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Original Research

Pregnancy Carpal Tunnel: Nerve/Tendon Ratio (NTR)—A New Paradigm

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Abstract

Background: Carpal tunnel syndrome (CTS) is a prevalent condition during gestation. The recent ability of ultrasound to provide comparable results with electrodiagnostic tests (EDx) has opened the door for investigating new parameters. The objective of this investigation is to explore the clinical importance of a new anthropometric independent parameter called the nerve/tendon ratio (NTR) when compared to EDx and to determine whether it has the utility to be used in clinical practice. **Methods**: In this prospective case-control study conducted between April 2023 and September 2023, 160 pregnant women displaying clinical symptoms of CTS who presented to the outpatient clinic underwent evaluation employing the Boston Carpal Tunnel Questionnaire, Visual Analog Scale, and provocative tests (Phalen and Tinnel). The pregnant women with clinical symptoms were divided into two groups: those with positive CTS in the EDx results (mild/moderate/severe) and those without EDx findings (control group). All pregnant women participating in the study had their median nerve cross-sectional area (MN-CSA), flexor carpi radialis (FCR), and MN-CSA/FCR ratio (expressed as a percentage called NTR) values examined. The sonographers were unaware of the clinical and EDx results. Subsequently, the data were examined utilizing logistic regression models, with a significance threshold established at $p < 0.05$. **Results**: In pregnant women with CTS, the MN-CSA values were observed to surpass those in the control cohort (10.03 ± 3.28 *vs.* 7.80 ± 2.50) ($p < 0.001$). The NTR values in the pregnant women with CTS were also higher than those in the control group (0.94 ± 0.39 *vs.* 0.81 ± 0.28) ($p = 0.045$). The best cut-off for MN-CSA values was calculated to be >8.5 mm^2. The best cut-off point for MN-CSA/FCR values was found to be $>0.82\%$. A receiver operating characteristic curve was generated, and the NTR cut-off point of 0.82% showed a sensitivity of 51.9% and a specificity of 67.9%. The positive predictive value and the negative predictive value were 61.2% and 59.1%, respectively, with the mentioned point as the diagnostic threshold (area under the curve 0.592 (95% confidence interval [CI]: 0.503–0.680)). Among ultrasound-related factors, patients with symptoms of CTS exhibited an association with MN-CSA (odds ratio [OR] of 6.396, 95% CI: 2.981–13.722). NTR was not identified as a risk factor for CTS ($p > 0.05$). **Conclusions**: Ultrasonography of the wrist may serve as an alternative diagnostic tool for CTS in pregnant women due to its rapid, non-invasive, and reproducible characteristics. Further research should focus on investigating the response to treatment. **Clinical Trial Registration**: the study was registered at https://clinicaltrials.gov (registration number NCT05839769).

Keywords: carpal tunnel syndrome; nerve/tendon ratio; median nerve; neuropathy; pregnancy; ultrasonography

1. Introduction

Carpal tunnel syndrome (CTS), the most prevalent mononeuropathy in pregnancy, arises from the compression of the median nerve as it traverses the carpal tunnel at the wrist. Clinically, individuals may experience hyperesthesia and paresthesia in the sensory distribution aligned with the median nerve in the hand. However, sensory manifestations were not confined solely to the territory of the median nerve but extended to extraterritorial areas, including those of the ulna and radial nerve territories in the hand [1]. In advanced instances, individuals might exhibit diminished strength in the intrinsic muscles of the hand, which are innervated by the median nerve [2]. The occurrence of CTS in the overall population varies between 1% and 5%. CTS is more widespread in females than males, with a female-to-male ratio of 3:1. The likelihood of developing CTS is twofold in individuals classified as obese [3]. The exact cause of pregnancy-related CTS (PRCTS) is not fully understood, but it is believed that the symptoms are related to hormonal changes and localized swelling in the carpal tunnel [4].

In PRCTS, symptoms are often bilateral and typically more common in the third trimester [5]. There exists a robust consensus concerning clinical diagnosis, relying on patient history and physical examination, coupled with electrodiagnostic tests (EDx) [6]. The current gold standard in diagnosing CTS and evaluating nerve damage entails the use of electrophysiological nerve conduction studies (NCS). Nevertheless, a drawback is that 10 to 25% of NCS outcomes may yield false-negative results. Additionally,

NCS persists as a costly and time-intensive procedure for patients [7]. Recently, there has been a rise in the utilization of ultrasound for diagnosing CTS, attributed to its practical, cost-effective, and non-invasive characteristics [8]. The predominant ultrasound measurement in CTS is the cross-sectional area of the median nerve (MN-CSA) at the carpal tunnel entrance, serving to detect neuropathic edema. MN-CSA determinations have minimal consensus on normative values, as they may depend on anthropometric parameters, such as wrist circumference or body size [9]. As a result, there exists a notably wide range of variability in the diagnostic cut-off, spanning from 9 mm^2 to 14 mm^2 [10]. In this context, we advocate for the adoption of a straightforward and anthropometric-independent ultrasound parameter—the nerve tendon ratio (NTR)—expressed as a percentage, for diagnosing clinically defined CTS [11]. The objective of this study is to assess NTR, which is an anthropometric-independent sonographic value, in comparison with EDx for PRCTS, to determine whether this sonographic parameter has sufficient accuracy for practical clinical use.

2. Materials and Methods

This prospective case-control study received approval from the Prof. Dr. Cemil Tascıoglu City hospital clinical research ethics board and registered with the National Clinical Trials Registry https://clinicaltrials.gov (NCT05839769). The study took place at a tertiary training and research hospital (Prof. Dr. Cemil Tascıoglu City Hospital) from April 2023 to September 2023. The study encompassed 176 pregnant individuals aged 18 to 45, all in the third trimester of pregnancy. Of these, 160 pregnant individuals completed the study.

A medical history was acquired, followed by a thorough physical examination. The examination encompassed the evaluation of muscle strength in the upper extremities, sensory perception, muscle stretch reflexes, and specific provocation tests (specifically, Phalen and Tinnel). A clinical diagnosis of CTS was established taking into account symptoms such as pain in the wrist or hand, tingling sensations, and numbness in the hand or fingers. Furthermore, the diagnosis factored in findings during the physical examination, including diminished strength in thumb abduction or opposition, sensory deficits in the first three fingers, or a positive outcome in provocative tests. The Boston Carpal Tunnel Questionnaire (BCTQ) and Visual Analog Scale (VAS) scores were assessed in those with symptomatic CTS symptoms. CTS was categorized as severe in instances where there was atrophy of the thenar muscles or a 2-point discrimination surpassing 8 mm in at least one finger. This study excluded individuals who had received treatment for CTS with a wrist splint in the past 12 months, previous steroid injections for CTS, inflammatory joint disease, polyneuropathy, a history of trauma in the dominant hand in the past 12 months, previous CTS surgery, bifid median nerve, difficulty in filling out the questionnaires due to language challenges or cognitive limitations, multiple pregnancies, hypothyroidism, severe medical conditions (uncontrolled gestational diabetes, severe preeclampsia, threatened preterm birth, preterm rupture of membranes, medical conditions requiring urgent delivery), and pregnant individuals with known substance or alcohol abuse. All pregnant individuals participating in the study underwent EDx testing, and based on the EDx results, they were divided into two groups: one group with pathological EDx findings and the other with no EDx findings, forming the control group. The flowchart of the study design and the reasons for exclusion are summarized in Fig. 1.

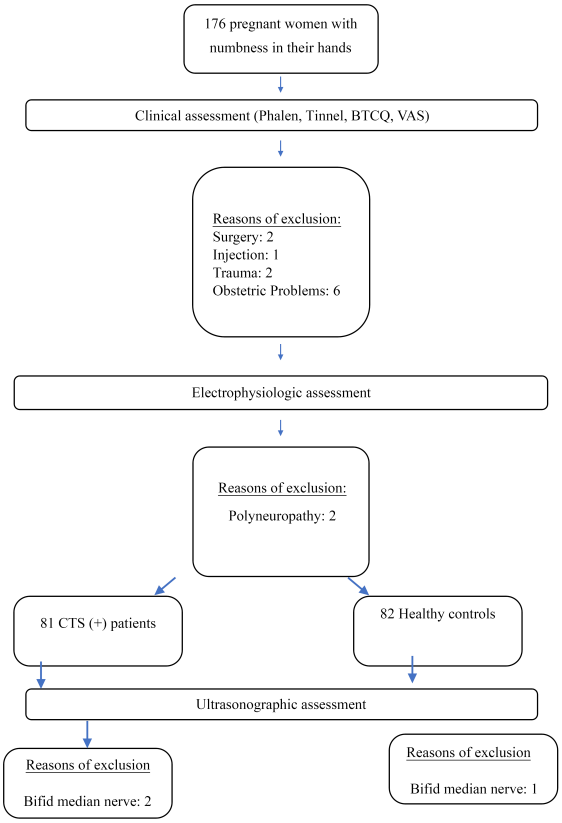

Fig. 1. Flowchart of the study design. BCTQ, Boston Carpal Tunnel Questionnaire; VAS, Visual Analog Scale; CTS, carpal tunnel syndrome.

In the power analysis conducted using the G*power 3.1 program (Christian-Albrechts-Universität Kiel, Kiel, Germany), the effect size for MN-CSA between the study groups was found to be 0.41 (A Novel Ultrasonographic Anthropometric-Independent Measurement of Median Nerve Swelling in Carpal Tunnel Syndrome: The "Nerve/Tendon Ratio" (NTR)) [11]. With an alpha error probability of 0.05 and a power value of 0.80, the sample size analysis determined that a total of 74 samples were required for each group.

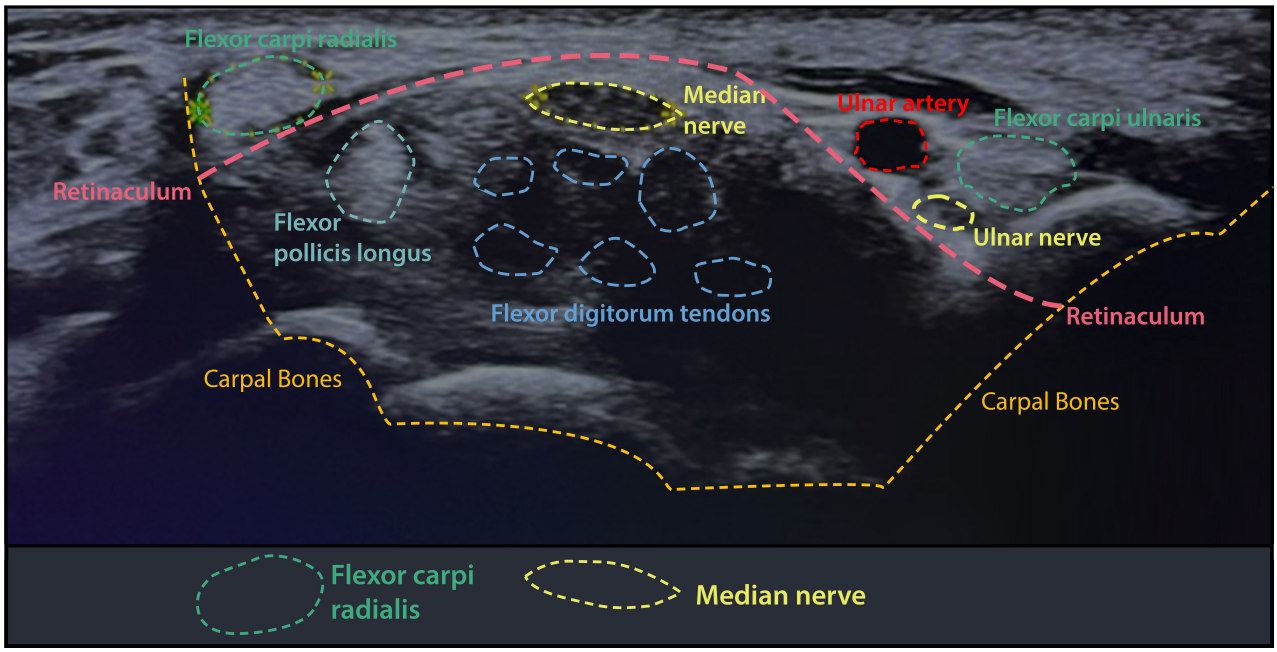

Fig. 2. A schematic view demonstrating the measurement of the cross-sectional areas of the median nerve and flexor carpi radialis in square millimeters (mm^2) using high-resolution ultrasound in the axial plane at the carpal tunnel entrance.

2.1 Ultrasound

Ultrasound examinations were conducted within one week following the electrodiagnostic study. The ultrasound measurements were independently conducted by two radiologists with specialized training in musculoskeletal ultrasound examinations. One radiologist possessed 25 years of experience in ultrasound, while the other had 15. Prior to the commencement of this study, thorough inter- and intra-rater reliability testing was carried out. In the examination, the anatomical structures were assessed using a high-resolution ultrasound device. These measurements encompassed the MN-CSA, the flexor carpi radialis (FCR) at the carpal tunnel entrance at the corresponding level, the cross-sectional area of the carpal tunnel inlet (CTI), and the cross-sectional areas of the median nerve in the forearm, situated 12 cm proximal to the wrist. In the measurements, once the location of these specified structures was identified, their circumferences were marked in the axial plane, and the cross-sectional areas were noted in square millimeters (mm^2). This process was performed separately for both wrists (Fig. 2). All measurements exhibited outstanding inter-rater reliability, assessed at all three levels for each parameter (intraclass correlation coefficient (ICC), 0.77–0.99), with the exception of the nerve cross-sectional area (CSA) in the forearm (fair to good with an ICC of 0.71) and at the carpal tunnel inlet (fair to good with an ICC of 0.43) [12]. The patients were assessed with a high-resolution ultrasound device (7–11 MHz linear probe, Toshiba Aplio 500, 2017 model, Toshiba Medical System Corporation, Tochigi, Japan).

The patients were seated on a chair opposite the radiologist table to ensure their comfort. The patient's arms were positioned lying flat on the examination table, and their hands placed in a free and neutral position. The radiologist conducted the examination while sitting across from the patient on the other side of the examination table. The radiologist refrained from inquiring about symptoms from the volunteers or patients to mitigate observer bias. The sonographers were unaware of the results of both the clinical and nerve conduction studies.

2.2 EDx Testing

EDx was performed by 2 neurophysiologists specialized in their field. All nerve conduction studies were conducted with skin temperature maintained at 34 °C. For evaluation, minimal median motor response across the abductor pollicis brevis, median mixed nerve action potential, and ulnar mixed nerve action potential data were obtained. Subsequently, patients underwent NCS on a Medelec Synergy Machine (Natus Neurology Incorporated, Oxford, UK), measuring sensory and motor latency, amplitude, and velocity. For the median motor nerve conduction study, recording electrodes were positioned over the abductor pollicis brevis, and the nerve was stimulated 6.5 cm proximally at the wrist. Bilateral mixed nerve conduction studies of the median and ulnar nerves were performed via palmar nerve stimulation, recording compound action potentials 8 cm proximally. Diagnosis was based on any of the following criteria: distal motor latency exceeding 4.3 ms, median mixed nerve latency exceeding 2.2 ms, or median-ulnar mixed latency difference greater than or equal to 0.4 ms. For all patients, the following parameters were docu-

mented: distal median motor latency, median motor compound muscle action potential amplitude, median mixed nerve latency, and median-ulnar mixed interlatency differences. CTS severity was classified using the EDx 3 scale: "no electrodiagnostic evidence" if median and ulnar mixed nerve studies were normal; "mild" if only the median mixed nerve action potential was abnormal or its latency exceeded the ipsilateral ulnar mixed nerve action potential by at least 0.4 ms; "moderate" if both the median mixed nerve conduction study and the median motor latency were abnormal or the median mixed nerve action potential was absent; and "severe" if the median mixed nerve conduction study was abnormal, and both the median compound muscle potential amplitude and latency were abnormal [13].

2.3 Boston Carpal Tunnel Syndrome Questionnaire

The BCTQ, a questionnaire comprising 19 questions, was employed to evaluate the severity of symptoms and functional condition in individuals with CTS. The answers are multiple-choice, and each question is assessed with at least one and up to five points. One point corresponds to the mildest symptom or the best functional capacity, while five points correspond to the most severe symptom or the worst functional status. A high average score for the patient indicates that their complaints are severe or that their functional capacity is inadequate. The symptom severity score is the total score obtained from 11 questions. The average symptom severity score is obtained by dividing the total score obtained for all questions by the current number of questions. The functional capacity score is the total score obtained from eight questions. The average functional capacity score is obtained by dividing this total score by eight [14]. The survey has been validated [15].

2.4 Pain Assessment

To assess the level of pain in the patients, the VAS was used. This scale is a commonly used, valid, and a reliable method for pain assessment in clinical settings [16]. The patients' pain intensity was evaluated by assigning a value between 0 (no pain at all) and 10 (unbearable pain) for pain severity during activity, at rest, and whether they experienced nighttime pain.

2.5 Statistical Analysis

Descriptive statistics, encompassing mean, standard deviation, median, minimum, and maximum values, were computed for continuous data. For discrete data, counts and percentage values were provided. The normal distribution of continuous data was evaluated using the Shapiro–Wilk test. For comparing continuous data and ultrasound measurements with the EDx result, the Student's *T*-Test was utilized for data exhibiting a normal distribution, while the Mann–Whitney U Test was employed for data that did not adhere to a normal distribution. Group comparisons of nominal variables in contingency tables were conducted using the chi-squared test and Fisher's exact test. The diagnostic performance of ultrasound measurement values was assessed using the area under the Receiver Operating Characteristic (ROC) curve (AUC). The optimal cut-off point was identified utilizing Youden's index. The diagnostic accuracy criteria for ultrasound values, including sensitivity, specificity, positive predictive value, and negative predictive value, were evaluated. To compare wrist ultrasound measurements in patients with pathological results in the EDx, the Kruskal–Wallis Variance Analysis was used to evaluate differences among those with mild, moderate, and severe conditions. The source of differences was examined using the Kruskal–Wallis multiple comparison test. The analysis was conducted using IBM SPSS for Windows 20.0 (SPSS Inc., Chicago, IL, USA) software, and a level of $p < 0.05$ was deemed statistically significant.

3. Results

The demographic data and obstetric findings of the groups classified as pathologic and normal based on electromyography (EMG) measurements are summarized in Table 1.

In pregnant women with CTS, BCTQ and VAS scores were found to be high ($p < 0.001$). In pregnant women with carpal tunnel syndrome, a higher functional severity score was observed compared to the control group ($p < 0.001$). Regarding VAS scores, in pregnant women with CTS, higher scores were observed during the night, activity, and at rest compared to the control group ($p < 0.001$). The findings are summarized in Table 2. Among pregnant women with severe CTS according to EMG, BCTQ scores were higher than in the mild and moderately affected groups ($p < 0.001$).

In pregnant women with CTS, MN-CSA values were found to be higher ($p < 0.001$). In pregnant women with CTS, MN-CSA/FCR values were also found to be higher ($p < 0.05$). The findings are summarized in Table 3.

The MN-CSA/FCR ratio values of the affected wrists in patients were found to be lower compared to healthy wrists ($p = 0.029$). There was no difference in MN-CSA values between pregnant women with mild, moderate, and severe CTS ($p > 0.05$). The NTR ratio was observed to be higher in pregnant women with severe CTS compared to those with mild and moderate CTS ($p < 0.05$). The findings are summarized in Table 4.

The AUC calculated for MN-CSA/FCR ratio values in distinguishing carpal tunnel diagnosis was found to be significant ($p < 0.05$). The best cut-off for MN-CSA values was calculated as >8.5 mm^2. The best cutoff for MN-CSA/FCR values was found to be $>0.82\%$. The findings are summarized in Table 5.

An MN-CSA value greater than 8.5 mm^2 was found to be a risk factor for CTS. MN-CSA values greater than 8.5 mm^2 increased the likelihood of CTS by 6.396 times ($p < 0.001$). The findings are summarized in Table 6.

Table 1. Demographic data and characteristic features of the groups.

	EDx normal (n = 81)	EDx pathologic (n = 79)	
	Mean ± SD	Mean ± SD	*p* value
	Median (IQR)	Median (IQR)	
Age (years)	30.79 ± 5.38 (20–43)	32.33 ± 4.41 (20–43)	0.073 [a]
Height (cm)	163.11 ± 5.70 163 (159–165)	163.10 ± 6.90 163 (159–166)	0.959 [c]
Weight (kg)	76.04 ± 10.73 75 (68–84)	77.62 ± 11.34 76 (72–85)	0.315 [c]
BMI (kg/m²)	28.67 ± 4.45 29 (25.21–31.17)	29.23 ± 4.52 28.72 (25.30–31.60)	0.540 [c]
Gravida median (IQR)	2 (2–3)	3 (2–4)	0.165 [c]
Parity median (IQR)	1 (1–2)	1 (1–2)	0.879 [c]
Complaint start week	30.99 ± 1.65 31 (30–32)	30.19 ± 1.39 30 (29–31)	0.002 [c]
Pregnancy week	32.81 ± 11.89 33 (32–34)	33.86 ± 2.28 34 (32–36)	<0.001 [c]
Weight gained during pregnancy	12.86 ± 3.00 13 (11–15)	11.52 ± 3.61 11 (10–13)	0.540 [c]
Previous type of birth			
NSD	33 (49.3)	50 (86.2)	<0.001 [b]
C/S	34 (50.7)	8 (13.8)	
Phalen			
Absent	21 (25.9)	18 (22.8)	0.644 [b]
Present	60 (74.1)	61 (77.2)	
Tinnel			
Absent	18 (22.2)	15 (19.0)	0.613 [b]
Present	63 (77.8)	64 (81.0)	
Smoking n (%)			
Absent	69 (85.2)	58 (73.4)	0.066 [b]
Present	12 (14.8)	21 (26.6)	
Educational background			
Primary school	11 (13.6)	12 (15.2)	0.026 [b]
Middle school	23 (28.4)	37 (46.8)	
High school	38 (46.9)	28 (35.4)	
University	9 (11.1)	2 (2.5)	
Job			
Housewife	52 (64.2)	54 (68.4)	0.578 [b]
Working	29 (35.8)	24 (31.6)	
Income			
Low	15 (18.5)	11 (13.9)	0.043 [b]
Middle	40 (49.4)	54 (68.4)	
High	26 (31.1)	14 (17.7)	
Family history			
Absent	81 (100)	61 (77.2)	<0.001 [b]
Present	0 (0)	18 (22.8)	
Unilateral CTS	21 (25.9)	18 (22.8)	0.644 [b]
Bilateral CTS	60 (74.1)	61 (77.2)	

a: Student's *t* test; b: chi-squared test/Fisher's exact test; c: Mann–Whitney U test. EDx, electrodiagnostic tests; SD, standard deviation; IQR, interquartile range; NSD, normal spontaneous delivery; C/S, cesarean section; BMI, body mass index.

4. Discussion

In this study, we found that NTR, independent of anthropometric measurements, is an alternative new parameter to EDx in pregnancy CTS. According to the EDx results, we also demonstrated that NTR is a non-invasive assessment in distinguishing pregnant women with mild, moderate, and severe symptoms of CTS.

Despite its common occurrence and recognizable clinical presentation, the optimal diagnostic strategy for CTS remains uncertain [17]. Clinical history and physical exam-

Table 2. Comparison of the scale results between the groups.

	EDx normal (n = 81)	EDx pathologic (n = 79)	*p* value
	Mean ± SD	Mean ± SD	
	Median (IQR)	Median (IQR)	
BCTQ symptom score	14.11 ± 2.49 13 (12–16)	30.59 ± 9.60 27 (24–36)	<0.001 [c]
Functional severity score	11.37 ± 1.18 11 (11–13)	21.33 ± 6.70 21 (15–25)	<0.001 [c]
VAS during activity	1.70 ± 0.69 2 (1–2)	4.78 ± 0.82 5 (4–5)	<0.001 [c]
VAS at night	1.60 ± 0.58 2 (1–2)	5.41 ± 1.09 5 (5–6)	<0.001 [c]
VAS at rest	2.05 ± 0.50 2 (2–2)	3.84 ± 1.07 4 (3–4)	<0.001 [c]

c: Mann-Whitney U Test.

Table 3. Comparison of EMG results with wrist ultrasound findings between the groups.

	EDx normal (n = 81)	EDx pathologic (n = 79)	*p* value
	Mean ± SD	Mean ± SD	
	Median (IQR)	Median (IQR)	
Wrist circumference	16.43 ± 0.79 16 (16–17)	16.51 ± 1.03 16 (16–17)	0.791 [c]
Forearm Median Nerve mm^2	4.74 ± 0.85 5 (4–5)	5.16 ± 1.60 5 (4–6)	0.100 [c]
MN-CSA mm^2	7.80 ± 2.50 7.5 (6–8.5)	10.03 ± 3.28 10 (8–12)	<0.001 [c]
FCR mm^2	9.66 ± 1.36 10 (9–10)	11.26 ± 3.28 11 (9–12)	0.001 [c]
Forearm Median Nerve/FCR (%)	0.49 ± 0.11 0.50 (0.41–0.55)	0.48 ± 0.16 0.44 (0.33–0.55)	0.071 [c]
MN-CSA/FCR (%)	0.81 ± 0.28 0.75 (0.62–0.83)	0.94 ± 0.39 0.83 (0.66–1.08)	0.045 [c]

c: Mann–Whitney U test.

EMG, electromyography; FCR, flexor carpi radialis; MN-CSA, median nerve cross-sectional area.

ination remain essential in screening, yet their diagnostic accuracies exhibit variability. In the literature, the prevalence of clinically suspected PRCTS ranges from 31% to 62%, whereas electrophysiologic confirmed PRCTS ranges from 7% to 43%. This variability can be attributed to differences in the methodologic approaches employed across studies [18]. If we address these methodologic differences, in the conducted systematic review, it was observed that there were very few publications on PRCTS that included EDx tests. Additionally, the studies had vastly different sample sizes, ranging from 18 to 10,873. Alternatively, understanding the performance of clinical parameters is also crucial [19]. In routine CTS practice, various provocative tests are available for the evaluation and diagnosis of CTS; however, individual tests are not sufficient, but combining multiple provocative tests has been shown to increase sensitivity and specificity [20]. In the course of this study, no significant difference in clinical provocative tests was identified between the groups. This also highlights the need for additional tests for the diagnosis of CTS. EDx is frequently used in the diagnosis of CTS and other neuropathies, but with its limited structure and high cost disadvantage, it requires an invasive methodology and an extended examination process. EDx, while valuable, lacks the capability to diagnose the underlying anatomical causes of compressive neuropathy [21].

The impact of neuropathies on daily life can be compounded by the unique challenges of pregnancy. In a study involving pregnant women with CTS, a significant increase in BCTQ scores and carpal tunnel findings was observed, especially in the final trimester. This situation has been suggested to lead to sleep problems and depressive symptoms in pregnant women [22]. Our study revealed that the BCTQ questionnaire played a significant role in distinguishing pregnant women with CTS. While statistically significant differences in terms of gestational weeks were

Table 4. Comparison of ultrasonographic measurements of affected wrists in pregnant women with mild, moderate, and severe CTS in those with pathologic findings in the EDx results.

	Mild (n = 15)	Moderate (n = 46)	Severe (n = 18)	*p* value
	Mean ± SD	Mean ± SD	Mean ± SD	
	Median IQR	Median IQR	Median IQR	
MN-CSA mm^2	8.60 ± 2.89 10 (7–10)	10.00 ± 3.07 10 (8–11)	11.33 ± 3.72 12 (8–14)	0.137 [d]
FCR mm^2	11.40 ± 3.11 10 (9–12)	11.97 ± 3.46 12 (9–15)	9.33 ± 2.11 10 (7–11)	0.014 [d]
Forearm median nerve/FCR (%)	0.39 ± 0.08 0.35 (0.33–0.40)	0.43 ± 0.12 0.41 (0.33–0.50)	0.67 ± 0.17 0.80 (0.50–0.83)	<0.001 [d]
MN-CSA/FCR (%)	0.75 ± 0.22 0.70 (0.70–0.83)	0.85 ± 0.21 0.80 (0.66–1.00)	1.30 ± 0.60 1.25 (0.66–1.70)	0.016 [d]
BCTQ	22.87 ± 3.64 23 (20–27)	27.35 ± 5.80 26.5 (24–31)	45.33 ± 3.44 45 (45–47)	<0.001 [d]

d: Kruskal–Wallis variance analysis.

Table 5. Diagnostic performance of ultrasound findings in predicting carpal tunnel diagnosis (pathologic in EDx results).

	AUC	*p*	Cutoff	Sensitivity	Specificity	PPV	NPV
	95% CI			95% CI	95% CI		
Forearm median nerve cross-sectional area (mm^2)	0.573 (0.047) 0.481–0.664	0.112	-	-	-	-	-
MN-CSA mm^2	0.719 (0.042) 0.637–0.801	<0.001	>8.5	0.683 0.574–0.775	0.753 0.649–0.831	0.729 0.653–0.795	0.709 0.631–0.777
FCR mm^2	0.656 (0.046) 0.567–0.745	0.001	>11.5	0.481 0.374–0.589	0.901 0.817–0.949	0.826 0.756–0.879	0.64 0.560–0.713
Forearm median nerve/FCR (%)	0.582 (0.046) 0.491–0.673	0.073	-	-	-	-	-
MN-CSA/FCR (%)	0.592 (0.045) 0.503–0.680	0.045	>0.82	0.519 0.410–0.626	0.679 0.571–0.771	0.612 0.531–0.689	0.591 0.511–0.667

AUC, Area under Curve; 95% CI, 95% confidence interval; PPV, positive predictive value; NPV, negative predictive value.

observed between pregnant women with CTS and normal pregnant women in our study, it did not have obstetric significance. There are significant variations in the natural course of PRCTS in the literature, and it is often believed that carpal tunnel findings may resolve after childbirth. However, it has been observed that CTS symptoms can persist for up to three years following pregnancy [23]. In a study involving postpartum CTS patients with risk factors, predictors of persistent CTS 12 months after childbirth were identified, including early onset before the third trimester, an escalation in the severity of CTS symptoms during pregnancy, and elevated depression scores postpartum [24].

Although ultrasonography has a practical nature and high diagnostic accuracy, there is considerable heterogeneity between MN-CSA values, ranging from 9 to 16.8 mm^2 [25]. Similarly, in our study, the best cut-off for MN-CSA for carpal tunnel was calculated to be >8.5 mm^2; MN-CSA above 8.5 mm^2 was identified as a risk factor in logistic regression. In a recent study on MN-CSA in pregnancy-related carpal tunnel, a value of 9.44 ± 2.68 mm^2 was found, which was higher than the control group, although the control group and carpal tunnel cases were not confirmed with EMG [26]. Another study related to the topic was conducted on dentists, where MN-CSA <10 mm^2 was considered normal [27]. In a recent meta-analysis involving 16 studies with a sample of 2292 wrists classified based on EDx results, threshold values were found to be 11.64 mm^2 for mild CTS, 13.74 mm^2 for moderate CTS, and 16.80 mm^2 for severe CTS [28]. In this study, CSA measurement was taken at the entrance of the median nerve. In a study investigating the diagnostic value of multiple ultrasound (US) parameters, MN-CSA and inlet CSA were found to be practical and measurable parameters in confirming CTS [29]. Individual MN-CSA in CTS can be affected by people's height, weight, and wrist circumference, so independent anthropometric measurements have come into play. The most studied of these is the wrist-forearm ratio [29]. In a published study, it was found that the WFR (Wrist-to-Forearm Ratio) in patients with CTS showed an increase in comparison to asymptomatic controls. A WFR of ≥1.4 provided 100% sensitivity for detecting patients with CTS, while us-

Table 6. Multivariable logistic regression analysis for risk factors in carpal tunnel disease using ultrasound measurements.

	Regression coefficient	OR	95 % CI		*p* value
MN-CSA >8.5 mm^2	1.856 (0.389)	6.396	2.981	13.722	<0.001
NTR >0.82%	0.070 (0.394)	1.073	0.496	2.32	0.859

OR, odds ratio; NTR, nerve/tendon ratio.

ing solely median nerve area at the wrist yielded a sensitivity of 45–93%, contingent on the chosen cut-off value [29]. However, the disadvantages of measurements are that they are time-consuming and relatively complex for clinical applications.

To the best of our knowledge, our literature search suggests that our study is the first to include the prognostic diagnostic value of NTR in pregnant women and to compare it with EDx. In a study conducted in non-pregnancy-related carpal tunnel cases, NTR yielded comparable results with MN-CSA and was less affected by anthropometric measurements; in the respective study, an MN-CSA cut-off value of 8 mm^2 was calculated, and NTR was calculated as 0.83% [11]. In our study, NTR was found to be 0.82%, which is promising in terms of its novelty and practicality in pregnancy-related carpal tunnel; it also had significance in distinguishing severe cases from mild and moderate cases, but our analysis found that it was not a risk factor in pregnancy-related carpal tunnel. The considerable range of sensitivities and specificities documented in the literature has hindered a meaningful assessment of ultrasound's efficacy as a screening or confirmatory tool in diagnosing CTS. While ultrasound may not completely supplant EDx as the established diagnostic gold standard for of CTS, it may assume the role of EDx as the first-line test depending on the cross-sectional area value chosen by the investigator [30]. Historically, EDx has served as the confirmatory test for diagnosing CTS. Nonetheless, ultrasound has sparked interest as an alternative diagnostic test for CTS [31]. Studies have used either EDx or clinical diagnosis as the reference standard when determining the sensitivity and specificity of ultrasound in the diagnosis of CTS [32]. A meta-analysis revealed that ultrasound exhibited a sensitivity of 77.6% and a specificity of 86.8% in diagnosing CTS. Notably, these values remained competitive when using EDx as the benchmark (80.2% sensitivity and 78.7% specificity) [33]. Furthermore, compared to clinical diagnosis as the reference, ultrasound displayed comparable or even superior performance (77% sensitivity and 93% specificity) relative to Graham's benchmark EDx values (69% sensitivity and 97% specificity) [33,34]. In our study, NTR cut-off point of 0.82% demonstrated a sensitivity of 51.9% and a specificity of 67.9%. While ultrasound may not substitute EDx as the most discerning and precise diagnostic test for CTS, considering the values presented in these studies, it holds promise as an alternative to EDx as the primary confirmatory test.

In the management of CTS in pregnant women, conservative treatments, such as splints and exercises, continue to be the first recommended approach. In our follow-up, 1 pregnant woman with severe postpartum CTS was treated surgically. Despite the extensive study of diagnostic tests over the last 30 years, which has resulted in high sensitivity and specificity, the diagnosis of CTS remains a focal point of ongoing research. Developments in ultrasound provide more pathophysiologic information about the median nerve and surrounding structures. This information not only heightens diagnostic precision but also enriches our comprehension of the pathology of CTS, offering supplementary insights. Nonetheless, there persist some challenges in ultrasound evaluation. The primary limitation is the need for standardized protocols for image analysis using ultrasound. Secondly, clarification of morphological differences in the median nerve based on race, gender, and physique is essential for the diversity of studies. Exploring the diagnostic relevance of ultrasound across diverse disease populations, such as those with chronic conditions (diabetes and chronic kidney disease), excluding pregnancy, will expand knowledge in this domain. Another consideration is that due to reports of variability in carpal tunnel features, patients with CTS related to these diseases may require different threshold values. Measurement cutoff values need to be determined due to these differences. Additionally, research should be conducted on measurement parameters for longitudinal assessment. Longitudinal images are useful in cases of focal nerve compression as they show the compressed part of the nerve and also the proximal and/or distal swollen parts. However, they are not often used as a quantitative parameter. This is because there is no clear reference point indicating the positional relationship with the wrist surface, and visualizing the long-axis view of the median nerve is relatively challenging. Another problem is that the relationship between these ultrasound findings and the progression of the disease is still unclear. These findings may reflect the pathologic anatomy and kinetics associated with CTS. However, it is still unknown whether predicting outcomes or defining risk factors based on ultrasound findings is possible, and the role of ultrasound examination in deciding on treatment options remains uncertain [35]. A limitation of our study was that we performed statistical analysis to check if there were differences between NTR of women with mild *vs*. moderate *vs*. severe CTS, despite the small sample size for each group. The NTR ratio was observed to be higher in pregnant women with severe CTS compared to those with mild and moderate CTS.

In conjunction with traditional neurophysiologic tests, nerve ultrasonography has gained prominence in the diagnosis of CTS, and emerging imaging methods such as ultrasound elastography and magnetic resonance imaging (MRI) tractography further substantiate these findings. Treatment for CTS should be individualized based on patient characteristics. Although clinical evaluation, neurophysiology, and imaging offer supportive evidence, the selection of the optimal approach for diagnosis and treatment relies on the clinician's experience. In the future, the assessment of ultrasound parameters' response to treatment should also be considered.

The strengths of our study include the comprehensive administration of diagnostic tests without bias. The blinding of radiologists and the close interobserver correlation coefficient, along with the radiologists' specialized expertise in the neuromuscular field, strengthened our findings.

Despite the plethora of new methods introduced for the diagnosis and treatment of CTS, there is a continued need for further prospective, well-designed, longitudinal studies. These studies are essential to validate the effectiveness of these new approaches and assess their applicability in clinical research settings.

5. Conclusions

Ultrasonography of the wrist may serve as an alternative diagnostic tool for CTS in pregnant women due to its rapid, non-invasive, and reproducible characteristics. Further research should focus on investigating the response to treatment.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

FŞ designed the research study. FŞ, VM and RYB performed the literature search and analyzed the data. All authors contributed to the editorial changes in the manuscript. All authors read and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All methods were carried out in accordance with relevant guidelines and regulations. The case-control study received ethical approval from Istanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee, with approval Date: 03.04.2023 NO: 96. Participation in the study was voluntary, and participants could withdraw from the study at any time. Informed consent was obtained from all study participants. For illiterate participants, informed consent was taken from legally authorized representatives.

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Conflict of Interest

The authors declare no conflict of interest.

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