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Original Research

The Inlet and Outlet Ratio: Retrospective and Prospective Study on an Improved Diagnostic Ultrasound Tool for Carpal Tunnel Syndrome

Stefanie Hirsiger, MD, [*] Nora Schlimme, MD, [*] Jean-Benoît Rossel, PhD, [†] Samuel Christen, MD, [*] Adriaan Ockert Grobbelaar, MD, [*] Esther Vögelin, MD [*]

[*] *Department of Hand and Plastic Surgery, Inselspital Bern, University of Bern, Bern, Switzerland*
[†] *CTU Bern, University of Bern, Bern, Switzerland*

A R T I C L E I N F O

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Purpose: This study hypothesized that ratios of sonographic cross-sectional areas (CSAs) throughout the median nerve provide a more reliable tool for diagnosing carpal tunnel syndrome (CTS) than a single CSA value. We first tested this hypothesis in a retrospective cohort and subsequently confirmed it in a prospective blinded case-control series.
Methods: Seventy patients were included in the retrospective study, and 50 patients and matched controls were included for the prospective study. We evaluated 4 CSAs, at the forearm, inlet, tunnel, outlet, and their ratios (R*forearm*, R*inlet*, R*outlet*, R*outlet forearm*) to evaluate compression of the median nerve. All patients underwent nerve conduction studies. For the prospective cohort, Disabilities of the Arm, Shoulder, and Hand scores and Boston Carpal Tunnel Questionnaire scores were evaluated, and ultrasound was performed by 2 examiners for each participant.
Results: The Boston and Disabilities of the Arm, Shoulder, and Hand scores showed worse subjective function in patients with CTS than in controls. Three ultrasonography parameters (CSAs at the inlet, R*inlet*, and R*outlet*) correlated significantly with subjective function. Age and R*inlet* were significantly correlated with severity of CTS in the nerve conduction studies. In both the retrospective and prospective patient groups, the numbers of CSAs at the inlet and outlet were significantly higher than that of CSAs at the tunnel, whereas in the control group, no such compression was found. Of the single measurements, CSAs at the inlet had the best diagnostic performance with an optimized cutoff of 11.75 mm^2. The R*inlet* and R*outlet* ratios performed even better and showed the highest adjusted odds ratios for predicting CTS of all parameters (cutoff R*inlet*, 1.25; R*outlet*, 1.45). Inter-observer correlation was generally high, with better values for single CSAs than for ratios.
Conclusions: The 3 CSA measurements of the median nerve and the associated ratios improved diagnostic power for ultrasonography in CTS in our study.
Type of study/level of evidence: Diagnostic I.

Carpal tunnel syndrome (CTS) is the most common compressive neuropathy in humans and has a high prevalence of 3.8% in the general population.[1,2] Thus, it is one of the pathologies most commonly encountered in clinical practice as a hand and peripheral nerve surgeon. Diagnosis is primarily based on a combination of patient history and clinical examination.[3] To confirm median nerve compression, electrophysiological studies and advanced imaging is often used.[4,5] A gold standard for the diagnosis of CTS is currently lacking.[6]

The optimal adjunctive examination should be available, cheap, and noninvasive and have a high diagnostic power. Nerve conduction studies (NCSs) are widely used to confirm the diagnosis of CTS but are invasive and can be painful.[7,8] For most patients with suspected CTS, the treatment is not influenced by NCS.[1] Hence, the

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Corresponding author: Stefanie Hirsiger, MD, Department of Plastic and Hand Surgery, Inselspital, University Hospital of Bern, University of Bern, Freiburgstrasse 10, 3010 Bern, Switzerland.

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routine use of NCS has been questioned recently.[7] Nevertheless, it provides information about nerve function, whereas ultrasonography (US) can only provide morphologic data. Ultrasonography is a noninvasive, low-cost, and effective diagnostic technique for CTS.[9] There is a good correlation between the diagnostic capacity of NCS and US in CTS.[6,10−12] Despite all these advantages, US has not routinely replaced NCS.[13]

Although some high-quality studies and meta-analyses have tried to define the best US measurement, there is currently no consensus.[14,15] The most frequently used value is the cross-sectional area (CSA) of the nerve.[16] As a consequence of the compression within the carpal tunnel, the median nerve can develop swelling (pseudoneuroma) proximally or distally because of impaired perfusion and edema. Nevertheless, as the thickness of median nerves varies widely between individuals, we are, like many others, convinced that multiple measurements are necessary.[15,17] Cross-sectional areas at the forearm, the inlet (CSA*i*), within the tunnel (CSA*t*), and at the distal outlet (CSA*o*) of the carpal tunnel as well as retinacular bowing and flattening of the nerve have been used as diagnostic markers for CTS with varying sensitivity and specificity.[16−18]

Some studies have tried to combine several measurements, such as adding multiple values as a surrogate marker to improve diagnostic accuracy.[15,17] The most popular ratio is the inlet-to-forearm ratio (R*forearm*), and proposed optimal cutoffs for ratios vary between 1.13 and 1.6; however, the diagnostic accuracy is not optimal in most studies.[16,19,20] In our clinical experience, some patients only have a pseudoneuroma-like thickening of the median nerve distal to the carpal tunnel but not proximal to it and vice versa. In the present study, we tested our hypothesis that ratios at the inlet and outlet of the carpal tunnel versus the tunnel value would be more useful than the previously established single CSA values or the wrist-to-forearm ratio (R*forearm*) for diagnosing CTS. We decided to first test our hypothesis with a retrospective data set and then conduct a prospective study with a control group to confirm our findings.

Materials and Methods

The studies were undertaken in our tertiary hand surgical department. First, a retrospective chart review and analysis was performed. Because our findings were promising, we planned and conducted a prospective case-control study with 2 independent ultrasound examiners to test our hypothesis and evaluate interobserver reliability. The studies were both approved by the responsible local ethics committee in Bern (retrospective study number 2019-02207 and prospective study number 2018-02271) and conducted according to the “strengthening the reporting of observational studies in epidemiology” (STROBE) statement.[21] Written informed consent was obtained from all subjects before the study.

The inclusion criteria for the retrospective study included the following: positive NCS, US including all 4 CSA measurements, successful carpal tunnel release performed as treatment, and written general informed consent. The inclusion criteria for patients for the prospective study included the following: typical symptoms for CTS (nocturnal dysesthesia in fingers, dysesthesias, or sensory deficit of digits I−III with or without motor weakness of thenar muscles) and written specific informed consent. The inclusion criteria for controls for the prospective study included the following: none of the latter symptoms and written specific informed consent. The exclusion criteria for patients for both studies included the following: age of <18 years, with known polyneuropathy, current pregnancy, secondary CTS (tumors and local trauma), or missing consent/refusal of consent.

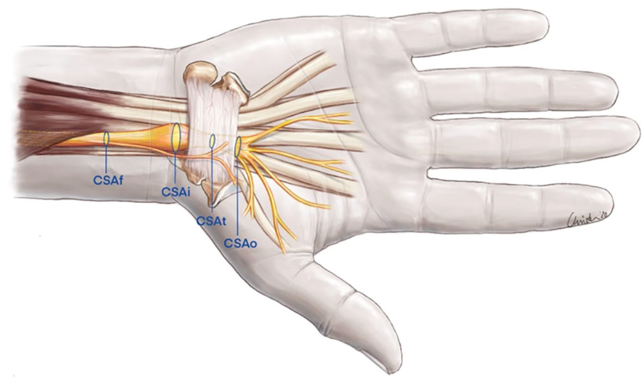

Figure 1. Measurement points along the course of the median nerve through the carpal tunnel. Graphic illustration of a palmar view of the wrist with median nerve showing constriction over the carpal tunnel.

The results of the NCS were stratified for severity into five groups from negative to severe.[22] The Boston Carpal Tunnel Questionnaire and Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire were completed upon inclusion in the prospective study.[23]

Statistical evaluation

In the retrospective study, the nonparametric Shapiro-Wilk test was used to examine data for normality. The Wilcoxon signed-rank test was applied to evaluate for differences between continuous but non-Gaussian distributions. Spearman correlation coefficients were used to evaluate correlation between the variables. *P* values of <.05 were considered significant.

In the prospective study, a power analysis was conducted by the Clinical Trials Unit of the University of Bern on the basis of the results of the retrospective data. Regarding the primary measure outlet CSA ratio, a total sample size of 100 (50 patients and 50 controls) was suggested to allow the detection of a medium effect size of 0.57 between the 2 groups with a power of 80% at a two-sided α level of 0.05. Assuming a sensitivity and specificity of 90%, this sample size will result in an exact 95% CI ranging from 78% to 97%. For continuous variables, chi-squared and Student *t* tests were used. Because bilateral data sets were included (patients with bilateral symptoms and all controls), the ultrasound measurements were not independent, and thus, clustered linear regression was performed with each measure or ratio as a dependent variable and the binary variable that indicates whether the patient suffers from CTS as a predictor. The coefficient associated with this variable gives the mean difference between both groups. CIs and *P* values were then computed by considering each patient as a cluster. Comparison between the retrospective and prospective groups was performed in the same way. All measurements were then evaluated for their odds ratio predicting CTS, with adjustment for age, sex, and DASH sore, using logistic regression. Nerve conduction study severity was correlated with outcome scores, age, and ultrasound measurements. Receiver operating characteristic curves were built to find the optimal discriminative value between patients and controls and optimized cutoffs. Bland-Altman plots and intraclass correlation coefficients were calculated for interobserver reliability for each measurement. For those calculations, each patient was considered a cluster. Standard errors and *P* values were then estimated using bootstrap methods. Limits of agreement in the Bland-

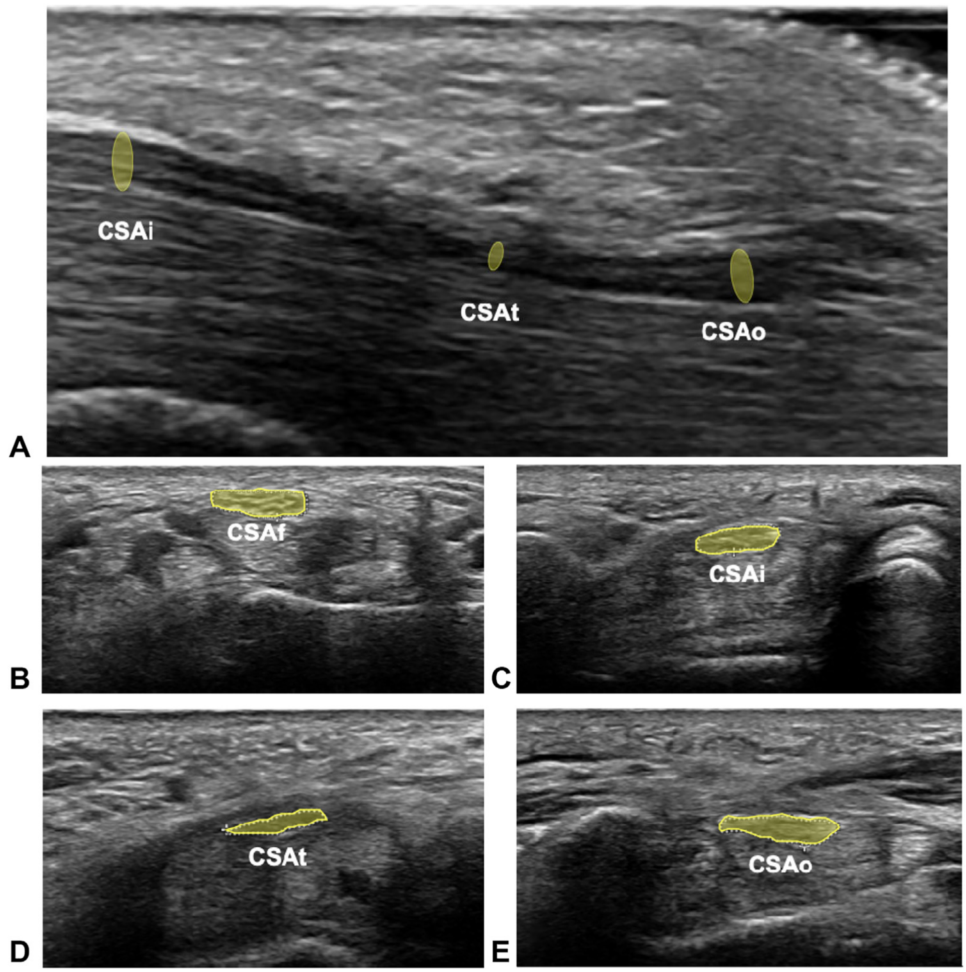

Figure 2. In vivo longitudinal and axial ultrasound of the median nerve. **A** Longitudinal view of the median nerve over the carpal tunnel. (CSAf would be more proximal and is thus not shown on this image). **B**−**E** Axial view of the median nerve at the different measurement points.

Table 1
Patient Characteristics in the Retrospective and Prospective Cohort

Patient Parameters	Retrospective	Prospective	
	Patients (n = 70)	Patients (n = 50)	Controls (n = 51)
Age (y), mean (total range)	66 (21−92)	59 (27−89)	58 (21−91)
Sex: male/female	27/43	25/25	25/26
Bifid nerves	8	4	11
	Wrists (n = 81)	Wrists (n = 76)	Wrists (n = 102)
Affected side: right/left/bilateral	52/29/11	40/36/26	All bilateral
Severity of CTS according to NCS: normal/mild/moderate/severe	0/30/23/28	9/2/45/20	None
DASH score, mean (SD)	Not available	35.1 (24.3)*	8.1 (9.7)
Boston score, mean (SD)	Not available	50.5 (15.8)*	25.1 (7.6)

* $P < .001$ (patients vs controls).

Altman plots were computed using the method described previously.[24]

Clinical setup

For the retrospective study, all patients were examined sonographically by the same fellowship-trained hand surgeon with more than 10 years of median nerve ultrasound experience (E.V.). For the prospective study, all participants underwent ultrasound by E.V. and a consultant with 3 years of median nerve ultrasound experience for the calculation of interobserver correlation.

The patient was positioned seated in front of the examiner. The wrist was placed in supination and neutral flexion/extension, lying relaxed on the dorsum of the hand. A nut-sized portion of ultrasound gel was applied, and the probe (retrospective: 17 MHz Epiq 5G [Philips Medical System]; prospective: 22 MHz Affinity 70G, Linear Array Transducer [Philips Medical System]) was positioned with minimal pressure. First, the surrounding soft tissue structures were assessed and scanned for tumors, cysts, or displaced bone

Table 2
Cross-Sectional Area Measurements of the Median Nerve*

CSA values	Retrospective	Prospective	
		Patients	Controls
CSA*f*	12.7†,‡ (± 3.3)	13.4†,‡ (± 4.1)	10.7 (± 2.7)
CSA*i*	14.9†,‡ (± 4.6)	14.7†,‡ (± 4.7)	10.6 (± 2.7)
CSA*t*	8.8‡ (± 2.5)	8.9‡ (± 2.8)	10.4 (± 2.3)
CSA*o*	15.0†,§ (± 4.6)	16.7†,‡ (± 6.7)	12.8 (± 3.7)

* CSA values are in square millimeters and ratios. Continuous data are shown as means (±SD).
† $P < .001$ versus CSAt.
‡ $P < .001$ versus controls.
§ $P < .005$ versus controls.

Table 3
Ratios of CSA Measurements*

Ratios	Retrospective	Prospective	
		Patients	Controls
R*forearm*	1.2† (± 0.4)	1.1† (± 0.2)	1.0 (± 0.2)
R*inlet*	1.8†,‡,§ (± 0.5)	1.7†,‡,§ (± 0.6)	1.0§ (± 0.2)
R*outlet*	1.8†,‡,§ (± 0.6)	1.9†,‡,§ (± 0.7)	1.2‡,‖ (± 0.2)
R*outlet forearm*	1.2 (± 0.5)	1.2 (± 0.3)	1.2‡ (± 0.3)

* Continuous data are shown as means (±SDs).
† $P < .001$ versus controls.
‡ $P < .001$ versus R*forearm*.
§ $P < .001$ versus R*outlet forearm*.
‖ $P < .001$ versus R*inlet*.

fragments. The median nerve was then localized; a schematic representation of the measurement points is shown in Figure 1. The structure of the nerve was then assessed longitudinally (Fig. 2A). Subsequently, the median nerve CSA on the inner border of the hyperechogenic rim (corresponding to the epineurium) was measured in an axial plane (Fig. 2B–E) using the continuous tracing method. If the median nerve was bifid, the two parts were measured separately and then added together to a CSA value. Cross-sectional area was first measured at the distal forearm approximately 2 cm proximal of the bracelet lines, where the median nerve appears from below the muscle to the surface of the superficial flexor tendons (cross-sectional area at the forearm [CSA*f*]). Cross-sectional area at the inlet was then measured at the entrance of the carpal tunnel. Our reference was the view between the scaphoid tubercle and pisiform bone, where the probe was positioned to find the correct orthogonal orientation to the nerve. Cross-sectional area within the tunnel was measured as the smallest CSA within the carpal tunnel, and CSA*o* was measured distal to the carpal tunnel as the largest CSA of the median nerve before separating into common digital nerve branches. These absolute CSA values and the respective ratios (inlet/forearm = R*forearm*, inlet/tunnel = R*inlet*, outlet/tunnel = R*outlet*, and outlet/forearm = R*outlet forearm*) were evaluated and compared.

Results

Epidemiologic data

Patient characteristics are displayed in Table 1. For the retrospective study, 70 patients operated on between June 2016 and April 2020, thereof 11 patients who underwent bilateral surgery were included, resulting in 81 wrists for evaluation.

For the prospective study, 50 patients (76 wrists) and 51 controls (102 wrists) were included between December 2019 and September 2020. There was no significant difference between the group with CTS and the control group regarding sex- and age-matched correlation. Patient-reported outcome measures (DASH and Boston scores) showed significantly inferior function in the patient group. Age was similar in the retrospective and prospective cohorts (Table 1). There were 8 patients (11.4%) with bifid nerves in the retrospective group and 4 patients (5.3%) and 11 controls (10.8%) with bifid nerves in the prospective cohort. Because the subsets were too small, a stratified analysis could not be performed.

Single CSA values

The CSA measurements are summarized in Table 2. Mean values for the CSA measurements and ratios did not differ between the two patient groups (retrospective and prospective). In both patient groups, the CSA*f*, CSA*i*, and CSA*o* were significantly higher than the CSA*t*, in congruency with a compression within the tunnel. Cross-sectional areas at the inlet and CSA*o* did not differ significantly. In the control group, all CSA measurements were similar. When comparing the US measurements between the two patient and control groups, proximal and distal values (CSA*f*, CSA*i*, and CSA*o*) were significantly higher, whereas the tunnel value was lower than that in the control group.

Combined CSA values: ratios

The CSA ratios are summarized in Table 3. The values between the retrospective and prospective patient groups did not differ significantly. When comparing the ratios between each other, the R*inlet* and R*outlet* were significantly higher than the R*forearm* and R*outlet forearm* in both the retrospective and prospective patient groups. The R*outlet* was also significantly higher than the R*outlet forearm* in patient groups, whereas in the control group, R*outlet* and R*outlet forearm* were similar but higher than R*forearm* and R*inlet*. When comparing the two patient groups to the control group, R*inlet*, R*outlet*, and R*forearm* were significantly different, whereas R*outlet forearm* was not.

Correlations

Age at surgery was significantly positively correlated with NCS severity of CTS in both the retrospective and prospective patient groups (eg, in the prospective group, $\rho = 0.49$; 95% CI, 0.25–0.72; $P < .001$). No significant correlation of age with the different ultrasound measurement was found.

In the prospective patient group, CSA*i*, R*inlet*, and R*outlet* were significantly correlated with patient-reported outcomes (DASH and Boston scores). The severity of CTS in NCS was less clearly correlated with the US measurements. Only R*inlet* was significantly correlated with severity (Table 4). Potentially this can be explained by uneven distribution between the severity groups (Table 1).

Test performance

Using receiver operating characteristic curve calculations, test performance for CTS for each variable was evaluated. Of the four single values, CSA*i* had the best performance (area under the curve, 0.79), with an optimized cutoff of 11.75 mm^2 (sensitivity, 0.78; specificity, 0.70), using Youden's criterion. The R*inlet* and R*outlet* performed even better (area under the curve, 0.93 and 0.90, respectively). The optimized cutoffs were 1.25 (sensitivity, 0.80; specificity, 0.92) for R*inlet* and 1.45 (sensitivity, 0.80; specificity, 0.85) for R*outlet* (Fig. 3). Concerning diagnostic accuracy, CSA*f*, CSA*t*, and CSA*o* were positively associated and CSA*t* was negatively associated with the occurrence of CTS in the univariate logistic regression. When adjusting for age, sex, and DASH score, the R*inlet* and R*outlet* showed the highest odds ratios for predicting CTS of all

Table 4
Spearman Rank Correlation Coefficients Between the DASH Score, Boston Score, and Severity in NCSs Versus Ultrasound Measurements*

	DASH Score	Boston Score	Severity in NCS
CSA*f*	0.27 (0.09 to 0.45;.004)	0.32 (0.14 to 0.51;.001)	−0.05 (−0.30 to 0.20;.687)
CSA*i*	**0.34 (0.18 to 0.51; <.001)**	**0.42 (0.26 to 0.57; <.001)**	0.06 (−0.15 to 0.28;.566)
CSA*t*	−0.24 (−0.41 to −0.07;.007)	−0.26 (−0.42 to −0.10;.001)	−0.19 (−0.45 to 0.07;.161)
CSA*o*	0.20 (0.03 to 0.37;.023)	0.27 (0.10 to 0.45;.002)	−0.04 (−0.26 to 0.18;.717)
R*forearm*	0.22 (0.06 to 0.38;.008)	0.24 (0.09 to 0.40;.003)	0.18 (−0.05 to 0.40;.121)
R*inlet*	**0.54 (0.42 to 0.67; <.001)**	**0.63 (0.53 to 0.73; <.001)**	**0.29 (0.08 to 0.50;.007)**
R*outlet*	**0.48 (0.34 to 0.62; <.001)**	**0.57 (0.46 to 0.68; <.001)**	0.14 (−0.10 to 0.38;.255)
R*outlet forearm*	−0.02 (−0.17 to 0.13;.781)	0.02 (−0.12 to 0.17;.756)	−0.03 (−0.28 to 0.22;.840)

Significant values are marked in bold letters.
* Data are given as Spearman correlation coefficient ρ (95% CI; *P* value).

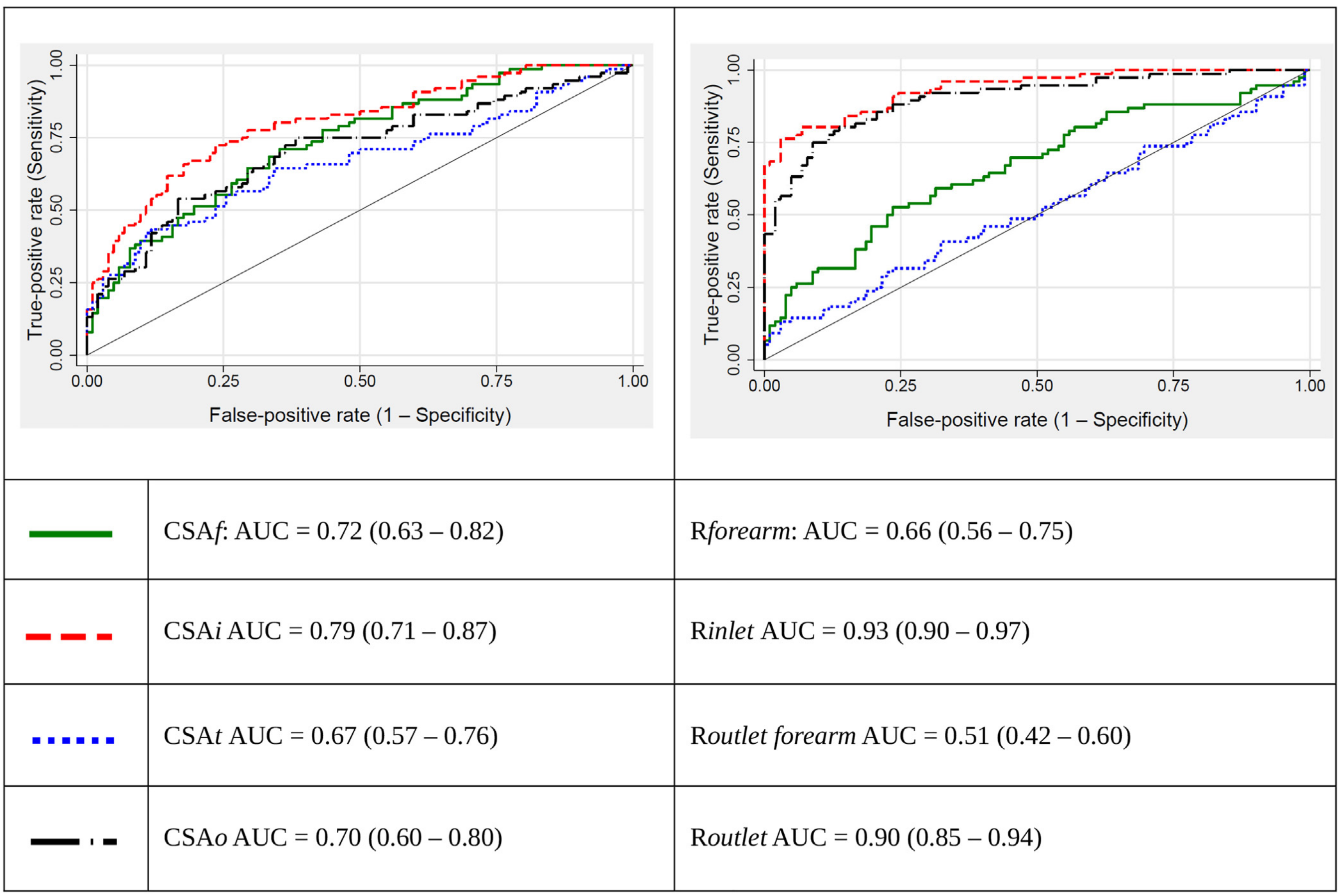

Figure 3. Receiver operating curves. The area under the curve (AUC) and 95% CI for each ultrasound measure and ratio.

measurements (Supplementary Table 1, available online on the *Journal*'s website at www.jhandsurg.org).

Interobserver agreement

Interobserver agreement showed no significant bias between the examiners. It showed limits of agreement of approximately 5 mm^2 for the CSA at the forearm, inlet, and tunnel and approximately 8 mm^2 at the outlet, whereas examiner 2 measured slightly higher values for the inlet, tunnel, and outlet CSA (Supplementary Fig. 4A, available online on the *Journal*'s website at www.jhandsurg.org). The difference between examiners correlated to the height of the ratio; the higher the difference between the two CSA values, the higher the difference between examiners (Supplementary Fig. 4B, available online on the *Journal*'s website at www.jhandsurg.org). The intraclass correlation coefficient was generally high, with better values for single CSAs than for ratios (Supplementary Table 2, available online on the *Journal*'s website at www.jhandsurg.org).

Discussion

Carpal tunnel syndrome is a very common nerve compression disorder, and patients may experience an important impairment in quality of life.[25] Depending on the severity and duration of the symptoms, relief by conservative treatment or surgery can be offered.[26]

Before surgery is indicated, confirmation of the diagnosis is important. Ultrasonography has been suggested as an alternative to electrodiagnostic studies in CTS; however, a gold standard for measurements is still lacking.[6,19] Cross-sectional area at the inlet is the most commonly used criterium in the literature. However, in some studies, CSA*i* had the best diagnostic accuracy,[17] and in others, CSA*o* was superior.[27,28] Furthermore, there is no consensus about the optimal cutoff values, ranging from 9.0 to 12.6 mm^2 for inlet-level measurements and from 9.5 to 10.0 mm^2 for outlet-level measurements.[14] The present study was designed to find the best measurement for diagnosing CTS by US. We hypothesized that multiple measurements of the median nerve over the carpal tunnel and associated ratios would perform better to diagnose CTS than single values. We first conducted the retrospective evaluation. Because the results were promising, a prospective case-control study was performed to confirm our findings and compute optimal cutoff values. In CTS, the median nerve is typically compressed by the transverse retinaculum over the carpal tunnel.[24,25] This was confirmed in this study because we found a significant reduction of the CSA within the carpal tunnel in both the retrospective and prospective patient groups but not in the control groups. Clinical symptoms correlated with severity of CTS and ultrasound findings in the literature.[29,30] In line with this, patient-reported outcomes (DASH and Boston scores) showed significantly diminished hand function in patients with CTS compared with that in controls in our study.

Age significantly correlated with severity of NCS in this study, showing more severe CTS in older patients. Nevertheless, NCSs do not always correctly depict clinical symptoms, and US can be helpful to confirm diagnosis in NCS-negative CTS.[31,32] In our prospective patient group, we had 9 of 50 patients with negative NCS but positive clinical scores and ultrasound findings. In contrast to other studies, we did not find any significant correlation of age with the different measurements, and only the ratio inlet was correlated with severity.[11,30,33] This might be explained by the fact that some levels in the classification of CTS were underrepresented. To answer which ultrasound measurement had the best test characteristic in our study, we computed receiver operating characteristic curves. Of the single CSA measurements, CSA*i* demonstrated the best diagnostic performance, and the optimized cutoff value was 11.75 mm^2. The inlet and outlet ratios performed even better and showed the highest adjusted odds ratios for predicting CTS of all parameters. The optimized cutoffs were 1.25 for the inlet and 1.45 for the outlet ratio. Of note, the classic inlet-to-forearm ratio (R*forearm*) cannot be recommended on the basis of our data because it showed much inferior performance. This might be explained by our relatively distal measurement point of the median nerve for CSA*f* because measuring where the median nerve is superficial from the superficial flexors could already be affected with pseudoneuroma in CTS. Because ultrasound is operator-dependent, we compared two examiners with different degrees of experience.[5] Interobserver agreement intraclass correlation coefficient was generally high, with better values for single CSAs than for ratios. Our results for the CSA measurements and ratios in the prospective cohort confirmed the results of the retrospective data set with almost identical mean values in the patient groups and significant differences to controls, suggesting that the technique is quite exact.

Based on the results of our studies, three CSA values throughout the median nerve should be measured in CTS: at the inlet, within the tunnel, and at the outlet distal to the retinaculum. The best diagnostic performance was obtained by using the inlet-to-tunnel and outlet-to-tunnel ratios for diagnosis of CTS.

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