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ORIGINAL RESEARCH

Diagnosis of carpal tunnel syndrome with ultrasound: should we go more distal?

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ABSTRACT

Objectives To assess the value of adding the ultradistal level to other more thoroughly studied levels of the carpal tunnel when measuring the cross-sectional area (CSA) of the median nerve (MN) by ultrasound (US) in diagnosing patients with primary carpal tunnel syndrome (CTS).

Methods Patients clinically diagnosed with primary CTS and healthy controls were included. The MN-CSA was measured by US at three wrist levels: proximal, distal and ultradistal. The best cut-off to differentiate cases and controls was determined for the CSA and for the difference between levels of the same wrist. The performance of different definitions for US-CTS compared with the clinical diagnosis of CTS was evaluated: (1) CSA above cut-off at each level; (2) CSA-difference above cut-off at each level; (3) ≥1 level with CSA above cut-off and (4) ≥1 CSA-difference above cut-off. Definition 3, excluding the ultradistal level, and combinations of definitions were also tested.

Results In total, 219 patients and 39 controls were included. The CSA was higher in patients (10.5–16.8 mm^2) than controls (6.2–7.6 mm^2). The difference between groups was maximal at the ultradistal level (right: 10.1 mm^2; left: 8.3 mm^2). The CSA cut-offs were 11 mm^2, 9 mm^2 and 10 mm^2 at the right, and 10 mm^2, 8 mm^2 and 10 mm^2 at the left, for the proximal, distal and ultradistal levels, respectively. Definition 3 yielded the best balance between sensitivity (98%) and specificity (95%) (right hand). Removing the ultradistal level from definition 3 decreased sensitivity to 90%, maintaining the same specificity.

Conclusions Adding the ultradistal level improves the performance of US for diagnosing CTS. We suggest adding it in clinical practice when investigating CTS.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Few studies have assessed the morphology of the median nerve (MN) distally to the outlet of the carpal tunnel (the ultradistal level) in patients with primary carpal tunnel syndrome (CTS), as well as the advantages of considering this data in CTS diagnosis.

WHAT THIS STUDY ADDS

⇒ Our work is the largest so far to study the behaviour of the MN at the ultradistal level and also the positive impact of considering it in primary CTS diagnosis by ultrasound (US).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We suggest a US protocol for diagnosing CTS in the clinical practice that includes the ultradistal level and maximises diagnostic performance.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common peripheral entrapment neuropathy and occurs when the median nerve (MN) gets compressed at the non-displaceable osteofibrous carpal tunnel.[1] The disease affects up to 5% of the population and is more prevalent in women.[2–4] CTS can be idiopathic or 'primary', when no underlying cause is identified, occurring mainly because of wrist overuse (repetitive occupational or recreational movements), or 'secondary' to an underlying condition, such as inflammatory joint diseases (eg, rheumatoid arthritis), metabolic diseases (eg, thyroid disorders or diabetes), pregnancy or mechanical compression (eg, cysts or wrist fracture sequelae).[5]

Clinical examination is crucial for diagnosing CTS, but nerve conduction studies (NCSs) and ultrasound (US) can be used for additional validation of the diagnosis, especially if invasive therapies are considered.[6] When measured at the carpal tunnel by US, the MN cross-sectional area (CSA) is increased in CTS patients. There is no consensus on how and where to measure the MN when CTS is suspected. Different levels at the forearm and wrist have been proposed by different authors, with the distal forearm, carpal tunnel inlet (scaphoid/pisiform level) and outlet (trapezium/hook of the hamate level) being the most reported.[6–10]

In entrapment neuropathies, nerve compression and traction lead to microvascular changes, which alter the biochemical environment of neural connective tissue.[11] Anatomically, the MN gets compressed predominantly at the carpal tunnel inlet or

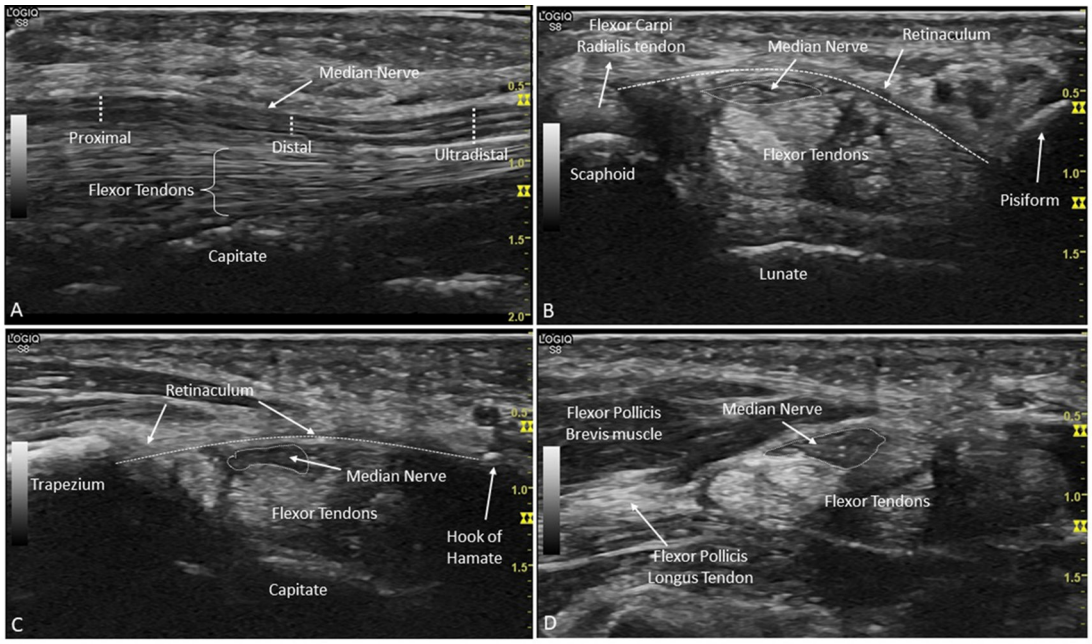

Figure 1 B-mode ultrasound images of the median nerve at the volar wrist. (A) Longitudinal view of the median nerve at the carpal tunnel; (B) Transverse view at the proximal level of the wrist; (C) Transverse view at the distal level of the wrist; (D) Transverse view at the ultradistal level of the wrist.

outlet, the latter being the narrowest part of the carpal tunnel.[11] It has been known for decades that the CSA of the MN measured by US is increased in CTS patients at these critical levels or proximal to them (ie, at the distal forearm). More recently, Ng *et al* demonstrated (using both US and MRI) that the MN is also enlarged after exiting the carpal tunnel.[12 13] We hypothesise that this 'ultradistal' (UD) level of the MN, as we call it, the place where the MN has already exited the carpal tunnel but has not yet divided into its digital branches (online supplemental figure 1), should be considered when investigating CTS by US.

Our aim is to further test whether the MN is enlarged at the UD level in patients with CTS and also to evaluate the impact of adding the UD level to other more comprehensively studied levels (carpal tunnel inlet and outlet) in the performance of US for diagnosing CTS.

METHODS

Study design and population

We conducted a case–control study in which consecutive patients with a clinical diagnosis of CTS followed in the rheumatology department of two tertiary care centres were included. Patients were clinically assessed by an experienced rheumatologist for the presence of sensory and/or motor symptoms in both hands within a territory corresponding to the MN's, namely, dysesthesia, including hypoesthesia and paraesthesia, occurring either spontaneously (especially if with a nocturnal predominance), with tasks requiring overuse of the wrists or hands or with persistent wrist flexion or extension positions. On physical examination, MN territory sensory changes, Tinel's, Phalen's or Durkan's positive tests and thenar eminence atrophy or weakness were considered. Taking the previous findings into consideration, an integrated clinical judgement was made to make a diagnosis of CTS, and patients with a clinical diagnosis of bilateral CTS were included ('patient group'). Rheumatologists did not have knowledge of the US evaluation. Patients were excluded if they had concomitant presence of neurological symptoms of more proximal territories of the upper limb (eg, brachial plexus root distribution) or a possible secondary cause of CTS (eg, inflammatory joint diseases, such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus or gout, metabolic diseases such as diabetes mellitus and thyroid diseases, previous wrist fracture, trauma or surgery). The 'control group' included healthy healthcare providers from both centres. Individuals were only included in the control group if they never had signs or symptoms suggestive of CTS. After US characterisation, only wrists with non-bifid nerves and with complete data at each of the three levels of measurement (proximal, distal and UD) were included in the analysis.

US methodology

A General Electric Logic S8 US machine with an ML 6-15 probe was used in both centres. The CSA (in mm^2) was measured using the tracing area tool, and the MN tracing was performed by the inner limit of the epineurium. B-mode settings were individually optimised for the best MN depiction, aiming for the best accuracy of measurement. The CSA was measured in both wrists of each individual of both groups in a transverse view, at three anatomical locations (figure 1): the 'proximal level' (P), where the pisiform and scaphoid bones are

Table 1 Description of the basic US parameters assessed and the definition of US-CTS diagnosis

Absolute CSA and ΔCSA parameters	Description
CSA	CSA measured in each anatomical level: CSA-P, CSA-D and CSA-UD
ΔCSA	Difference in CSA between two different levels of the same wrist: ΔP-D, ΔUD-P and ΔUD-D
Numbered definitions of US-CTS	**Description**
All levels considered	
CSA	CSA≥cut off*, each level separately
CSA-difference	ΔCSA≥cut off*, each difference separately
CSA-all-levels	CSA≥cut off in at least one level
CSA-all-differences	ΔCSA≥cut off in at least one difference
CSA-all-levels and CSA-all-differences	Definitions 3 and 4 fulfilled
CSA-all-levels or CSA-all-differences	Definitions 3 or 4 fulfilled
Level-conditioned definitions	
3.1. CSA-P-or-D	CSA≥cut off in at least one of the P or D levels
5.1. CSA-P-or-D and CSA-difference-ΔP-D	Definition 5 but with CSA and ΔCSA parameters considering the P and D levels only: CSA≥cut off at the P or D levels and ΔP-D≥cut off
5.2. CSA-UD and CSA-difference-ΔUD-D	Definition 5 but with CSA and ΔCSA parameters that consider the UD level: CSA-UD≥cut off and ΔUD-D≥cut-off
6.1. CSA-P-or-D or CSA-difference-ΔP-D	Definition 6 but with CSA and ΔCSA parameters considering the P and D levels only: CSA≥cut off at the P or D levels or ΔP-D≥cut-off
6.2. CSA-UD or CSA-difference-ΔUD-D	Definition 5 but with CSA and ΔCSA parameters that consider the UD level: CSA-UD≥cut off or ΔUD-D≥cut-off

*Cut-offs were determined after receiver operating curve analysis, with calculation of sensitivity, specificity and area under de curve and correspond to the best cut-off value obtained by the maximum Youden index value. Determined cut-offs classify individuals as having or not US-CTS.
CSA, cross-sectional area; CTS, carpal tunnel syndrome; D, distal; P, proximal; UD, ultradistal; US, ultrasound; Δ-CSA, variation of CSA between two levels of the same wrist.

both visible and correspondent to the carpal tunnel inlet; the 'distal level' (D), where both the trapezium and the hook of the hamate are both visible, correspondent to the carpal tunnel outlet; and the 'UD level', a level that is distal to the carpal tunnel outlet but proximal to the MN division into the digital branches, being considered the place where the CSA is maximal throughout this very short section. The practical landmark used for measuring the UD level was the inflection point of the flexor pollicis longus tendon fibres towards the thumb, where their change of direction is evident, from transverse to a longitudinal perspective or, alternatively, where the hook of the hamate disappears when scanning distally. In addition to CSA measurements, the type of MN (uno or bifid) and features that could lead to secondary compression of the MN at the carpal tunnel, such as cysts or tenosynovitis, were also recorded. Sonographic evaluations were performed by two rheumatologists experienced in musculoskeletal sonography (GF more than 20 years of experience, SF more than 15 years of experience). A meeting was held to standardise the exploration of the MN as described above. Thereafter, the inter-rater reliability for the measurement of CSA at all three levels was assessed in 48 patients with suspected CTS (not included in the main study). A high agreement between the two observers was obtained (intraclass correlation coefficient ≥0.87).

Clinical variables

Data on age (years), symptom duration (years), type of symptoms (sensitive vs motor), sex (male and female) and secondary causes of CTS were collected using a standardised data collection form.

Statistical analysis

Absolute CSA per anatomical level and differences across levels

The mean CSA was calculated at each anatomical level (CSA-P, CSA-D, CSA-UD). We then tested whether there was a significant difference in CSA between patients and controls, for each level, by independent samples t-tests. Since age and sex can influence the values of CSA, we also tested the difference between groups with multivariable linear regression models, with CSA as the outcome, the diagnostic group (patients vs controls) as explanatory variable, and adjusting for age and sex, separately for each level. Subsequently, we calculated the difference in CSA between two levels of the same wrist (Δ-CSA): (1) proximal and distal levels (ΔP-D); (2) the UD and proximal levels (ΔUD-P) and (3) the UD and distal levels (ΔUD-D). All calculations were performed separately for

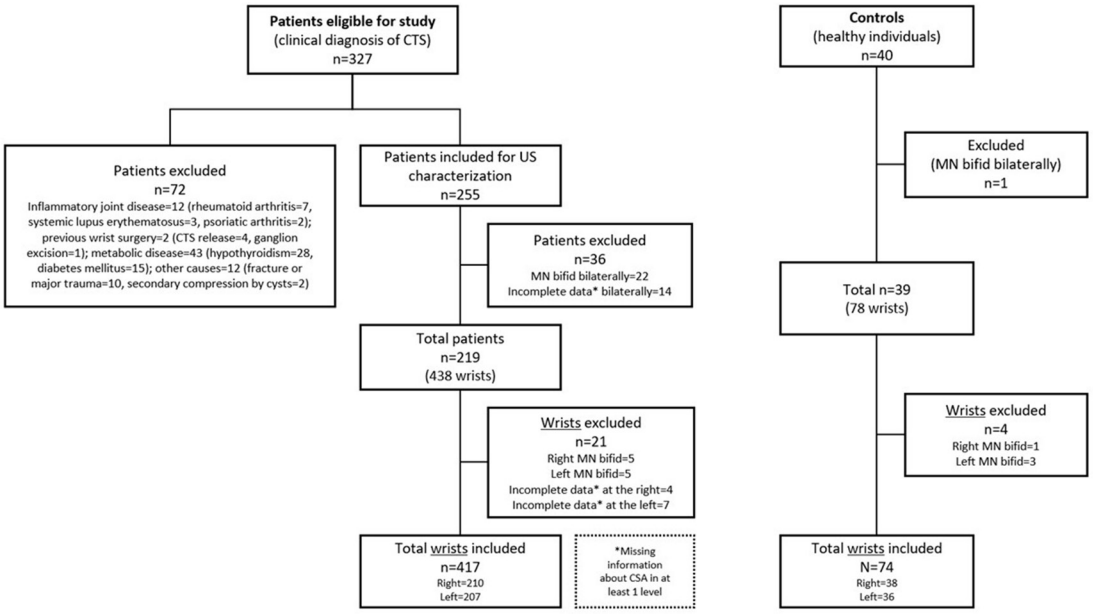

Figure 2 Screening and selection of patients with a clinically diagnosed CTS, to form the patient group (left) and of healthy individuals to form the control group (right). *Missing information about CSA in at least one level. CSA, cross-sectional area; CTS, carpal tunnel syndrome; MN, median nerve; US, ultrasound.

each hand since measurements from both hands of the same patient are, by definition, correlated.

Diagnostic performance

We tested the diagnostic performance of different definitions of CTS in US (US-CTS) (table 1). In definition 1 (CSA), we considered the absolute value of the CSA, separately at each level (CSA-P, CSA-D and CSA-UD). In definition 2 (CSA-difference), we considered the difference of CSA across levels, separately for each difference (ΔP-D, ΔUD-P and ΔUD-D). For each definition, we determined the best cut-off defined as the value that best discriminates between patients and controls. A receiver operating characteristics analysis was performed and the sensitivity (sens), specificity (spec) and area under the curve (AUC) were calculated. The best cut-off was determined by the maximum Youden index (sens+spec−1), which yields the best balance between sensitivity and specificity. Patients with an absolute CSA (definition 1) or with a difference in CSA (definition 2) equal to or above the best cut-off were defined as a positive diagnosis of US-CTS.

We then tested whether combining information from all levels of measurement (CSA-P, CSA-D and CSA-UD, in case of CSA) or all differences (ΔP-D, ΔUD-P and ΔUD-D, in case of ΔCSA) yielded a better diagnostic performance than considering each level or difference separately, as in definitions 1 (CSA) and 2 (CSA-difference), respectively. In definition 3 (CSA-all-levels), patients were considered to have US-CTS if they had at least one of the levels (CSA-P, CSA-D or CSA-UD) with an absolute CSA above the best cut-off, using the previously determined cut-off; and in definition 4 (CSA-all-differences) if they had at least one difference between levels (ΔP-D, ΔUD-P or ΔUD-D) above the best cut-off (as previously determined). Finally, US-CTS was defined by combining definition 3 (CSA-all-levels) and 4 (CSA-all-differences) as follows: (1) definition 5 (CSA-all-levels and CSA-all-differences): having at least one level with an absolute CSA above the best cut-off and at least one level with the difference above the best cut-off (ie, fulfilling definitions 3 and 4) and definition

Table 2 Demographic and clinical characteristics of the patients and controls

Characteristics	Patients	Controls
N included	219	39
Age at inclusion	50.6 (11.3)*	41.6 (13.1)*
Minimum	25	24
Maximum	80	65
Sex		
Female	196 (89.5%)	31 (79.5%)
Male	23 (10.5%)	8 (20.5%)
Symptom evolution		
Duration	3.4 (3.6)*	–
Patients with symptoms for ≤2 years	125 (57%)	–
Patients with symptoms for ≤5 years	197 (90%)	–
Minimum (years)	<1	–
Maximum (years)	20	–
Symptom type		
Exclusive sensory symptoms	213 (97%)	–
Sensory symptoms plus strength reduction complaints	6 (3%)	–

*Mean (SD), in years.

6 (CSA-all-levels or CSA-all-differences): having at least one level with an absolute CSA above the best cut-off or at least one level with the difference above the best cut-off (ie, fulfilling definitions 3 or 4). Each US definition of CTS was compared with the clinical diagnosis of CTS as gold standard, and sensitivity, specificity and AUC were calculated.

Lastly, and to further test the relevance of including the UD level in US protocols instead of using only the proximal and distal levels, the diagnostic performance of five 'level-conditioned definitions' of US-CTS were analysed: definition 3.1 (CSA-P-or-D): patients were considered to have US-CTS if they had at least one of the P or D levels with an absolute CSA above the best cut-off; definition 5.1 (CSA-P-or-D and CSA-difference-ΔP-D): having at least one of the P or D levels with an absolute CSA above the best cut-off and the ΔP-D above the best cut-off; definition 5.2 (CSA-UD and CSA-difference-ΔUD-D): having the CSA-UD and ΔUD-D above the best cut-off; definition 6.1 (CSA-P-or-D and CSA-difference-ΔP-D): having at least one of the P or D levels with an absolute CSA above the best cut-off or the ΔP-D above the best cut-off and definition 6.2 (CSA-UD or CSA-difference-ΔUD-D): having the CSA-UD or ΔUD-D above the best cut-off. We did not consider definition 4.1, since applying the rule of considering the proximal and distal levels to definition 4 overlaps with definition 2 (CSA-difference) for the ΔP-D difference.

RESULTS

A total of 327 patients with a clinical diagnosis of CTS and 40 healthy individuals were screened for the patient and control groups, respectively. After selection, 417 wrists from 219 patients with CTS and 74 wrists from 39 healthy individuals were included for the final analysis (figure 2).

Patients with CTS were older (mean age: 51 vs 42 years) and more often female (90% vs 80%), compared with individuals from the control group (table 2). The mean (SD) symptom duration in the patient group was 3.4 (3.6) years, with more than half (57%) having symptoms for less than 2 years. All patients reported sensory symptoms, and only 6 (3%) had concomitant strength reduction.

MN morphology

In the patient group, the mean CSA at different levels varied between 10.5 mm^2 and 16.8 mm^2. In the control group, the mean CSA varied between 6.2 mm^2 and 7.6 mm^2 (table 3). Both in patients and controls, the CSA was larger on the right than on the left hand at all levels. There was a statistically significant difference in mean CSA between patients and controls at all levels, also when adjusting for age and gender. The largest difference of CSA between groups was found at the UD level on both sides: right: 10.1 mm^2; left: 8.3 mm^2. The smallest difference was found at the distal level also on both hands: difference-patients-controls-D-right=5.1 mm^2; difference-patients-controls-D-left=4.1 mm^2. In patients with CTS, not only was the CSA increased, but there was also a larger difference between levels within the same wrist, when compared with controls. The mean Δ-CSA varied between 1.3 mm^2 and 5.6 mm^2 in the patient group and between 0.0 $mm^2$and 1.4 mm^2 in the control group. In the patient group, the ΔUD-D value was the highest on both hands (right: 5.6 mm^2; left: 4.6 mm^2) (table 3).

Table 3 Mean values of CSA at different levels and of Δ-CSA between levels of the same wrist, in patients and controls

	Patients	Controls	Patients vs controls
Mean CSA			
	Mean CSA (SD) (min-max) in mm^2	Mean CSA (SD) (min-max) in mm^2	CSA mean diff.* (95% CI) in mm^2
Right			
Proximal	15.0 (5.9) (6–52)	7.6 (1.4) (5–11)	7.0 (5.1 to 9.0)
Distal	11.2 (4.1) (4–31)	6.2 (1.6) (3–11)	5.1 (3.7 to 6.5)
UD	16.8 (6.1) (5–44)	6.2 (1.5) (3–9)	10.1 (8.1 to 12.1)
Left			
Proximal	13.8 (5.4) (6-42)	7.3 (1.8) (4–11)	6.2 (4.3 to 8.0)
Distal	10.5 (3.7) (5-25)	6.4 (1.8) (4–10)	4.1 (2.8 to 5.4)
UD	15.1 (6.2) (5-42)	6.3 (1.8) (3–11)	8.3 (6.1 to 10.4)
Mean Δ-CSA			
	Mean Δ-CSA (95% CI) in mm^2	Mean Δ-CSA (95% CI) in mm^2	
Right			
ΔP-D	3.9 (3.1 to 4.7)	1.4 (1.0 to 1.9)	
ΔUD-P	1.8 (0.9 to 2.7)	−1.4 (−1.9 to −1.0)	
ΔUD-D	5.6 (4.8 to 6.5)	0.0† (−0.5 to 0.5)	
Left			
ΔP-D	3.3 (2.6 to 4.0)	0.9 (0.4 to 1.4)	
ΔUD-P	1.3 (0.5 to 2.2)	−1.0 (−1.5 to −0.4)	
ΔUD-D	4.6 (3.8 to 5.4)	−0.1† (−0.6 to 0.5)	

*Multivariable linear regression model adjusted for age and gender.
†Not statistically significant (p≥0.05). All the remaining differences in this table were statistically significant (p<0.05).
CSA, cross-sectional area; CTS, carpal tunnel syndrome; D, distal; diff, difference; P, proximal; UD, ultradistal; Δ-CSA, variation of CSA between two levels of the same wrist.

Diagnostic performance of the US definitions of CTS

The best cut-off value for the CSA and Δ-CSA at each anatomical level is shown in table 4. Irrespective of the anatomical level, sensitivity was higher for definition 1 (CSA) (range: 72%–91%) than definition 2 (CSA-difference) (47%–71%) with similar levels of specificity (72%–100%). The diagnostic performance was better for both definitions on the right compared with the left hand (table 4). The UD level yielded the best balance between sensitivity and specificity for definition 1 (CSA) (right hand AUC: 0.982, left hand AUC: 0.956) and definition 2 (CSA-difference) (for the ΔUD-D, right hand AUC:

Table 4 Performance of the definitions 1 (CSA) and 2 (CSA-difference) for CTS diagnosis by US, including their respective cut-off values

US-CTS definition	Cut-off in mm^2	AUC (95% CI)	Sens	Spec	Maximum Youden
CSA					
Right					
CSA-P	≥11 mm^2	0.953 (0.928 to 0.978)	79.1%	97.4%	0.764
CSA-D	≥9 mm^2	0.899 (0.854 to 0.943)	72.4%	94.7%	0.671
CSA-UD	≥10 mm^2	0.982 (0.969 to 0.995)	91.4%	100%	0.914
Left					
CSA-P	≥10 mm^2	0.928 (0.895 to 0.962)	81.6%	91.7%	0.733
CSA-D	≥8 mm^2	0.867 (0.809 to 0.925)	80.7%	72.2%	0.529
CSA-UD	≥10 mm^2	0.956 (0.929 to 0.982)	83.6%	94.4%	0.780
CSA-difference					
Right					
ΔP-D	≥4 mm^2	0.657 (0.593 to 0.721)	47.1%	97.4%	0.445
ΔUD-P	≥1 mm^2	0.719 (0.659 to 0.779)	59.1%	92.1%	0.512
ΔUD-D	≥3 mm^2	0.837 (0.789 to 0.884)	71.0%	97.4%	0.683
Left					
ΔP-D	≥3 mm^2	0.666 (0.599 to 0.732)	53.6%	86.1%	0.397
ΔUD-P	≥2 mm^2	0.685 (0.618 to 0.752)	50.2%	91.7%	0.419
ΔUD-D	≥2 mm^2	0.790 (0.735 to 0.844)	70.1%	91.7%	0.617

Definition 1: CSA: CSA≥cut off, each level separately.
Definition 2: CSA-difference: ΔCSA≥cut off, each difference of levels separately.
AUC, area under the curve; CSA, cross-sectional area; CTS, carpal tunnel syndrome; D, distal; P, proximal; Sens, sensitivity; Spec, specificity; UD, ultradistal; US, ultrasound; Δ-CSA, variation of CSA between two different levels of the same wrist.

0.837, left hand AUC: 0.790). The best performance of the UD level was mostly driven by a higher sensitivity. For instance, for definition 1 (CSA) on the right hand, the sensitivity was 79% for CSA-P and 91% for CSA-UD.

Considering US-CTS present if CSA in ≥1 level is above the cut-off (definition 3) resulted in improved sensitivity with minimal decrease in specificity (table 5). For instance, the CSA-UD alone had a sensitivity of 91% and a specificity of 100% on the right hand (the best performance for definition 1). Definition 3 (CSA-all-levels) on the right hand captured more cases of CTS (sensitivity: 98%) while maintaining excellent specificity (95%). A similar gain in sensitivity is observed with definition 4 (CSA-all-differences) (which is positive if Δ-CSA in ≥1 level is above the cut-off) as compared with definition 2 (CSA-difference).

Definition 5 (CSA-all-levels and CSA-all-differences) and definition 6 (CSA-all-levels or CSA-all-differences) added little diagnostic value compared with definition 3 (CSA-all-levels) and definition 4 (CSA-all-differences) separately. When both CSA in ≥1 level above the cut-off (definition 3) and Δ-CSA in ≥1 level above the cut-off (definition 4) are required (definition 5: CSA-all-levels and CSA-all-differences), specificity increased but at the cost of sensitivity as compared with either definition alone (table 5). The opposite is observed for definition 6 (CSA-all-levels or CSA-all-differences) compared with definitions 3 and 4 alone.

When the UD level is removed from definitions 3 (CSA-all-levels), 5 (CSA-all-levels and CSA-all-differences) and 6 (CSA-all-levels or CSA-all-differences), an important decrease in sensitivity is observed without meaningful gains in specificity (table 6). One example is with definition 3 (CSA-all-levels) which has the best balance between sensitivity (98%) and specificity (95%) of all definitions for the right hand. Removing the UD level resulted in a decrease in sensitivity to 90% while maintaining the same specificity (95%). Combining the CSA with Δ-CSA was also no better than CSA alone for the UD level.

DISCUSSION

US has proven already to be an important tool for diagnosing CTS, and that is supported by our results. In addition, we show that the diagnostic performance of US considering the proximal and distal levels, those more extensively characterised in literature so far, can be improved by adding the UD level to the US protocol in clinical practice.

Clinical symptoms and physical examination have long been the pillar of CTS diagnosis, while US, NCS and MRI can be used as complementary exams for confirmation

Table 5 Performance of the definitions 3 (CSA-all-levels), 4 (CSA-all-differences), 5 (CSA-all-levels and CSA-all-differences) and 6 (CSA-all-levels or CSA-all-differences) for CTS diagnosis by US

US-CTS definition	AUC (95% CI)	Sens	Spec
CSA-all-levels			
Right	0.961 (0.924; 0.999)	97.6%	94.7%
Left	0.839 (0.763; 0.914)	95.7%	72.2%
CSA-all-differences			
Right	0.885 (0.831; 0.939)	87.6%	89.5%
Left	0.800 (0.724; 0.875)	85.0%	75.0%
CSA-all-levels and CSA-all-differences			
Right	0.931 (0.907; 0.954)	86.2%	100%
Left	0.885 (0.839; 0.931)	82.6%	94.4%
CSA-all-levels or CSA-all-differences			
Right	0.916 (0.857; 0.975)	99.1%	84.2%
Left	0.754 (0.671; 0.837)	98.1%	52.7%

Definition 3: CSA-all-levels: CSA≥cut off in at least one level.
Definition 4: CSA-all-differences: ΔCSA≥cut off in at least one difference.
Definition 5: CSA-all-levels and CSA-all-differences: definitions 3 and 4 fulfilled.
Definition 6: CSA-all-levels or CSA-all-differences: definitions 3 or 4 fulfilled.
AUC, area under the curve; CSA, cross-sectional area; Sens, sensitivity; Spec, specificity; US-CTS, ultrasound diagnosis of carpal tunnel syndrome.

Table 6 Performance of the definitions 3.1 (CSA-P-or-D), 5.1 (CSA-P-or-D and CSA-difference-ΔP-D), 5.2 (CSA-UD and CSA-difference-ΔUD-D), 6.1 (CSA-P-or-D or CSA-difference-ΔP-D) and 6.2 (CSA-UD or CSA-difference-ΔUD-D) for CTS diagnosis by US

US-CTS definition	AUC (95% CI)	Sens	Spec
3.1. CSA-P-or-D			
Right	0.921 (0.880; 0.963)	89.5%	94.7%
Left	0.820 (0.744; 0.897)	91.8%	72.2%
5.1. CSA-P-or-D and CSA-difference-ΔP-D			
Right	0.724 (0.690; 0.758)	44.7%	100%
Left	0.759 (0.724; 0.793)	51.7%	100%
5.2. CSA-UD and CSA-difference-ΔUD-D			
Right	0.925 (0.899; 0.952)	85.1%	100%
Left	0.867 (0.826; 0.909)	76.2%	97.2%
6.1. CSA-P-or-D or CSA-difference-ΔP-D			
Right	0.920 (0.873; 0.967)	91.9%	92.1%
Left	0.760 (0.677; 0.844)	93.7%	58.3%
6.2. CSA-UD or CSA-difference-ΔUD-D			
Right	0.946 (0.915; 0.978)	91.9%	97.4%
Left	0.879 (0.822; 0.936)	87.0%	88.9%

Definition 3.1: CSA-P-or-D: CSA≥cut off in at least one of the P or D levels.
Definition 5.1: CSA-P-or-D and CSA-difference-ΔP-D: definition five but with CSA and ΔCSA parameters considering the P and D levels only: CSA≥cut off at the P or D levels and ΔP-D≥cut off.
Definition 5.2: CSA-UD and CSA-difference-ΔUD-D: definition five but with CSA and ΔCSA parameters that consider the UD level: CSA-UD≥cut off and ΔUD-D≥cut-off.
Definition 6.1: CSA-P-or-D or CSA-difference-ΔP-D: definition six but with CSA and ΔCSA parameters considering the P and D levels only: CSA≥cut off at the P or D levels or ΔP-D≥cut-off.
Definition 6.2: CSA-UD or CSA-difference-ΔUD-D: definition five but with CSA and ΔCSA parameters that consider the UD level: CSA-UD≥cut off or ΔUD-D≥cut-off.
AUC, area under the curve; CSA, cross-sectional area; D, distal; P, proximal; Sens, sensitivity; Spec, specificity; UD, ultradistal; US-CTS, ultrasound diagnosis of carpal tunnel syndrome; Δ-CSA, variation of CSA between two different levels of the same wrist.

and treatment consideration. US is a non-invasive, painless, fast and innocuous method, contrasting with NCS, and it is also much cheaper, more readily available and less time-consuming than MRI.

US studies mainly use the CSA parameter in absolute value for diagnosis, with cut-offs varying between 9 mm^2 and 15 mm^2 at different levels of the carpal tunnel and at proximal levels in the forearm.[6 10 14 15] A meta-analysis comparing US and electromyography (EMG)/NCS for the diagnosis of CTS has shown a pooled sensitivity of 80% (95% CI 73% to 88%) and a specificity of 90% (95% CI 83% to 96%) for the US diagnosis, vs 89% (95% CI 84% to 95%) and 77% (95% CI 64% to 90%) for the EMG and NCS combined.[16] Another meta-analysis reported a sensitivity of 78% (95% CI 72% to 84%) and a specificity of 87% (95% CI 79% to 95%) for US diagnosis.[17] These systematic literature reviews show that US (without considering the UD level) has a high specificity for CTS but with a somewhat lower sensitivity compared with EMG/NCS. MRI can yield higher sensitivities and specificities (approximately 94%)[13] but has limitations such as cost, time and availability. In previous studies, the ratio of CSA between two different levels was also studied.[10] In the current study, we opted to include the difference of CSA between levels since differences have been shown to perform slightly better than ratios.[10]

The UD level has been studied only more recently in relatively small studies (N<70) both using MRI and US. With MRI, a maximum sensitivity and specificity of 100% and 94%, respectively, was observed when considering the CSA at the carpal tunnel inlet or at the UD level >15 mm^2.[13] US performance was not as good, with a maximum sensitivity and specificity of 89% and 88%, respectively, when considering the CSA at the carpal tunnel inlet or at the UD level >14 mm^2.[12] In the current study, we have also found that patients with CTS have the MN swollen at the UD level. This information improves our understanding of what happens to the morphology of the MN when it is compressed in the carpal tunnel. The fact that, in patients, the mean CSA is lower at the distal level than at proximal and UD levels supports

the hypothesis that the hook of the hamate level, the narrowest point of the carpal tunnel, is the preferential site of compression, with the MN getting swollen in a higher magnitude proximal and distal to it.

Regarding our cut-offs for CSA at different levels, those for the proximal and distal levels resemble those reported in previous studies,[6 10 14 15] and the cut-off for the UD level is similar to our cut-off for the proximal level. US-CTS definitions using solely the CSA parameter—definition 1 (CSA) and definition 3 (CSA-all-levels)—performed better than corresponding definitions using the Δ-CSA parameter—definition 2 (CSA-difference) and definition 4 (CSA-all-differences), respectively—and better than definitions combining CSA with Δ-CSA—definition 5 (CSA-all-levels and CSA-all-differences) and definition 6 (CSA-all-levels or CSA-all-differences). These data provide no justification for calculating the Δ-CSA as it does not improve the performance of US-CTS.

Adding the UD level to the US protocol can improve sensitivity while maintaining a high specificity, when comparing to only using the proximal and distal levels. In fact, in the current study, US reached a maximum sensitivity and specificity of 98% and 95%, respectively, at the right hand, for definition 3 (CSA-all-levels). On the left hand, sensitivity and specificity for definition 3 (CSA-all-levels) were 96% and 72%, respectively. When considering the proximal and distal levels only, which means applying definition 3.1 (CSA-P-or-D), sensitivity drops to 90% and 92% on the right and left hands, respectively, while specificity remains unchanged.

Based on our results, we propose a new US protocol to study primary CTS in clinical practice: measuring the CSA at the proximal, distal and UD levels and applying the rule of definition 3 (CSA-all-levels). If the CSA is equal to or superior to our determined cut-offs in at least one of the three levels, a CTS diagnosis can be established (box 1). Of note, since the current study evaluated only patients with primary CTS, extrapolation of our findings to secondary CTS should be avoided before future studies can eventually confirm the same in secondary CTS. Previous studies have shown that the morphology of the MN can vary, for example, in patients with rheumatoid arthritis, in comparison with primary CTS.[18]

Box 1 US protocol for diagnosing carpal tunnel syndrome (CTS) by ultrasound

Ultrasound protocol for primary CTS diagnosis
- ⇒ Measure the cross-sectional area (CSA) of the median nerve at the following locations of the wrist:
  - ⇒ Proximal (scaphoid bone).
  - ⇒ Distal (hook of the hamate bone).
  - ⇒ Ultradistal (after exiting carpal tunnel and before division into digital branches).
- ⇒ Check if the CSA is equal to or above the following cut-offs:
  - ⇒ Right hand
    - ⇒ Proximal: 11 mm^2.
    - ⇒ Distal: 9 mm^2.
    - ⇒ Ultradistal: 10 mm^2.
  - ⇒ Left hand
    - ⇒ Proximal: 10 mm^2.
    - ⇒ Distal: 8 mm^2.
    - ⇒ Ultradistal: 10 mm^2.
- ⇒ Diagnose CTS if the CSA is equal to or above cut-off in at least one level of the same hand.

Our study has some limitations worth noting. First, there was a discrepancy in the results between right and left hands. The cut-off values were higher, and the performance was also better, on the right hand. For example, definition 3 (CSA-all-levels) was not better than definition 1 (CSA) for the UD level on the left hand, as it was on the right hand, because of a small decrease in specificity in the first. One likely explanation is the common right-hand dominance, contributing to a higher severity of CTS on the right hand than on the left hand, possibly influencing the US ability to discriminate between cases and controls. This expected discrepancy justified our choice to analyse each hand separately, and our findings convey an important message for the practising clinician using US to diagnose CTS in clinical practice. Assessing hand dominance prior to US performance is key to the appropriate interpretation of the US findings. Unfortunately, we do not have data on hand dominance, but it is well known that right-hand dominance is more prevalent. Moreover, the lack of data on other CTS diagnosing methods, such as NCS or MRI, did not allow to compare the performance of the US with other diagnostic tests. Lastly, being a case–control study, the diagnostic performance can be overestimated due to the exclusion of less well-defined, and therefore, more challenging to diagnose, cases.

Keeping the above limitations in mind, applying definition 3 (CSA-all-levels, that is, at least one of the levels—CSA-P, CSA-D or CSA-UD—with an absolute CSA above the cut-off), our suggested protocol yields an excellent diagnostic performance. It should be noted that this is the largest study to include the UD level, resulting in one of the best accuracies of US for CTS diagnosis, as compared with previously reported studies also to those evaluating other methods, such as NCS and MRI. Identifying and measuring the CSA-UD takes less than 1 min, requiring no particular skill for a US professional, and our whole protocol, including the three levels, can be comfortably performed in less than 5 min (US time), with meaningful gains in diagnosis accuracy in the clinical setting. With our protocol, the CSA is measured only at the wrist, the source of the problem, not considering the measurement of more proximal levels at the forearm. It can also give a picture of the MN's morphology throughout the carpal tunnel, which is additionally informative when planning therapeutic procedures such as 'US-surgery' techniques or classical open surgery. Incomplete sectioning is very rare but sometimes used, particularly in difficult mini-open procedures (also rare). Isolated UD swelling can encourage surgeons to guarantee a complete distal sectioning of the transverse ligament, increasing surgery

success. US can also add safety to the procedure since it allows previous investigation of the anatomy and possible variants (mainly those occurring with the superficial palmar arch, palmar sensory branch or motor branch).

We consider that US can be considered as the method to start with when CTS is suspected in clinical practice because of its excellent performance and advantages over the alternative methods.

In summary, US is a valuable method for diagnosing primary CTS, given its high sensitivity and specificity. Our study is the largest conducted so far that characterises the MN at the UD level and shows the added values of this level in identifying CTS as diagnosed by the clinician. We propose a US protocol of three levels of CSA measurement, for maximal performance: the already-in-use proximal and distal levels, with the addition of the UD level.

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REFERENCES

1 Padua L, Coraci D, Erra C, *et al*. Carpal tunnel syndrome: clinical features, diagnosis, and management. *Lancet Neurol* 2016;15:1273–84.
2 Aroori S, Spence RAJ. Carpal tunnel syndrome. *Ulster Med J* 2008;77:6–17.
3 Sevy JO, Syndrome VMCT. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023. StatPearls Publishing LLC, 2023.
4 Sassi SA, Giddins G. Gender differences in carpal tunnel relative cross-sectional area: a possible causative factor in idiopathic carpal tunnel syndrome. *J Hand Surg Eur Vol* 2016;41:638–42.
5 Wipperman J, Goerl K. Carpal Tunnel Syndrome: Diagnosis and Management. *Am Fam Physician* 2016;94:993–9.
6 Osiak K, Elnazir P, Walocha JA, *et al*. Carpal tunnel syndrome: state-of-the-art review. *Folia Morphol (Warsz)* 2022;81:851–62.
7 Tai TW, Wu CY, Su FC, *et al*. Ultrasonography for diagnosing carpal tunnel syndrome: a meta-analysis of diagnostic test accuracy. *Ultrasound Med Biol* 2012;38:1121–8.
8 Kanagasabai K. Ultrasound of Median Nerve in the Diagnosis of Carpal Tunnel Syndrome-Correlation with Electrophysiological Studies. *Indian J Radiol Imaging* 2022;32:16–29.
9 Takata SC, Kysh L, Mack WJ, *et al*. Sonographic reference values of median nerve cross-sectional area: a protocol for a systematic review and meta-analysis. *Syst Rev* 2019;8:2.
10 Dejaco C, Stradner M, Zauner D, *et al*. Ultrasound for diagnosis of carpal tunnel syndrome: comparison of different methods to determine median nerve volume and value of power Doppler sonography. *Ann Rheum Dis* 2013;72:1934–9.
11 Aboonq MS. Pathophysiology of carpal tunnel syndrome. *Neurosciences (Riyadh)* 2015;20:4–9.
12 Ng AWH, Griffith JF, Lee RKL, *et al*. Ultrasound carpal tunnel syndrome: additional criteria for diagnosis. *Clin Radiol* 2018;73:214.
13 Ng AWH, Griffith JF, Tong CSL, *et al*. MRI criteria for diagnosis and predicting severity of carpal tunnel syndrome. *Skeletal Radiol* 2020;49:397–405.
14 Linehan C, Childs J, Quinton AE, *et al*. Ultrasound parameters to identify and diagnose carpal tunnel syndrome. A review of the literature. *Australas J Ultrasound Med* 2020;23:194–206.
15 Lange J. Carpal tunnel syndrome diagnosed using ultrasound as a first-line exam by the surgeon. *J Hand Surg Eur Vol* 2013;38:627–32.
16 Zaki HA, Shaban E, Salem W, *et al*. A Comparative Analysis Between Ultrasound and Electromyographic and Nerve Conduction Studies in Diagnosing Carpal Tunnel Syndrome (CTS): A Systematic Review and Meta-Analysis. *Cureus* 2022;14:e30476.
17 Fowler JR, Gaughan JP, Ilyas AM. The Sensitivity and Specificity of Ultrasound for the Diagnosis of Carpal Tunnel Syndrome: A Meta-analysis. *Clin Orthop Relat Res* 2011;469:1089–94.
18 Smerilli G, Di Matteo A, Cipolletta E, *et al*. Ultrasound assessment of carpal tunnel in rheumatoid arthritis and idiopathic carpal tunnel syndrome. *Clin Rheumatol* 2021;40:1085–92.