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Carpal tunnel syndrome in rheumatoid arthritis patients: the role of combined ultrasonographic and electrophysiological assessment

Wafaa Mahmoud*, Mona Mansour Hassab El-Naby and Ahmed Abdellatif Awad

Abstract

Background: Carpal tunnel syndrome (CTS) is known as one of the most common neurological extra-articular manifestations in rheumatoid arthritis (RA) patients. Studies on CTS in RA depend mostly on electrophysiological assessment. Few studies have used ultrasonography for evaluation of the local causes with much focus on wrist arthritis and tenosynovitis as the main cause of entrapment neuropathy of the median nerve in RA. The aim of our study is to assess the local causes of carpal tunnel syndrome in rheumatoid arthritis patients by ultrasonography and whether inflammatory or anomalous variations could affect decision-making and patient management.

Results: Carpal tunnel syndrome was diagnosed in 71 out of 74 examined RA wrists by nerve conduction studies (NCSs) and was categorized from minimal to severe according to Padua et al.'s (Ital J Neurol Sci 18:145–50, 1997) grading criteria. Median nerve CSA at the level of the carpal tunnel inlet and flattening ratio showed statistically significant relation with CTS severity. Bifid MN was found in 20 wrists (10 mild CTS wrists and 10 moderate CTS wrists), a persistent median artery was found in 4 wrists with moderate CTS, and an accessory muscle bundle was present in 3 wrists (2 mild CTS and 1 moderate CTS). The majority of the examined hands (85.1%) showed flexor tendon tenosynovitis at the wrist level and radio-carpal joint synovitis. The US7-joint score using GSUS7 & PDUS7 for synovitis, tenosynovitis and erosions showed significant relation with patients' disease activity by DAS28 score. Significant relations between CTS severity and the following nerve conduction studies' parameters, median nerve distal motor latency (DML), motor/sensory NCV, peak sensory latency, amplitude of SNAP, and median-radial latency difference test, were observed.

Conclusion: Synovial inflammation and local causes of median nerve compression such as bifid median nerve, persistent median artery, and accessory muscle bundle are collectively contributing factors in the etiology of carpal tunnel syndrome in rheumatoid arthritis patients. Ultrasonographic visualization of these inflammatory and anomalous variations enables early detection of CTS and highlights the possibility of non-arthritic-related causes. Using the 7-joint ultrasound (US7) score for assessment of synovitis, tenosynovitis, and erosions in rheumatoid arthritis patients is of valuable role in reflecting inflammation and its relation to the development of CTS in RA patients.

Keywords: Carpal tunnel syndrome, Rheumatoid arthritis, Ultrasonography, Nerve conduction studies

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Background

Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting the joints. It is the most common inflammatory polyarthritis seen in clinical practice which is characterized by a progressive symmetric inflammation of affected joints resulting in cartilage destruction, bone erosion, and disability [1]. Despite the fact that RA predominantly involves joints, it is a multi-systemic disorder that can affect cardiovascular, pulmonary, and nervous systems and skin [2]. Carpal tunnel syndrome (CTS) is the most common of all neurological extra-articular manifestations in RA [3]. CTS is a constellation of signs and symptoms, which can be explained by several pathological mechanisms, all contributing to the compression of the median nerve. Previous studies have shown that CTS in RA patients is mainly related to the inflammatory process in tendons, joints, and the median nerve itself [4], and the assessment of CTS was based mainly on clinical history, physical examination, and nerve conduction studies (NCSs) for diagnosis [5]. Although electrodiagnosis is the gold standard for diagnosing CTS, approximately 25% of patients presented with clinical CTS, show normal NCSs. Recently neuromuscular ultrasound (NMUS) has been increasingly used in the diagnosis of CTS (sensitivity: 77.6%; specificity: 86.8%) as it proved its ability to show carpal tunnel anatomy and morphological changes [6]. Our aim is to assess the local causes of CTS in rheumatoid arthritis patients using ultrasonography and how this could affect patients' management.

Patients and methods

Patients

This study was planned as a cross-sectional study. Thirty-seven patients who have been diagnosed as RA according to 2010 ACR/EULAR classification criteria [7], were recruited from the Physical Medicine, Rheumatology, and Rehabilitation department. An informed consent was obtained from each patient. Patients were excluded if they have a history due to any other known causative disorder such as hypothyroidism, gout, systemic lupus erythematosus, diabetes mellitus, chronic renal failure, cancer, acromegaly, history of CTS surgery, wrist fracture, and repetitive trauma to the hand and any orthopedic or neurologic disorders mimicking CTS such as brachial plexopathy, thoracic outlet syndrome, drug-induced neuropathy, and folic acid deficiency.

Methods

Clinical assessment

Demographic characteristics, body mass index (BMI), laboratory investigations, and treatment modalities were evaluated for each patient. Swollen and tender joint count, [erythrocyte sedimentation rate, global assessment visual analog scale (VAS 0–100 mm), and disease activity score (DAS 28) was calculated [8]. Health assessment questionnaire disability index (HAQ-DI) for RA was used for each patient [9]. Provocative tests for CTS including Phalen, Tinel, reversed Phalen, median nerve compression, and hand elevation test were applied to each hand [10]. The two Boston CTS questionnaire (BCTQ) scales were obtained from each patient; the functional scale (BQ-FSS) testing 8 items and the symptom severity scale (BQ-SSS) testing 11 items and the scores were assigned from 1 point (mildest) to 5 points (most severe). Each score was calculated as the mean of the responses of the individual items. Patients were divided into 4 groups according to their mean score: extreme (4.1–5.0 points), severe (3.1–4.0 points), moderate (2.1–3.0 points), and mild (1.1–2.0) points [11].

Nerve conduction studies

Patients were subjected to NCSs following the guidelines of the American Academy of Neurology and the American Association of Electrodiagnostic Medicine for diagnosis of CTS [12].

Electrophysiological studies were performed in a quiet room with a constant temperature sat at 25°C using a thermostat of air conditioners. Using NIHON KOHDEN (Neuropack) device. All patients were seated in a comfortable position with the forearm supinated. Skin temperature of the hand was maintained between 32.0 and 34.0 °C. All participants underwent median and ulnar nerve sensorimotor NCS for both hands. Standard techniques of supramaximal percutaneous stimulation were used. Ground electrode was placed over the dorsum of the hand. Any abnormalities in ulnar nerve conduction studies were excluded. Comparative studies were used including: median-radial peak sensory latency difference test (abnormal if >0.4ms) [13] and 2nd lumbrical-interosseous latency difference test (abnormal if > 0.5 ms) [14].

The severity of CTS was classified into 6 groups according to the grading scale by Padua et al. [15]:

- *Negative:* nerve conduction studies are normal, with no electrophysiological evidence of CTS.
- *Minimal:* exclusive abnormal segmental and/or comparative study
- *Mild:* abnormal digit-wrist conduction and normal DML
- *Moderate:* abnormal digit-wrist conduction and abnormal DML

- *Severe:* absence of sensory response and prolonged distal motor latency.
- *Extreme:* absence of motor and sensory response.

Ultrasound examination

Sonographic evaluation was performed by an expert sonographer using equipment (Logic P5 –R4.0, General Electric, Milwaukee, Wisconsin, USA) by a linear probe multi-frequency ranging from 7 to 13 MHz and blinded to the physical and electrophysiologic findings of the subjects. The sonographer who performed the study has over 10-year experience in the field of MSUS and NMUS and received training by EULAR certified tutors (high level of training). Each wrist was scanned in both longitudinal and transverse views as indicated by the 2017 EULAR standardized procedures for US imaging in rheumatology [16]. Patients were seated in a comfortable position facing the examiner, with the forearm resting on the bed and fingers in a neutral position.

The median nerve was assessed in the transverse section at the carpal tunnel inlet (the level of the pisiform bone) and 12 cm proximal to this point in the forearm. The cross-sectional area (CSA) of the MN was calculated using the continuous trace method by outlining the perimeter just inside the hyperechoic epineurium at the wrist and forearm. The CSA of any bifid/trifid nerve was calculated by adding the individual CSAs of the 2 components. Other neuromuscular parameters were evaluated such as: wrist-to-forearm ratio (normal up to 1.4), echogenicity, flattening ratio (width/height) (normal up to 3:1), and mobility of the median nerve (it was examined by asking the patient to flex and extend the fingers and wrist while observing the median nerve dives deep to the flexor tendons during finger and wrist flexion as an indicator of normal mobility). Notching of the median nerve (the notch sign) which is pathognomonic for ongoing compression was examined in the longitudinal section [17]. Muscle intrusion with wrist movement was observed as well.

The 7-joint US score (US7) was performed for 7 joints in each patient including the wrist, 2nd MCP, 3rd MCP, 2nd PIP, 3rd PIP, 2nd MTP, and 5th MTP. The sum of synovitis scores in the GSUS (0–27) and PDUS (0–39) modes, tenosynovitis in the GSUS (0–7) and PDUS (0–21) modes, and erosions (0–14) in the GSUS mode was calculated [18] and correlated with disease activity by DAS28 and CTS severity.

GSUS was performed as follows [18]:

Wrist joint

- In the dorsal aspect: the probe was parallel to the extensor digitorum tendons (dorso-median).
- In the palmar aspect: the probe was placed parallel to the median nerve (palmo-median).
- In the ulnar aspect: the probe was set parallel to the extensor carpi ulnaris tendon.

MCP2 and MCP3 joints:

- In the palmar view: for synovitis and tenosynovitis
- Erosions were detected from the dorsal, palmar, and radial (MCP2 joint) aspects, or from the dorsal and palmar aspects (MCP3 joint).

PIP2 and PIP3 joints:

- In the palmar view: for synovitis and tenosynovitis
- Erosions were detected from the dorsal and palmar aspects.

MTP2 and MTP5 joints:

- In the dorsal view: for synovitis
- Erosions were detected from the dorsal and plantar aspects (MTP2 joint) and from the dorsal, plantar, and lateral (MTP5 joint) aspects.

Synovitis by GSUS was analyzed semi-quantitatively:

0 = absence, 1 = mild (Grade 1 describes a small hypoechoic/anechoic line beneath the joint capsule), 2 = moderate (Grade 2: the joint capsule is elevated parallel to the joint area), 3 = severe synovitis (Grade 3 characterizes a strong distension of the joint capsule) [18].

Synovitis and tenosynovitis by PDUS were assessed from the palmar and dorsal aspects in each joint region evaluated, except for MTP joints from the plantar aspect only. It was scored semi-quantitatively as follows [19]:

- Grade 0 = no intraarticular color signal.
- Grade 1 = up to 3 color signals or 2 single and 1 confluent signal in the intraarticular area.
- Grade 2 = greater than grade 1 to <50% of the intraarticular area filled with color signals.
- Grade 3 = ≥50% of the intraarticular area filled with color signals.

Tenosynovitis and erosions were registered as being absent (0) or present (1). Erosion was defined as an interruption of the bone surface in 2 perpendicular planes and tenosynovitis as a hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath [20].

The US7 score includes a combination of semi-quantitative gray scale (GS) and PD findings obtained by a formula that includes the sum of different parameters. Its score ranges from 0 to 27 for GS and from 0 to 39 for PD [21]:

GS_synovitis (GSUS-score 7) = GS_ D_ wrist + GS_ P_ wrist + GS _U_ wrist + GS_ P_ MCP2 + GS _P_ MCP3 +GS_P_PIP2+GS_P_PIP3+GS_D_MTP2+GS_D_ MTP5=9 (scanning) ×3 (highest GS score 0–3)= 27.

PD_synovitis (PDUS-score 7) = PD_D_wrist+PD_P_wrist+ PD_U_wrist+PD_D_MCP2+PD_P_MCP2+PD_D_MCP 3+PD_P_MCP3+PD_D_PIP2+PD_P_PIP2+PD_D_PIP3+PD_P_ PIP3+PD_D_MTP 2 +PD_D_MTP5=13 (scanning)×3 (highest PD score 0–3)=39.

Statistical analysis

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, and inter-quartile range (IQR) when data were found non-parametric. Also, qualitative variables were presented as numbers and percentages.

The comparison between groups regarding qualitative data was done by using the *chi-square test* and/or *Fisher's exact test* when the expected count in any cell was found less than 5.

The comparison between two independent groups with quantitative data and parametric distribution was done by using *independent t-test* while non-parametric distribution was done by using the *Mann-Whitney test*.

The comparison between more than two groups regarding quantitative data and parametric distribution was done by using *one-way ANOVA test* while non-parametric distribution was done by using the *Kruskal-Wallis test*.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following:

P value > 0.05: Non significant (NS)
P value ≤ 0.05: Significant (S)
P value ≤ 0.01: Highly significant (HS).

Results

This study was conducted on 74 wrists of 37 rheumatoid arthritis patients recruited from the Physical Medicine, Rheumatology & Rehabilitation Department, from June 2021 to January 2022. The participants included 31 females (83.8%) and 6 males (16.2%), with a mean age of 48.5±9.3 (range 32–65) and a mean disease duration of 13.24 ± 5.78. Twenty-five of the patients had a positive family history of rheumatoid arthritis, RF was positive in 32 patients (86.5%). Anti-CCP was positive in 31 patients (83.7%) [30 of them had bilateral CTS, 1 had unilateral CTS] and negative in the remaining 6 patients [4 of them had bilateral CTS, 2 had unilateral CTS]. Modified DAS28 score had a mean of 5.68 ± 0.98, where 25 patients (67.6%) had high disease activity and 12 patients (32.4%) had moderate disease activity. Patients on only conventional synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs) represented 48.6% and those on a combination of conventional and biologic DMARDs were 52.4 and had lower disease activity. The demographic and clinical characteristics were shown in Table 1.

Our study showed statistically significant relation between patients' disease activity by DAS28 score and the (HAQ-DI) score, which had a mean of 2.31 ± 0.39. As for BCTQ functional and severity scales, it showed a mean of 2.97 ± 0.73 and 3.23 ± 0.76, respectively. The functional status using BCTSQ could not be accurately assessed and might be over-evaluated due to the overlap between symptoms of arthritis and CTS in terms of pain and weakness. Provocative tests for CTS showed positive Tinel's sign in 50 wrists (67.6%), positive Phalen test in 29 wrists (39.2%) and positive reversed Phalen in 43 wrists (58.1%). The clinical questionnaires and provocative tests are shown in Table 2.

CTS was diagnosed in 71 RA wrists out of 74 (95.9%) and were classified using Padua L et al.'s [15] grading criteria into normal: 3 wrists (4.1%), minimal: 7 wrists (9.5%), mild: 40 wrists (54.1%), moderate: 21 wrists (28.4%), and severe: 3 wrists (4.1%). According to previous findings, the majority of our RA patients had CTS, which resulted in minor discrepancies in the demographic and clinical data of those with CTS and those without. Our study revealed a significant relation between median nerve delayed distal motor latency (DML), slowing in motor or sensory NCV, delayed peak latency, and decreased amplitude of SNAP of the median nerve and the severity of CTS ($p \leq 0.05$). The mean DML of MN in our study was 3.40 ± 0.25 in mild CTS, 5.14 ± 0.53 in moderate CTS, and 6.23 ± 1.17 for the severe group. In this study, we used the 2nd lumbrical-interosseous latency difference test with a cutoff value (> 0.5) as a median-ulnar comparative test to diagnose CTS. However, it did not yield a significant relation with CTS. Also, a significant relation between CTS severity and median-radial sensory latency difference test was obtained. The previous electrodiagnostic findings are demonstrated in Table 3.

Ultrasound examination revealed synovitis in radiocarpal (RC) joint and flexor tendons in 63 wrists (85.1%) (Figs. 1 and 2). The 7-joint US assessment showed a mean sum score of GSUS synovitis and tenosynovitis of 7.09 ± 2.80 and 3.82 ± 1.35, respectively. PDUS for synovitis

Table 1 Demographic and clinical data of the studied patients

	No. = 37
Sex	
Female	31 (83.8%)
Male	6 (16.2%)
Age (Years)	
Mean ± SD	48.51 ± 9.31
Range	32–65
Disease duration (Years)	
Mean ± SD	13.24 ± 5.78
Range	5–28
Family history	
Negative	25 (67.6%)
Positive	12 (32.4%)
Rheumatoid factor	
Negative	5 (13.5%)
Positive	32 (86.5%)
BMI (Kg/m2)	
Mean ± SD	31.85 ± 7.71
Range	22–46.6
Morning stiffness (mins)	
Median (IQR)	30 (15–30)
Range	15–60
Deformities	
Present	17 (45.9%)
Absent	20 (54.1%)
ESR (mm/hr)	
Mean ± SD	47.16 ± 19.70
Range	20–95
CRP (mg/l)	
Median (IQR)	12(7.7–20.9)
Range	2.9–70.2
Medication	
cs DMARDS	18 (48.6%)
cs DMARDS+ Anti-TNF	19 (51.4%)
Tender joint count (Joints)	
Mean ± SD	10.51 ± 4.06
Range	1–19
Swollen joint count (Joints)	
Mean ± SD	7.14 ± 3.39
Range	1–15
VAS	
Mean ± SD	65.14 ± 13.87
Range	40–90
Modified DAS	
Mean ± SD	5.68 ± 0.98
Range	3.8–7.05
Classification of modified DAS score	
High	25 (67.6%)
Moderate	12 (32.4%)

Table 2 Clinical questionnaires and provocative tests

HAQ-DI score	Mean ± SD	2.31 ± 0.39
	Range	1.5–3
HAQ-DI classification	Mild to Moderate	0 (0.0%)
	Moderate to severe	15 (40.5%)
	Severe to very severe	22 (59.5%)
BCTQ-Functional status scale (FSS)	Mean ± SD	2.97 ± 0.73
	Range	1.3–4.1
BQ-FSS classification	Mild	5 (13.5%)
	Moderate	13 (35.1%)
	Severe	17 (45.9%)
	Extreme	2 (5.4%)
BCTQ-Symptoms severity scale (SSS)	Mean ± SD	3.23 ± 0.76,
	Range	1.5–4.5
BQ-SSS classification	Mild	4 (10.8%)
	Moderate	8 (21.6%)
	Severe	19 (51.4%)
	Extreme	6 (16.2%)
Tinel's sign	Negative	24 (32.4%)
	Positive	50 (67.6%)
Phalen Test	Negative	45 (60.8%)
	Positive	29 (39.2%)
Reversed Phalen	Negative	31 (41.9%)
	Positive	43 (58.1%)
Median n. compression	Negative	53 (71.6%)
	Positive	21 (28.4%)
Hand elevation test	Negative	65 (87.8%)
	Positive	9 (12.2%)

showed a mean sum score of 4.70 ± 1.70 (Fig. 3) and PDUS tenosynovitis showed a median (IQR) of 2 (2–4). The erosion sum score had a median (IQR) of 2 (1–4) (Fig. 4). The previous findings were statistically related with RA disease activity by DAS28 score. Additionally, a highly significant relation between the severity of CTS and each of GSUS synovitis ($p = 0.009$), tenosynovitis ($p = 0.001$), and erosions sum score ($p = 0.014$) was observed. On the contrary, no relation between CTS severity and RC joint/flexor tendon synovitis was detected, although 95.2% of patients with moderate CTS had RC joint/flexor tendon synovitis and 71% of patients with mild CTS had RC joint/flexor tendon synovitis. This result could be attributed to the small number of normal patients (3 patients). Ultrasound findings in RA patients and their relation to CTS severity are shown in Table 4.

This study showed larger CSA of the MN at the level of carpal tunnel inlet in RA patients with electrophysiological CTS in comparison to normal ones

Table 3 Relation between carpal tunnel syndrome severity and electrodiagnostic findings

Median NCS wrist	Severity of CTS					Test value	*P*-value	Sig.
	Normal	Minimal	Mild	Moderate	Severe			
	No. = 3	No. = 7	No. = 40	No. = 21	No. = 3			
DML (ms) at wrist								
Mean ± SD	3.00 ± 0.20	3.16 ± 0.18	3.40 ± 0.25	5.14 ± 0.53	6.23 ± 1.17	99.499[a]	0.000	HS
Range	2.8–3.2	3–3.5	2.8–3.9	4.5–6.5	5.2–7.5			
CMAP amplitude (mv)								
Mean ± SD	10.13 ± 3.00	10.46 ± 2.57	9.89 ± 3.16	8.20 ± 2.51	6.37 ± 0.58	2.300[a]	0.067	NS
Range	7.2–13.2	8.9–16	5.2–18.1	4.8–13.2	5.7–6.7			
Motor NCV (m/s)								
Mean ± SD	54.87 ± 2.41	57.44 ± 4.57	56.18 ± 7.04	48.88 ± 7.49	47.33 ± 2.08	5.156[a]	0.001	HS
Range	52.1–56.5	52–61.8	42.3–73.3	36–61.8	45–49			
SPL (ms)								
Mean ± SD	2.80 ± 0.36	2.91 ± 0.53	3.10 ± 0.53	3.87 ± 0.71	0.00 ± 0.00	31.032[a]	0.000	HS
Range	2.5–3.2	2–3.8	2.12–3.8	2.6–4.7	0–0			
SNAP amplitude (uv)								
Mean ± SD	37.03 ± 17.05	23.84 ± 5.44	23.48 ± 7.70	15.15 ± 6.82	0.00 ± 0.00	13.415[a]	0.000	HS
Range	19.3–53.3	18.1–34.9	8.9–42	8.7–35.8	0–0			
Sensory NCV (m/s)								
Mean ± SD	49.47 ± 5.46	49.74 ± 10.01	40.34 ± 9.25	29.99 ± 4.56	0.00 ± 0.00	28.106[a]	0.000	HS
Range	43.2–53.2	27.9–56.1	25–58.4	24–37.6	0–0			
Median-Radial thumb latency difference (>0.4)								
Median (IQR)	-0.2 (-0.4– -0.2)	0.8 (0.5–0.9)	0.6 (-0.3–0.6)	0.8 (-0.1–0.8)	0 (0– 2.4)	17.402[b]	0.002	HS
Range	-0.4–-0.2	0.5–0.9	-0.6–0.8	-0.3–1.5	0–2.4			
2[nd]lumb-1st IO latency difference (>0.5)								
Median (IQR)	0.3 (0.3–0.5)	0.3 (0.3–0.3)	0.25 (0.12–0.6)	0.4 (0.4–0.4)	0.4 (0.4–0.7)	7.522[b]	0.111	NS
Range	0.3–0.5	0.3–0.9	0.1–3.3	0.1–0.9	0.4–0.7			

P value ≤0.05: *S* Significant

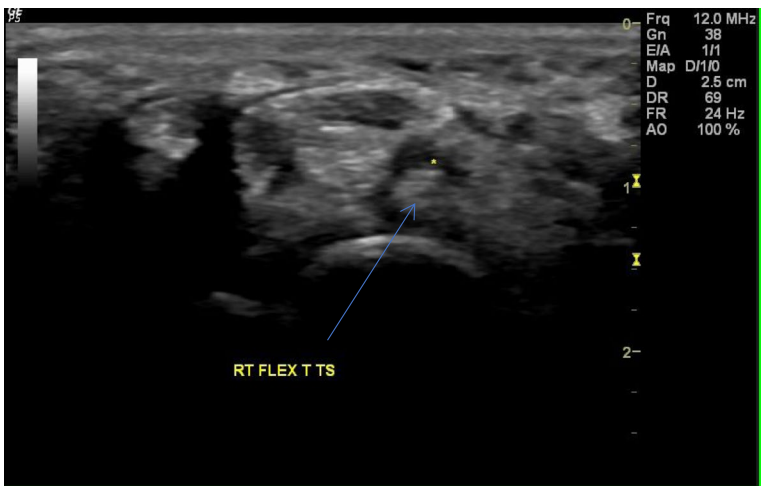

Fig. 1 Ultrasound scan showing gray scale ultrasound transverse palmar scan of the median nerve with flexor tendon below the nerve at the carpal tunnel showing the hypoechoic area surrounding the flexor tendon (blue arrow) indicating flexor tendon (FT) tenosynovitis (yellow star)

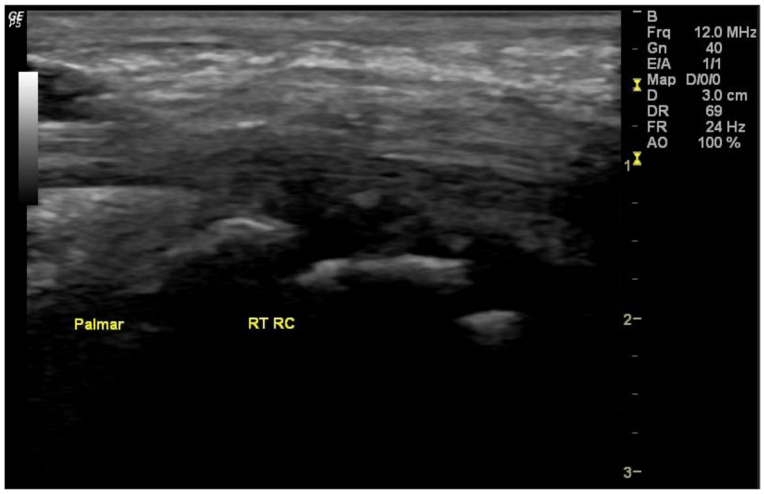

Fig. 2 Ultrasound scan of a patient (4) with disease activity score (DAS28) = 5.67 showing longitudinal gray scale ultrasound scan of the right radiocarpal (RC) joint nondisplaceable, poorly compressible tissue occupying the joint space and distending the capsule

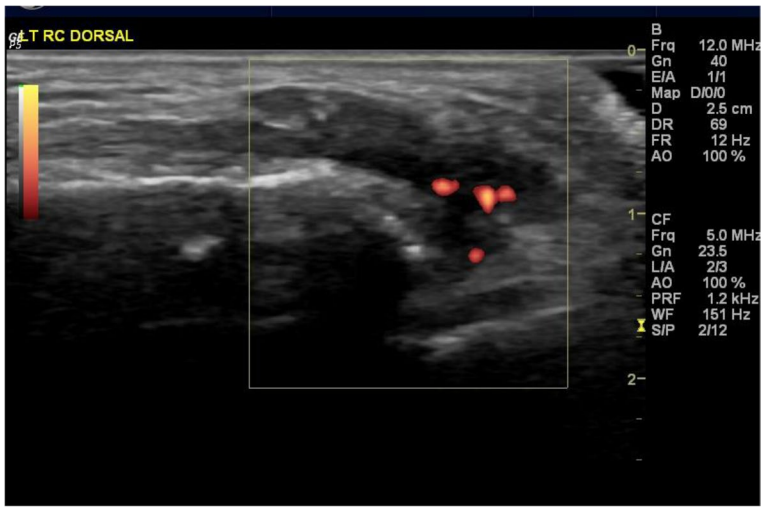

Fig. 3 Ultrasound scan of a patient with disease activity score (DAS) 28 = 6.4 showing power Doppler (PD) longitudinal dorsal scan of left radiocarpal (RC) joint with positive power Doppler signal Grade II

with a mean CSA in RA wrists without CTS (7.67 ± 1.15), and in minimal CTS (9.14 ± 1.77), mild (9.63 ± 2.79), moderate (11.60 ± 2.76), and severe (21.00 ± 6.93) (Fig. 5). The flattening ratio (FR) (width/height) of the MN was also related to the severity of CTS (p = 0.008) with a mean of 2.09 ± 1.04, 2.93 ± 1.08, and 3.43 ± 1.62 in mild, moderate, and severe CTS, respectively. Mobility of the MN was affected in 21 wrists that showed impaired mobility and it was not related to CTS severity. Bifid MN was found in 20 wrists (10 mild CTS wrists+ 10 moderate CTS wrists) (Fig. 6), persistent median artery was found in 4 wrists with moderate CTS, and accessory muscle bundle (FDS) was present in 3 wrists (2 mild CTS wrists+ 1 moderate CTS) (Fig. 7). Notch sign was seen in 14 wrists only (Fig. 8). NMUS findings and their relation with CTS are shown in Table 5. As for the relation between (CSA of MN at the wrist) and DAS28, disease duration, and functional status by BCTQ as well as severity scale by BCTQ, the median nerve CSA was not related to any of them except for the severity scale by BCTQ, which was shown in Table 6.

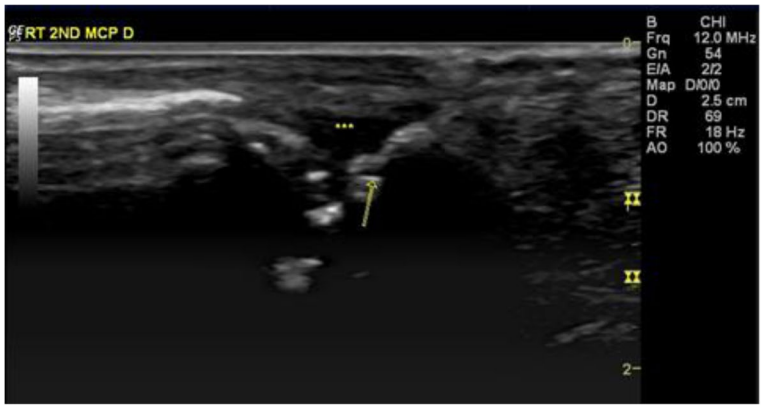

Fig. 4 Longitudinal gray scale ultrasound scan of the dorsal surface of right 2nd metacarpophalangeal (MCP) showing hypoechoic partially displaceable, poorly compressible tissue occupying the joint space and distending the capsule. Also, there are multiple areas of intraarticular discontinuity of the cortical bony surface (erosions) (yellow arrow), also seen in the transverse section (TS)

Table 4 Relation between ultrasound findings (including the US7 joint score) and carpal tunnel syndrome severity

Ultrasound findings	Severity of CTS					Test value	*P*- value	Sig.
	Normal	Minimal	Mild	Moderate	Severe			
	No. = 3	No. = 7	No. = 40	No. = 21	No. = 3			
RC joint/ flexor tendon synovitis								
Present	3 (100.0%)	6 (85.7%)	31 (77.5%)	20 (95.2%)	3 (100.0%)	4.586	0.332	NS
Absent	0 (0.0%)	1 (14.3%)	9 (22.5%)	1 (4.8%)	0 (0.0%)			
The US7 Joint score								
Synovitis GSUS7 sum score (0–27)								
Mean ± SD	6.33 ± 2.89	7.14 ± 4.06	6.18 ± 2.58	8.81 ± 2.14	8.00 ± 1.73	3.643	0.009	HS
Range	3–8	3–14	2–12	4–11	7–10			
Synovitis PDUS7 Sum score (0–39)								
Mean ± SD	3.67 ± 2.31	3.71 ± 1.38	4.55 ± 1.75	5.33 ± 1.53	5.67 ± 0.58	2.016	0.102	NS
Range	1–5	2–6	1–8	3–7	5–6			
Tenosynovitis GSUS7 Sum score (0–7)								
Mean ± SD	3.33 ± 1.15	3.86 ± 1.21	3.53 ± 1.28	4.05 ± 1.16	6.67 ± 0.58	4.951	0.001	HS
Range	2–4	2–6	1–7	2–6	6–7			
Tenosynovitis PDUS7 sum score (0–21)								
Median (IQR)	2 (1–3)	3 (2–4)	2 (2–4)	2 (2–5)	5 (3–5)	4.436	0.350	NS
Range	1–3	1–5	0–8	1–8	3–5			
Erosions Sum score (0–14)								
Median (IQR)	0 (0–2)	2 (1–2)	2 (1–4)	4 (2–5)	5 (5–5)	12.462	0.014	S
Range	0–2	0–4	0–6	0–6	5–5			

P value ≤0.05: *S* Significant

Discussion

CTS is known as one of the most common neurological extra-articular manifestations in RA patients. Diagnosis of CTS in RA mostly depends on electrophysiological assessment. There are a limited number of studies on the ultrasonographic evaluation of the median nerve and wrist region which focused on the detection of inflammation and local causes of entrapment. The aim of our study is to assess the local causes of carpal tunnel syndrome in rheumatoid arthritis patients by ultrasonography and how that could affect patients' management.

In this study, CTS was diagnosed in 71 RA wrists out of 74 (95.9%). This high incidence disagreed with other

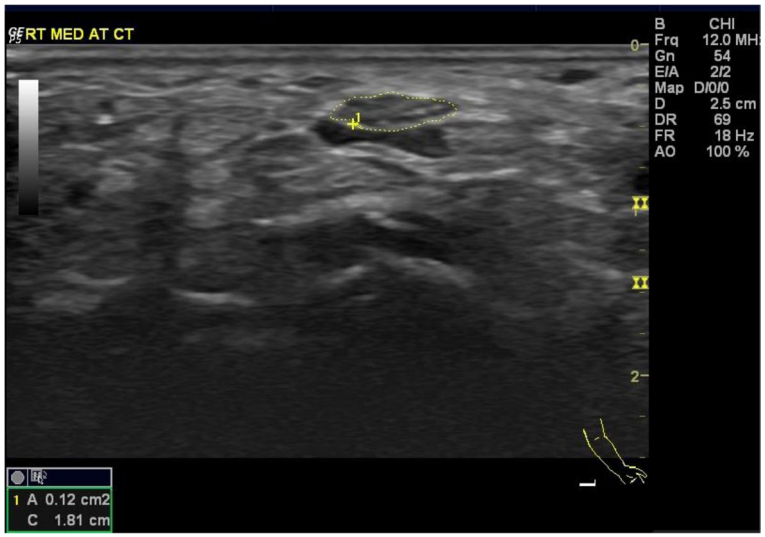

Fig. 5 Patient with disease activity score (DAS28) = 4.8 showing gray scale ultrasound of right median nerve at the level of the wrist with the cross-sectional area (CSA) (12mm^2)

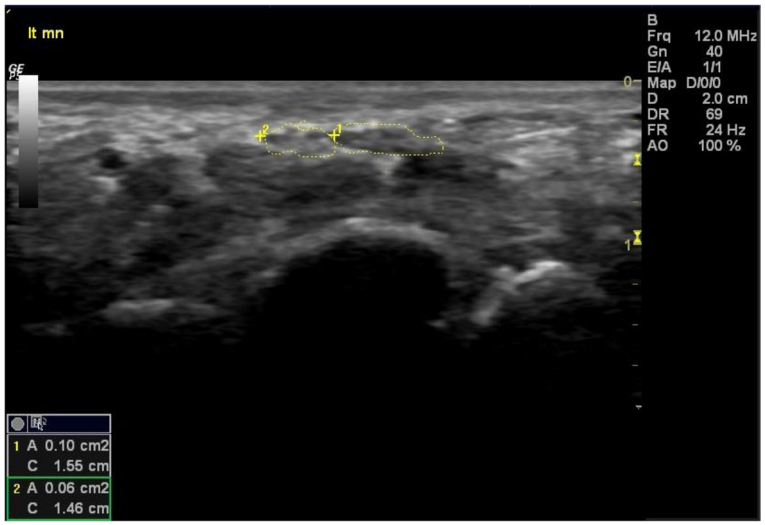

Fig. 6 Ultrasound of patient with disease activity score (DAS28) = 5.67 showing left bifid median nerve at the carpal tunnel level with the total cross-sectional area (CSA) (16mm^2)

studies that used US for assessing CTS in RA patients, such as Smerilli et al. [4] who reported a clinical diagnosis of CTS in RA patients in 23 wrists out of 114 (20.2%). Also, Karadag et al. [22] reported that CTS was found in 30 of 200 wrists in the RA group (15%) [12 mild (6%), 10 moderate (5%), 8 severe (4%)]. This disagreement could be explained by the fact that we used a more accurate methodology (Grading criteria by Padua et al. [15]) that diagnosed minimal affection of CTS in 7 cases, while Karadag et al. [22] used a classification criteria that did not include minimal cases (only mild, moderate and severe) and Smerilli et al. [4] graded them according to the historical-objective scale based on clinical assessment, not electrophysiological assessment. It might also be attributed to the larger sample size in their studies.

The presence of autoantibodies such as rheumatoid factors (RF) and Anti-CCP in RA patients is associated with a more severe course of the disease and multiple extra-articular manifestations [23]. In this study, rheumatoid factor (RF) was positive in 86.5% of all patients

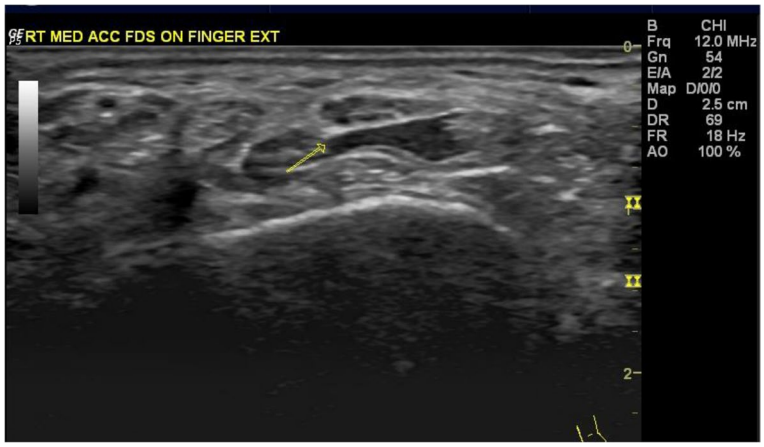

Fig. 7 Transverse section of the median nerve at the carpal tunnel showing intrusion of muscle fiber on the extension which appears hypoechoic (yellow arrow) and disappears on flexion of the fingers and wrist as the muscle contracts

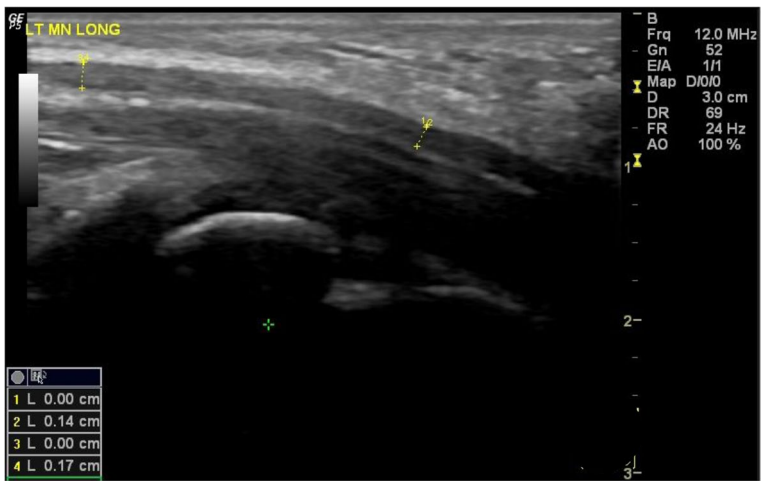

Fig. 8 Longitudinal section of left median nerve showing " notch sign" (abrupt reduction in the vertical dimension of the median nerve as it enters the carpal tunnel)

(with and without CTS), and it was classified as follows: RF (+ve) in 66.7% of patients without CTS, 66% (minimal CTS), 92.5% (mild CTS, 95.2% (moderate CTS) and 100% (severe CTS). This agreed with Kaya et al. [3] who reported positive RF in 72% of RA patients without CTS and in 50% of patients with mild CTS, 73.3% in moderate CTS, and 100% in severe CTS. It also agreed with Smerilli et al. [4] who reported RF positivity in 66.6 % in those without CTS and 71.4% of patients with CTS. As for Anti-CCP, it was positive in 31 patients (83.7%) [30 of them had bilateral CTS, 1 had unilateral CTS] and negative in the remaining 6 patients [4 of them had bilateral CTS, 2 had unilateral CTS]. This also agreed with Smerilli et al. [4] who reported Anti-CCP positivity to be more prevalent in RA patients with CTS than those without.

A significant relation between CTS severity and the following nerve conduction parameters: (median nerve distal motor latency (DML), motor/sensory NCV, peak sensory latency, amplitude of SNAP and median-radial latency difference test) was observed. This agreed with Lee et al. [24] in terms of the delayed sensory peak latency, slowing of motor NCV and decreased amplitude of the SNAP. Also, sensory (velocity, latency, and amplitude) and motor parameters (latency and amplitude) were significantly related to the clinical grading of severity (p-value < 0.001) in the study by Izadi et al. in 2018 [25]. A systematic review of literature by Demino and Fowler in [26] showed that the sensitivity and specificity of DML was found to be approximately 65% and 95%, respectively.

Table 5 Relation between carpal tunnel syndrome severity and neuromuscular ultrasound (NMUS) findings

Median nerve NMUS	Severity of CTS					Test value	*P*- value	Sig.
	Normal	Minimal	Mild	Moderate	Severe			
	No. = 3	No. = 7	No. = 40	No. = 21	No. = 3			
CSA (mm2) distal at wrist								
Mean ± SD	7.67 ± 1.15	9.14 ± 1.77	9.63 ± 2.79	11.60 ± 2.76	21.00 ± 6.93	12.756	0.000	HS
Range	7–9	7–11	5–14	7–16	13–25			
CSA (mm2) forearm								
Mean ± SD	8.67 ± 2.08	7.14 ± 1.86	8.03 ± 3.24	8.33 ± 1.85	14.67 ± 4.62	4.216	0.004	HS
Range	7–11	5–9	5–20	6–11	12–20			
Wrist :Forearm ratio (>1.4)								
Mean ± SD	0.92 ± 0.34	1.30 ± 0.18	1.30 ± 0.50	1.38 ± 0.31	1.60 ± 0.83	1.026	0.400	NS
Range	0.6–1.28	1.11–1.6	0.63–2.8	0.88–2.14	0.65–2.08			
Flattening ratio (>3)								
Mean ± SD	1.80 ± 0.20	1.86 ± 0.64	2.09 ± 1.04	2.93 ± 1.08	3.43 ± 1.62	3.755	0.008	HS
Range	1.6–2	1.3–3.2	1.12–5.3	1.3–4.3	2.5–5.3			
Echogenicity								
Normal	3 (100.0%)	7 (100.0%)	40 (100.0%)	21 (100.0%)	3 (100.0%)	–	–	–
Mobility								
Mobile	2 (66.7%)	4 (57.1%)	33 (82.5%)	12 (57.1%)	2 (66.7%)	5.289	0.259	NS
Impaired	1 (33.3%)	3 (42.9%)	7 (17.5%)	9 (42.9%)	1 (33.3%)			
Bowing of flexor retinaculum								
Present	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–
Absent	3 (100.0%)	7 (100.0%)	40 (100.0%)	21 (100.0%)	3 (100.0%)			
Notch sign								
Present	0 (0.0%)	1 (14.3%)	5 (12.5%)	7 (33.3%)	1 (33.3%)	5.123	0.275	NS
Absent	3 (100.0%)	6 (85.7%)	35 (87.5%)	14 (66.7%)	2 (66.7%)			
Accessory muscle								
Present	0 (0.0%)	0 (0.0%)	1 (2.5%)	2 (9.5%)	0 (0.0%)	2.413	0.660	NS
Absent	3 (100.0%)	7 (100.0%)	39 (97.5%)	19 (90.5%)	3 (100.0%)			
Persistent median artery								
Present	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (19.0%)	0 (0.0%)	10.672	0.031	S
Absent	3 (100.0%)	7 (100.0%)	40 (100.0%)	17 (81.0%)	3 (100.0%)			
Bifid MN								
Present	0 (0.0%)	0 (0.0%)	10 (25.0%)	10 (47.6%)	0 (0.0%)	9.413	0.052	NS
Absent	3 (100.0%)	7 (100.0%)	30 (75.0%)	11 (52.4%)	3 (100.0%)			
Ganglion cyst								
Present	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–	–
Absent	3 (100.0%)	7 (100.0%)	40 (100.0%)	21 (100.0%)	3 (100.0%)			

P value ≤0.05: *S* Significant

According to Moon et al. [27], median-radial sensory latency difference can give higher sensitivity than the conventional motor and sensory latency in diagnosing patients with CTS. This was in agreement with our study which showed significant relation between CTS severity and median- radial sensory latency difference [27]. In this study, we also used the 2nd lumbrical-interosseous latency difference test with a cutoff value >0.5 as a median-ulnar comparative test to diagnose CTS. However, it was not related to CTS severity. This might be due to the small latency differences in our results. This was in concordance with Yılmaz et al. [28], as in their CTS group, the mean difference was found to be (1.40 ms), whereas it was (0.12ms) in the control group, indicating a significant difference between the two groups ($p < 0.001$). The previous study was also in agreement with findings of Ozben et al. (2012), Kodama et al. (2014), and Banach et al. (2015) [29–31].

Table 6 Relation between Carpal tunnel syndrome ultrasound finding (CSA) and clinical parameters

	CSA (mm^2) distal at wrist	
	***P*-value**	**Significance**
Disease duration (Years)	0.255	NS
DAS 28	0.259	NS
BCTQ (Severity scale)	**0.017**	**S**
BCTQ (Functional scale)	0.110	NS

P value ≤0.05: *S* Significant

In the present study, we used the 7-joint US score as it combines soft tissue changes (synovitis and tenosynovitis) by gray scale (GS) and neovascularization by Power Doppler (PD) in addition to erosive bony changes and it reveals clinical correlation with diseases activity as well [21]. However, we performed the assessment for each hand separately in order to find how the 7 joint activity scores are related to different grades of nerve affection whether by EDX or to neuromuscular ultrasound parameters. There was statistically significant relation between the severity of CTS and each of GSUS7 synovitis ($p = 0.009$), tenosynovitis ($p = 0.001$), and erosions sum score ($p = 0.014$). To our knowledge, no previous studies demonstrated the relationship between the US7 score and CTS severity in RA patients. Moreover, there were statistically significant relation between the modified DAS28 score and synovitis sum score by GSUS7/PDUS7, tenosynovitis by PDUS7, and erosions sum score with p value of $p = 0.003$ and $p = 0.002$, and $p = 0.019$ and $p = 0.048$, respectively. This agreed with Zou et al. [32] where their US7 score was positively correlated with DAS28. This also came in accordance with Kamel et al. [21] where all clinical disease activity indices [CDAI (Clinical Disease Activity Index), GAS (global arthritis score) and RAPID3 (Routine Assessment of Patient Index Data 3)] were significantly positively correlated with GSUS7 and PDUS7 synovitis. This indicated that the use of the US7 joint score could add beneficial value in the assessment of RA disease activity, similar to DAS28 Zou et al. [32]. It also shows that activity of the wrist joints is related to the severity of CTS. As for the relation between CTS neuromuscular ultrasound findings (CSA of MN at the wrist) and DAS28, disease duration and functional status by BCTQ as well as severity scale by BCTQ, the median nerve CSA did not show in any relation with any of the above parameters except for the severity scale by BCTQ. However, we performed the BCTQ assessment for each hand separately in order to find how its scores are related to different grades of nerve affection whether by EDX or to neuromuscular ultrasound parameters. Disease activity was not related to CSA of the MN because disease activity is a rather status evaluation at the time of presentation while the CTS pathology physiological changes are due to increased pressure that happens gradually causing endoneural edema manifested by increased CSA by NMUS and segmental demyelination which appear in motor and sensory NCSs, reflecting a chronic process of the localized damage. As for the functional status using BCTQ, it could not be accurately assessed and might have overlapped with the symptoms of RA due to the similarity between those of arthritis and those of CTS in terms of hand pain, weakness, and disability. For the same previously mentioned reasons, the disease duration of CTS could not be well distinguished from that of arthritis by our RA patients, especially in subclinical CTS cases.

Regarding the etiology of CTS in this study, flexor tendons tenosynovitis and/or radio-carpal joint synovitis by US was found in 63 of the examined wrists (85.1%). A percentage of up to 95.2% of patients with moderate CTS had radio-carpal (RC) joint/flexor tendon synovitis and 71% of patients with mild CTS had RC joint/flexor tendon synovitis, while 100% of severe CTS cases had RC joint synovitis/flexor tenosynovitis. This agreed with Smerilli et al. [4] who reported a higher rate of inflammatory findings at carpal tunnel level (i.e. finger flexor tendons tenosynovitis and/or RC joint synovitis) in RA wrists with CTS compared with RA wrists without CTS (39.1% vs 15.4%) as well as a positive correlation between CTS and inflammatory finding ($p = 0.4$). In this study, the mean CSA of the median nerve at the wrist showed a statistically significant relation with CTS severity. This came in accordance with Kaya et al. [3] who reported mean CSA for normal RA wrists to be 8.31 ± 2.11, and those with mild CTS (8.5 ± 2.12), moderate (10.0 ± 2.32), and severe (11). This also agreed with the study by Smerilli et al. [4] which reported mean CSA in RA patients without CTS to be 8.6 ± 2.1 and with CTS (10.6 ± 4.2) and respectively. In addition to Karadag et al. [22] who reported median of CSA for RA wrists without CTS 9 (6.0–12.0) and with CTS 13.0 (9.0–15.3). Our study showed increased CSA of the MN in CTS wrists in comparison to wrists without CTS. This agreed with the study by Hammer et al. (2006), Karadag et al. (2012), Smerilli et al. (2021), and Kaya et al. (2021) [3, 4, 22, 33]. However, the mean CSA in our study showed higher values especially in the severe group than in the above-mentioned studies as our patients were either manual workers or housewives; they also had more active disease and longer disease duration compared to the fore mentioned studies.

In the present study, both CSA enlargement (up to 25mm^2 in severe CTS) and inflammatory findings were considered prominent features that were clearly detected

by US in the group of RA patients with CTS. While in the study by Smerilli et al. [4], marked median nerve swelling was the most dominant finding in idiopathic CTS (non-RA patients) with mean CSA (17.7 ± 4.5). On the other hand, synovial tissue inflammation at the carpal tunnel level was the most characteristic sonographic feature in RA patients with CTS. The fact that both features were apparent in our study might be due to the higher disease activity of RA in our study group and the small number of normal wrists. In the study by Aktürk et al. [6], the mean CSA of the median nerve at the forearm level showed no difference between those with CTS and controls. This came in contrast to our study which reported enlarged CSA proximally at the FA level in those with CTS [6]. This finding might suggest the presence of a proximal cause of entrapment (i.e., pronator syndrome) which might have been subclinical at the time of presentation with only symptoms similar to those of CTS (no forearm muscles weakness or wasting). Both CTS and pronator syndrome can coexist forming a sort of double crush syndrome [34]. This was in agreement with the study by Saba and Sultan [35] who reported that the patients with very mild and mild CTS electrophysiologically had no concomitant PS in contrast to patients with moderate to severe CTS who had electrophysiological evidence of pronator syndrome. The presence of advanced CTS manifestations and more CTS electrophysiological severity are indicators for searching for a proximal median entrapment neuropathy. Having risk factors that can cause a single lesion along the course of a nerve, make the nerve liable to a second lesion further along its course especially when it passes in an anatomical narrow segment. This confirms that overuse and repetitive movement of the upper limb (i.e., in the form of excessive work rates or duration of work, inadequate work breaks or rest periods, and monotonous work without task variations) are the predisposing factors of CTS as well as pronator syndrome. This notion highlights the significance of further investigating the nerve along its whole course with both ultrasonography and EDX for the detection of subclinical causes of entrapment, especially in populations with a background of occupational risk factors.

Using a single cut-off value to diagnose CTS might have underestimated the prevalence of CTS in a study population, given the variability of the median nerve among individuals with different body weight, age, and sex. Therefore, using CSA of the proximal median nerve at the forearm level as an internal control parameter has previously been proposed and proved of value. In this study, we used the cutoff value of the wrist-to-forearm ratio (WFR) (>1.4) as identified by Preston and Shapiro [17]. We found that the mean (WFR) in the group of patients with mild CTS (largest group) was 1.30 ± 0.50 and in patients without CTS, it was 0.92 ± 0.34, although it showed no significant relation with CTS severity.

Impaired mobility of the median nerve was observed in only 21 wrists and it was not related to CTS severity. This disagreed with Aktürk et al. [6], who reported decreased MN mobility in the CTS patient group. This could be explained by the higher number of normal hands (controls) in their study in relation to ours (only 3 hands), which resulted in a better comparative study.

In the present study, bifid MN was found in 10 wrists with mild CTS and 10 wrists with moderate CTS, however, it was not related to the severity of CTS. This came in accordance with Kasiu et al. [36] who used the same electrophysiological severity classification criteria as ours. The previous findings agreed with the results of Walker et al. [37] and Chen et al. [38] who found no association between either bifid MN and persistent median artery or the risk of development of CTS; additionally, they reported the likelihood of their coexistence of together [37, 38].

Persistent median artery was found only in 4 wrists with moderate CTS, and it was significantly related to its severity. This is mostly due to absence of persistent median artery in the remaining examined wrists (normal and CTS wrists). This condition could coexist with thrombosed persistent median artery as in the case study of a 39-year-old female patient with symptoms of CTS with thrombosed persistent median artery as a cause of compression, and was started on anticoagulants, as reported by Rzepecka-Wejs et al. [39].

In the current study, accessory muscle bundle was present in three of the studied wrists (1 mild) & (2 moderate) CTS and it was not related to CTS severity. Yet, one cannot ignore the value of its identification using dynamic ultrasonography, especially in severe cases undergoing surgical intervention with the persistence of symptoms. In the cohort by Vögelin et al. [40], 1 CTS wrist underwent surgical decompression without clinical improvement. Sonographic examination of the unimproved wrist showed a CSA of 16.5 mm^2 and an aberrant flexor muscle appearing as a hypoechoic mass which intruded into the carpal tunnel and compressed the MN on finger extension. Surgical resection of this aberrant flexor muscle of the index finger resulted in a better clinical outcome [40].

In view of the previous literatures and the present study we can point out to the importance of this study to emphasize that more than one cause for median nerve entrapment could be found in a case with clinically symptomatizing and electrophysiologically diagnosed CTS, here comes the importance of neuromuscular ultrasound which would reveal the presence of many of these causes which could affect the physician's decision if present and the surgical plan if indicated.

For a rheumatoid arthritis patient, the most common cause of CTS is active joint inflammation (i.e., synovitis and tenosynovitis) which requires a strict treat-to-target strategy; however, other causes such as bifid nerve, persistent median artery, and muscle intrusion could be an associated anomalous disorder that can exacerbate the condition if mechanical irritation to the nerve happens with any vocational or avocational activity that requires flexion-extension of the wrist and could result in increased pressure inside the tunnel/ flow of blood in a persistent artery or cause irritation of the nerve in case of bifid or trifid nerve or muscle intrusion. Control of disease activity, splinting, and avoiding mechanical irritation are the broad outlines of the first line of management in mild–moderate CTS. In case of severe affection which necessitates surgical management, the neuromuscular ultrasound is of great diagnostic value to give the surgeon a picture of the present anomalous variations that could be taken into account during surgical CT release operation. Control of the disease activity and the wrist and hand inflammation is important for an optimum surgical outcome to help speed recovery and prevent postoperative complications such as complex regional pain which is common to occur after surgery in a painful limb. The recent advances in ultrasonographic guided injections and the hydrodissection of the median nerve could be an option for cases having mild to moderate CTS. Furthermore, follow-up of the activity of RA and the response of treatment of CTS by ultrasonographic assessment is a noninvasive and easily accessible method.

Limitations

This study has its limitations including the small sample size and the lack of patient follow-up. Absence of inter readers and intrareaders reliability was also one of the study limitations. More attention should be given to the intraneural vascularity of MN by PD ultrasonography.

Future studies

Further future studies are recommended to be done on a larger number of patients with long-term follow-up to show how these patients will respond to different management protocols and better disease control. Also, it is interesting to examine the association between carpal tunnel and pronator syndrome in RA patients.

Conclusions

Although, electrodiagnosis is the gold standard for diagnosis of CTS, performing NMUS proved to be beneficial in revealing the etiopathogenesis of CTS, especially in the group of patients with rheumatoid arthritis where causes other than synovial inflammation must be put into consideration. Median nerve CSA, being higher in the CTS group, could be considered as an accurate predictor for the detection of CTS, especially in early subclinical cases with normal NCS. Using the US7 joint score in the assessment of synovitis, tenosynovitis, and erosions by grayscale and power Doppler US in RA patients proved valuable for monitoring disease activity and progression and reflects that the activity of the wrist and hand joints correlated with the severity of CTS.

Abbreviations

BCTQ: Boston Carpal Tunnel Questionnaire; b-DMARDs: Biologic disease-modifying anti-rheumatic drugs; BMI: Body mass index; CDAI: Clinical Disease Activity Index; CTS: Carpal tunnel syndrome; CSA: Cross-sectional area; cs-DMARDs: Conventional synthetic disease-modifying anti-rheumatic drugs; DAS: Disease activity score; DML: Distal motor latency; FSS: Functional severity scale; FT: Flexor tendon; GAS: Global arthritis score; GS: Gray scale; GSUS: Gray scale ultrasound; HAQ-DI: Health assessment questionnaire- disability index; MCP: Metacarpophalangeal; MTP: Metatarsophalangeal; MN: Median nerve; NCS: Nerve conduction study; NMUS: Neuromuscular ultrasound; PD: Power Doppler; PDUS: Power Doppler ultrasound; PIP: Proximal interphalangeal; RA: Rheumatoid arthritis; RAPID3: Routine Assessment of Patient Index Data 3; RC: Radiocarpal; SNAP: Sensory nerve action potential; SSS: Symptom severity score; TS: Transverse section; US: Ultrasound; WFR: Wrist to forearm ratio.

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Authors' contributions

All authors have contributed to designing the study, collecting and analyzing, interpreting the data, and preparing and revising the manuscript. Design of the study: WM, MM, and AA. Recruitment of patients: WM. Data collection: WM. Manuscript preparation and revision: WM, MM, and AA. All authors have approved the final version of the manuscript.

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Availability of data and materials

The data will be available upon request.

Declarations

Ethics approval and consent to participate

An approval was obtained from the ethics committee of the Faculty of Medicine, Ain Shams University and the approval number was (FWA 000017585). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Informed written consents were obtained from all patients.

Consent for publication

Not applicable.

Competing interests

Prof. Dr. Mona Mansour Hassab El-Naby is the chief editor at the journal "Egyptian Rheumatology and Rehabilitation".

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