (106). In our study, calculated likelihood ratios suggested as well, that most reliable results are expected for TFCC central and peripheral injuries. The highest LR+ was seen at 3T MRI for SL injuries, showing strong evidence for the validity of positive results. Nevertheless, LR- was higher than in case of TFCC tears, suggesting that patients with negative MRI might still have an SL ligament tear. The probability of a correct diagnosis was lowest for LT tears. In comparison, a previous study by De Santis et al. (64) found moderate probability for correct positive diagnosis for SL tear, and small probability for correct positive diagnosis for TFCC tear. Interestingly, they have found negative LR+ for LT tears, meaning that in their study the chance to get a positive MRI diagnosis was higher for patients who did not have LT ligament injury than of those who had it. They mention however, that in their retrospective study, MRIs were performed at multiple centres and were often evaluated by radiologist who were not specialized in musculoskeletal imaging. The meta-analysis by Hafezi-Nejad (98) also investigated the efficacy of MRI for SL ligamentous lesions and found that 3T MRI had a more reliable diagnostic performance compared to 1.5T machines. In their study, significant difference was seen between negative likelihood ratios; 1.5T MRI had a LR- of 0.65 (0.52 – 0.87) and 3T had a LR- of 0.33 (0.22 – 0.51). Compared to their results, we have found that 1.5T had a better performance, with a LR- of 0.47 (0.24 – 0.82), not far behind to 3T machines (LR-: 0.25 (0.16 – 0.49), both having a moderate probability for a negative MRI result when SL injury was not present.

9.1.3. The validity of 2PD measurements in diagnosing CTS

Our prospective clinical study found significant positive correlation between 2PD and electrophysiological severity categories, validating the utility of such measurements

during the physical examination for CTS. The relationship suggests that 2PD measurement has the potential to screen for patients with potentially severe CTS.

Characteristic clinical signs and elements of patient history soon orient physicians to the diagnosis of CTS. For the definition of severity, which is the basis of adequate therapy (107), auxiliary examinations are often indispensable.

In the literature, the role and validity of 2PD measurement in the diagnosis of CTS has been controversial. Electrophysiological studies have long been considered as gold standard diagnostic tool for CTS, and several authors used them as comparison for the results of 2PD measurements. However, most studies aimed to define a 2PD threshold functioning as one of the diagnostic tests for CTS. According to Buch-Jaeger and Foucher (33) sensitivity of 2PD measurements was only 6%, but specificity, on the other hand was 98%. The maximum for normal values was determined at 6 mm. Katz and Simmons (108) had similar results and advised against the use of 2PD measurement in establishing the diagnosis of CTS. They have found that the elongation of 2PD values is more likely to happen during later phases of the disease, therefore unfit for early diagnosis. Later, a study by Amirfeyz et al. (34) found a sensitivity of 54.4% and a specificity of 90%, using the same, 6 mm threshold.

Few studies sought the relationship between 2PD and different variables of electrophysiological studies or peripheral nerve ultrasound. Marlowe et al. (109) compared 2PD values to the onset latency, peak latency and the amplitude, but found that there was no significant relationship between them. Panagopoulos et al. (110) however, found a significant positive correlation between 2PD values and distal sensory latency, similarly to our study. They have also found no significant correlation between the CSA of the median nerve and 2PD values, another finding that was confirmed by our research.

The significant positive correlation between 2PD values and findings of the ENG enables the use of 2PD measurement as a potential screening method during physical examination. In case of mild, newly onset symptoms, non-operative treatment is often sufficient to reduce complaints (111). 2PD measurements offers a transparent tool as well for re-evaluation of the sensory function following conservative treatment, by being capable to detect subtle improvement or decline and facilitating the overall assessment of disease progression. With 69% diagnostic accuracy at a 9.5 mm cut-off value, this

screening method would identify the majority of patients with severe CTS, allowing clinicians to proceed with necessary auxiliary examinations in a timely manner and schedule surgery at an earlier appointment for the ones who need it the most.

2PD values showed a significant positive correlation with the results of the DASH questionnaire and the functional status scale (FSS) part of the Boston CTS questionnaire. These findings suggest that the progression of the disease and the decrease of sensory functions might affect everyday hand use of patients in a more coherent way, compared to the severity of symptoms, that are known to be intense in the beginning of the disease as well (112). According to our knowledge, this was the first study that compared 2PD values to patient reported outcome measures.

Regarding demographic data, 2PD showed a significant positive correlation with the age of patients. This tendency is also noticeable in the general population. Studies published by van Nes et al. (113), Shimokata et al. (114) and Bowden et al. (115) stated in agreement that 2PD values increase with age. Although measuring methods slightly differed, van Nes et al. (113) showed that 2PD values are expected to be between 8-9 mm for patients over the age of 80. Being aware that for elderly patients 2PD values that are considered pathological for younger patients, might be still within normal limits, clinicians can have a more individualized assessment of the sensory function of the hand. Our analysis did not find significant differences between male and female patients regarding 2PD values. The differences reported by the previously mentioned studies (113-115) between male and female patients were also non-significant. The duration of the symptoms did not seem to have a significant effect 2PD values. This relationship was not examined by other studies.

9.2. Strengths

The strength of our meta-analysis is the inclusion of a large number of eligible studies, examining three types of ligamentous injuries (TFCC, SL and LT ligament). According to our knowledge this is the most comprehensive review in this topic, analysing several technical aspects of the MRI.

Our clinical cohort study’s strength is in its prospective nature, that allowed us the systematic collection of valuable datapoints during physical examination. Comparing

2PD values to the findings of peripheral nerve ultrasound and of electrophysiological studies, as well as to patient reported outcome measures and demographic data, gave a complex validity to the use of 2PD measurements as a screening method during physical examination. This study is also aiming to estimate 2PD thresholds for different CTS severity categories.

Findings of both studies have the capacity to facilitate evaluation of diagnostic tests during the everyday clinical practice of hand surgeons, contributing to more effective patient care.

9.3. Limitations

Our research was limited by the heterogeneity of the included studies, regarding study designs, technical conditions and the use of different classification systems to assess the severity of ligamentous injuries. The effects of different technical conditions were analysed separately; however, it is possible that different conditions had an overlapping influence on the diagnostic performance that our study was unable to detect. As technical settings of MRI evolve rapidly, we were unable to distinguish between different types of wrist coil and 3D sequences. This study only assessed the diagnostic accuracy of native MRI. Though magnetic resonance arthrography (MRA) and the use of intravenous contrast materials are often used in the radiological diagnostic procedure, we have decided to focus on the native MRI due to its wider availability and non-invasive nature.

Our prospective cohort studies also had limitations. First, as all included patients underwent operative treatment, patients with mild symptoms were underrepresented. Nerve conduction studies were performed at several different locations, by different physicians, leading to heterogeneity in outcome measures and severity classifications. In many cases severity was determined taking into account the results of both EMG and ENG findings, whereas 2PD values gave information only about the sensory function. This explains at least partially the fact that correlation between 2PD and severity categories tough significant, were not robust.

10. CONCLUSIONS

MRI is a clinically reliable imaging modality in the preoperative diagnosis of wrist ligamentous injuries. Observed tendencies suggest highest accuracy in diagnosing TFCC injuries and decreased performance of low field imaging. However, significant differences were not detected between the examined subgroups based on technical conditions and anatomic location.

2PD measurement is quick, easily applicable diagnostic method, that has the power to act as a screening examination for potentially severe carpal tunnel syndrome, despite its lower accuracy compared to the gold standard electrophysiological examination. Its objective and cost-effective characteristic makes it ideal for follow-up evaluation of the sensory function of the hand as well.

11. IMPLEMENTATIONS FOR PRACTICE

Wrist MRI has the most reliable results for TFCC central and peripheral tears. Tough wrist MRI has an acceptable overall diagnostic accuracy; we advise physicians to correlate the results to the findings of physical examination as well, especially in case of SL and LT ligament tears. When in doubt, 3T MRI might offer more accurate results for the SL ligament injury, however the difference between 1.5T and 3T MRI was not significant in our study, therefore, in most cases 1.5T field strength seems to be sufficient to detect wrist ligamentous injuries.

We recommend the use of 2PD measurements as a screening method for severe CTS, as well as follow-up examination to assess sensory function of the hand in an objective and comparable way. We are convinced that this would contribute to a more effective scheduling of auxiliary diagnostic examinations as well as higher patient satisfaction and better surgical outcomes.

We hope that implementing our findings into the everyday practice will raise the standard of care and contribute to better results in diagnosing and follow-up of wrist ligamentous injuries and carpal tunnel syndrome.

12. IMPLEMENTATION FOR RESEARCH

Methodology issues

Our meta-analysis highlighted the heterogeneity of studies investigating the diagnostic accuracy of wrist MRI for ligamentous lesions, regarding study design and classification of the injuries. For the generalizability and comparability of the findings, we advise researchers to report in detail if they have investigated full-thickness or partial ligament tears and the location of these injuries, as it might influence surgical indication. Publishing detailed technical settings of the MRI would also help reproducibility and the finding of the most adequate setting. Blinding radiologists to clinical findings and hand surgeons to the findings of MRI would increase the validity of the reported MRI accuracy, though we understand the challenges of such a design in a clinical context.

Study design

Prospective clinical studies though time-consuming, have more control over the examined variables, limiting the number of missing datapoints in research focusing on detailed questions.

For 2PD measurements, a large-scale prospective study of the general population and of patients with CTS would increase our knowledge on the effect of age and possibly other factors, such as the presence of certain comorbidities on 2PD values, providing additional information in establishing threshold values to detect alarming sensory loss.

New aspects

Cooperation between medical specialties has a crucial importance in advancing both clinical research and everyday care of our patients. Developing internal guidelines and a structured report of findings of the physical examination, imaging modalities and nerve conduction studies would contribute to a more focused diagnostic procedure and the creation of high-quality databases, allowing precise prospective and retrospective clinical research. The correlation of arthroscopic and radiologic classification systems for wrist ligamentous injuries would also have a positive impact on surgical decision-making and pre-operative planning.

13. IMPLEMENTATION FOR POLICYMAKERS

Following physical examination, availability of auxiliary examinations, such as MRI, nerve conduction studies and peripheral nerve ultrasound often delays the selection of the most adequate care for patients.

Wrist MRI has an important role in the diagnosis of ligamentous injuries. This imaging modality is crucial to establish an adequate treatment plan and to indicate necessary surgical intervention in a timely manner to prevent long-term negative effect on the wrist joint.

Increasing availability of nerve conduction studies and peripheral nerve ultrasound, and the possibility to accelerate these examinations for patients with potentially severe CTS would contribute to higher patient satisfaction and overall better clinical results.

Therefore, we advise policymakers to increase availability of the above-mentioned diagnostic modalities.

14. FUTURE PERSPECTIVES

Based on the findings of our meta-analysis, we plan to conduct a prospective clinical study, comparing the efficacy of wrist MRI with different technical settings for different suspected ligamentous lesions. We plan to assess the additional value of structural reporting of physical examination, radiological findings and the results of wrist arthroscopy. We also plan to compare the rate of incidental findings on 1.5T and 3T MRI in view of the risk of potential overdiagnosis and indication of additional treatment options.

We plan to examine the validity of 2PD measurement by increasing our study population and by extending it to patients with mild symptoms, for whom carpal tunnel release surgery was not yet indicated. A meta-analysis reviewing the variability of 2PD values in regard of demographic data, the presence of comorbidities (e.g. diabetes) and vibration exposure is also part of our plans in connection with our research.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

1. **Hergár L**, Kovács N, Agócs G, Weninger V, Skaliczki G, Lutz E, Hegyi P, Kovács BK, Hetthéssy JR.
   No Evidence for the Superiority of 3 Tesla Magnetic Resonance Imaging Over 1.5 Tesla Magnetic Resonance Imaging for Diagnosing Wrist Ligamentous Lesions: A Systematic Review and Meta-analysis.
   ARTHROSCOPY 2024 Nov;40(11):2730-2741.e10.
   doi: 10.1016/j.arthro.2024.04.029. Epub 2024 May 10. PMID: 38735416.

D1, IF: 5.4

2. **Hergár L**, Agócs G, Váncsa S, Hegyi P, Hetthéssy JR.
   Assessing the severity of carpal tunnel syndrome during physical examination by measuring two-point discrimination: Post-hoc analysis of prospectively collected data.
   INJURY 2024 Sep;55 Suppl 3:111536.
   doi: 10.1016/j.injury.2024.111536. Epub 2024 Sep 17. PMID: 39300627.

Q1, IF: 2.0

16.2. Publications not related to the thesis

1. Weninger V, Agócs G, Kovács N, Váncsa S, **Hergár L**, Baek CJ, Hegyi P, Holnapy G, Skaliczki G.
   Hyaluronate Acid Plus Platelet-Rich Plasma Is Superior to Steroids for Pain Relief Less Than 6 Months Using Injection Therapy of Partial Rotator Cuff Tears: A Systematic Review and Network Meta-analysis.
   ARTHROSCOPY 2025 Feb;41(2):304-315.
   doi: 10.1016/j.arthro.2024.03.035. Epub 2024 Apr 9. PMID: 38599539.

D1, IF: 5.4

2. Kocsis K, Stubnya B, Váncsa S, Kói T, Kovács N, **Hergár L**, Hetthéssy J, Holnapy G, Hegyi P, Pap K.
   Diagnostic accuracy of ultrasonography in acute lateral ankle ligament injury: A systematic review and meta-analysis.
   INJURY 2024 Sep;55 Suppl 3:111730.
   doi: 10.1016/j.injury.2024.111730. Epub 2024 Sep 17. PMID: 39300628.

Q1, IF: 2.0

3. Hetthéssy JR ; **Hergár L.**
   Hatástanulmány a nyeregízületi arthrosis intraarticularis hialuronsavas kezeléséről Sinoval HL® injekcióval
   MAGYAR TRAUMATOLÓGIA ORTOPÉDIA KÉZSEBÉSZET PLASZTIKAI SEBÉSZET 66 : 1-4 pp. 31-37. , 7 p. (2023)
   doi: 10.21755/MTO.2023.066.0104.003

IF: -

4. Sallai P, Sebők B, **Hergár L,** Hetthéssy JR.
   Trigger finger and carpal tunnel syndrome: a meta-analysis of co-occurrence and risk.
   J Plast Surg Hand Surg. 2025 May 5;60:102-108.
   doi: 10.2340/jphs.v60.43199. PMID: 40323072.

Q2, IF: 0.9

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