**RESEARCH ARTICLE**

# Does the ratio of the carpal tunnel inlet and outlet cross-sectional areas in the median nerve reflect carpal tunnel syndrome severity?

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## Abstract
Although ultrasound measurements have been used in previous studies on carpal tunnel syndrome to visualize injury to the median nerve, whether such ultrasound data can indicate the severity of carpal tunnel syndrome remains controversial. The cross-sectional areas of the median nerve at the tunnel inlet and outlet can show swelling and compression of the nerve at the carpal. We hypothesized that the ratio of the cross-sectional areas of the median nerve at the carpal tunnel inlet to outlet accurately reflects the severity of carpal tunnel syndrome. To test this, high-resolution ultrasound with a linear array transducer at 5–17 MHz was used to assess 77 patients with carpal tunnel syndrome. The results showed that the cut-off point for the inlet-to-outlet ratio was 1.14. Significant differences in the inlet-to-outlet ratio were found among patients with mild, moderate, and severe carpal tunnel syndrome. The cut-off point in the ratio of cross-sectional areas of the median nerve was 1.29 between mild and more severe (moderate and severe) carpal tunnel syndrome patients with 64.7% sensitivity and 72.7% specificity. The cut-off point in the ratio of cross-sectional areas of the median nerve was 1.52 between the moderate and severe carpal tunnel syndrome patients with 80.0% sensitivity and 64.7% specificity. These results suggest that the inlet-to-outlet ratio reflected the severity of carpal tunnel syndrome.

***Key Words:*** *nerve regeneration; peripheral nerve injury; ultrasonography; carpal tunnel syndrome; diagnosis; cross-sectional area; classification; clinical laboratory technique; electrodiagnosis; median nerve; 973 Program; neural regeneration*

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## Introduction
Carpal tunnel syndrome (CTS) is the most common form of peripheral entrapment neuropathy, and occurs as a consequence of compression of the median nerve at the wrist (Alfonso et al., 2010; Atroshi et al., 2011). The most reliable method for confirming a clinical diagnosis of CTS is electrophysiological measurements, but false negatives occur with this method at a rate of 10–20% (Duncan et al., 1999). Recently, the focal swell of the median nerve at the carpal tunnel, assessed as the cross-sectional area (CSA) and wrist-to-forearm ratio, has been considered as a diagnostic criterion for CTS by many clinicians (Ashraf et al., 2009; Fowler et al., 2011; Shen and Li, 2012; Ajeena et al., 2013). However, the reported cut-off values vary between studies (Mhoon et al., 2012; Kim et al., 2014), most of which only took measurements of the median nerve CSA at a single site.

The hypothesis of this study was that measuring the median nerve CSAs at both the swollen and compressed sites improves the diagnostic sensitivity of high-resolution ultrasound for CTS.

## Subjects and Methods
### Participants
The experimental protocol was approved by the Ethics Committee of the Huashan Hospital, Fudan University, China. All the participants provided their written informed consent to particate in this study.

The diagnosis of CTS and severity grading were based on the clinical symptoms and signs and electrophysiological data. The CTS for each patient was classified as one of three stages: mild, moderate, or severe (Gu, 2010).

Seventy-seven patients who presented with symptoms of CTS between December 2013 and February 2014 were included in this study. The clinical symptoms included: (1) waking from sleep with a feeling of numbness or swelling, (2) clumsiness when using their hands to grip objects, and (3) hypotrophy or atrophy of the thenar eminence. Electrophysiological measurements were taken to further confirm the clinical signs.

The CTS patients were divided into three groups based on their clinical symptoms and signs and the electrophysiological results. (1) Mild CTS group: numbness, two-point discrimination < 4 mm and a motor latency of the median nerve < 4.5 ms; (2) moderate CTS group: numbness, hypoesthesia, two-point discrimination > 4 mm and < 10 mm, and a motor latency of the median nerve > 4.5 ms and < 10 ms; (3) severe CTS group: numbness, sensory deficit, hypotrophy or atrophy of the thenar eminence, two-point discrimination > 10 mm, and a motor latency of the median nerve > 10 ms.

Twenty-two healthy subjects were randomly chosen from the staff at the outpatient clinic to use as a control group that showed no signs or symptoms of CTS. They were subjected to the same medical examination and electrophysiological studies to verify their health. They had no history of wrist injury or surgery, as well as other peripheral nerve disorders.

### Ultrasound procedure

Ultrasonography was performed using a Philips iU 22 ultrasound system with a linear array transducer (Philips, Bothell, WA, USA) at 5–17 MHz. The examiner was blinded to the results of the clinical and electrophysiological tests. All wrists were scanned in the neutral position with the palm facing up and the fingers semi-extended (**Figure 1A**). The median nerve in the carpal tunnel was evaluated in both the transverse and sagittal planes. A location 10 cm proximal to the distal flexor crease was chosen as the forearm site. The CSA of the median nerve was measured proximal to the carpal tunnel at the level of the pisiform bone (**Figure 1B**).

Compression or swelling of the median nerve was assessed in the sagittal plane of the wrist (**Figure 1C**). The anteroposterior diameter of the compression and swelling sites of the median nerve and the transverse carpal ligament thickness were measured. In the transverse plane of the wrist, the configuration of the median nerve was observed at three different levels: the carpal tunnel inlet and outlet and the forearm. The CSA of the median nerve was measured at the carpal tunnel inlet (CSA-I), outlet (CSA-O), and at the forearm (CSA-F). The flattening ratio of the median nerve at the carpal tunnel outlet (defined as the ratio of the major-to-minor axes of the median nerve), inlet-to-outlet ratio (defined as the ratio of the CSA-I to CSA-O), and the wrist-to-forearm ratio (defined as the ratio of the CSA-I to CSA-F) were calculated. The CSA was calculated using a continuous trace on the ultrasound system. The epineurial rim was excluded from the measured area.

### Statistical analysis

The data were analyzed using SPSS Version 16 software (SPSS, Chicago, IL, USA). Two-sample *t*-tests were used to test the significance of differences between the normally distributed data in the control and CTS groups. To evaluate the differences between the mild, moderate, and severe CTS groups, Kruskal-Wallis *H*-tests were used for data with non-normal distributions. Chi-square tests were used for testing the association between qualitative variables. The area under the receiver operating characteristic curves and the cut-off measurement values were calculated. *P*-values less than 0.05 were considered statistically significant.

## Results

### Analysis of the baseline participant data

The cohort included 72 females (93.5%) and 5 males (6.5%) with ages ranging from 27 to 72 years (average: 51.4 years), and 46 right wrists (59.7%) and 31 left wrists (40.3%) were analyzed. The duration of the medical histories ranged from 3 to 120 months, with an average of 48 months. The control group included 20 females (90.9%) and 2 males (9.1%) aged from 35 to 55 years (average: 41.3 years), with 12 right wrists (54.5%) and 10 left wrists (45.5%). There were 11 patients (14.3%) with mild, 51 (66.2%) with moderate, and 15 (19.5%) with severe CST in the median nerve of the wrist (**Table 1**).

### Ultrasonography measurements

*CTS patients and controls*

Significant differences in the CSA-I, wrist-to-forearm ratio, inlet-to-outlet ratio, and transverse carpal ligament thickness were detected between the CTS and control groups ($P < 0.05$; **Table 2**). Using the cut-off values from the receiver operating characteristic curves (**Figure 2**), the accuracy of the ultrasonography measurements for diagnosing CTS was evaluated. The area under the curve of the CSA-I was 0.83 at a cut-off of 9.05 $mm^2$, indicating 85.7% sensitivity and 55% specificity. The area under the curve of the wrist-to-forearm ratio was 0.84 at a cut-off value of 1.41, indicating 81.8% sensitivity and 68.2% specificity. The area under the curve of the inlet-to-outlet ratio was 0.78 at a cut-off value of 1.14, indicating 77.9% sensitivity and 55.5% specificity. The area under the curve of the transverse carpal ligament thickness was 0.90 at a cut-off value of 3.77 mm, indicating 89.6% sensitivity and 81.8% specificity (**Table 3**).

*Classification of CTS*

Kruskal-Wallis *H*-tests were used to assess the significance of differences between the groups. The inlet-to-outlet ratio from ultrasound measurements was significantly different among the mild, moderate, and severe CTS patients ($P < 0.05$; **Table 4**). Using the cut-off values from the receiver operating characteristic curve, the accuracy of the ultrasonography measurements for diagnosing CTS was evaluated. The area under the curve of the inlet-to-outlet ratio indicated that the best cut-off value to discriminate between mild *versu*s moderate and severe was 1.29, and the cut-off value for moderate *versus* severe was 1.52 (**Table 5**).

## Discussion

The clinical diagnosis of CTS is mainly based on a patient's

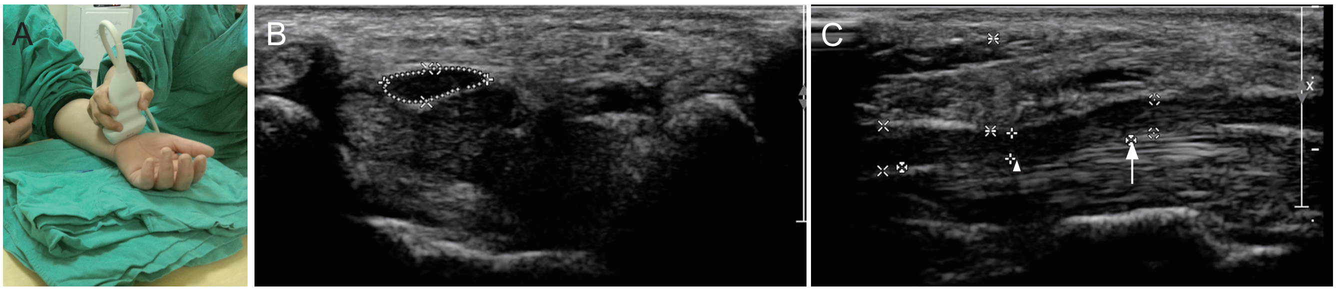


**Figure 1 Ultrasonography image of a median nerve in a patient with carpal tunnel syndrome.**
(A) Position of the ultrasound device with the wrist in a neutral position, palm facing up, and the fingers semi-extended. (B) A cross-sectional view of the median nerve at the carpal tunnel inlet. The median nerve is outlined with a dotted line and appears swollen. (C) A sagittal plane view of the median nerve at the carpal tunnel. Swollen (arrow) and compression (triangle) lesions of the median nerve in the sagittal plane of wrist are shown.

**Table 1 Basic characteristics of the subjects in control and CTS groups**

| | Control group ($n$ = 22) | CTS group ($n$ = 77) |
|---|---|---|
| Sex | | |
| Female ($n$) | 20 | 72 |
| Male ($n$) | 2 | 5 |
| Age (mean ± SD, year) | 41.3±5.68 | 51.4±8.22 |
| Wrist | | |
| Right ($n$) | 12 | 46 |
| Left ($n$) | 10 | 31 |
| Duration of symptoms (mean ± SD, month) | None | 48.0±20.8 |

CTS: Carpal tunnel syndrome.

**Table 2 Ultrasonography measurements from subjects in control and CTS groups**

| | Control group ($n$ = 22) | CTS group ($n$ = 77) |
|---|---|---|
| CSA-I ($mm^2$) | 8.55±1.56 | 12.86±4.83* |
| CSA-O ($mm^2$) | 7.72±1.41 | 8.66±3.27 |
| IOR | 1.11±0.10 | 1.50±0.55* |
| WFR | 1.32±0.24 | 2.03±0.81* |
| FR | 2.88± 1.01 | 3.01±0.91 |
| TCL-T (mm) | 3.52±0.46 | 4.74±1.00* |

*$P$ < 0.05, *vs*. the control group. Data are expressed as the mean ± SD (two-sample $t$-test). CTS: Carpal tunnel syndrome; CSA-I: cross-sectional area of the median nerve at the tunnel inlet; CSA-O: cross-sectional area of the median nerve at the tunnel outlet; IOR: inlet-to-outlet ratio; WFR: wrist-to-forearm ratio; FR: flattening ratio; TCL-T: transverse carpal ligament thickness.

**Table 3 Cut-off values for the ultrasonography measurements using the receiver operating characteristic curve**

| | Cut-off value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| CSA-I ($mm^2$) | 9.05 | 85.7 | 55.0 |
| WFR | 1.41 | 81.8 | 68.2 |
| IOR | 1.14 | 77.9 | 55.5 |
| TCL-T (mm) | 3.77 | 89.6 | 81.8 |

CSA-I: Cross-sectional area of the median nerve at the tunnel inlet; WFR: wrist-to-forearm ratio; IOR: inlet-to-outlet ratio; TCL-T: transverse carpal ligament thickness. Statistical analysis was performed using the receiver operating characteristic curves. $n$ = 99.

**Table 4 Ultrasonography parameters from patients with different severity CTS**

| | Mild CTS ($n$ = 11) | Moderate CTS ($n$ = 51) | Severe CTS ($n$ = 15) |
|---|---|---|---|
| CSA-I ($mm^2$) | 9.53±1.64 | 12.88±4.57* | 15.21±5.98* |
| CSA-O ($mm^2$) | 8.29±1.33 | 9.45±3.59 | 8.10±3.19 |
| IOR | 1.16±0.20 | 1.42±0.43* | 2.01±0.73*# |
| WFR | 1.62±0.25 | 1.98±0.73 | 2.53±1.08* |
| FR | 3.63±0.78 | 2.91±0.91* | 2.90±0.89 |
| TCL-T (mm) | 3.81±0.59 | 4.95±1.03* | 4.74±0.75* |

*$P$ < 0.05, *vs*. the mild CTS group; #$P$ < 0.05, *vs*. the moderate CTS group. Data are expressed as the mean ± SD (Kruskal-Wallis $H$-test). CTS: Carpal tunnel syndrome; CSA-I: cross-sectional area of the median nerve at the tunnel inlet; CSA-O: cross-sectional area of the median nerve at the tunnel outlet; IOR: inlet-to-outlet ratio; WFR: wrist-to-forearm ratio; FR: flattening ratio; TCL-T: transverse carpal ligament thickness.

characteristic symptoms and signs, often with confirmation using electrophysiological measurements (Beekman and Visser, 2003). Electrodiagnosis is a valuable technique for the diagnosis of CTS and evaluating its severity (Graham, 2008) by focusing on the dysfunction of the median nerve. Another technique, ultrasonography, provides a simple, noninvasive method for visualizing peripheral nerve pathology and the surrounding anatomic structures (Buchberger et al., 1991, 1992; Karadag et al., 2010).

Recent advances in ultrasonography have allowed its use as a tool to complement the diagnosis, classification, treatment, and follow up of CTS in patients (Mondelli et al., 2008; Smidt and Visser, 2008; Visser et al., 2008; Vogelin et al., 2010). The use of diagnostic ultrasound for confirming a clinical diagnosis of CTS is a more cost-effective strategy than current methods (Fowler et al., 2013). The CSA of nerve was previously reported to be the most reliable and accurate measurement (Koyuncuoglu et al., 2005; Bartels et al., 2008). In the present study, the CSA was measured at the carpal tunnel inlet and outlet, which were defined by the pisiform and hamate bones. The CSA-I is the most commonly used parameter for diagnosing CTS. Many studies have reported

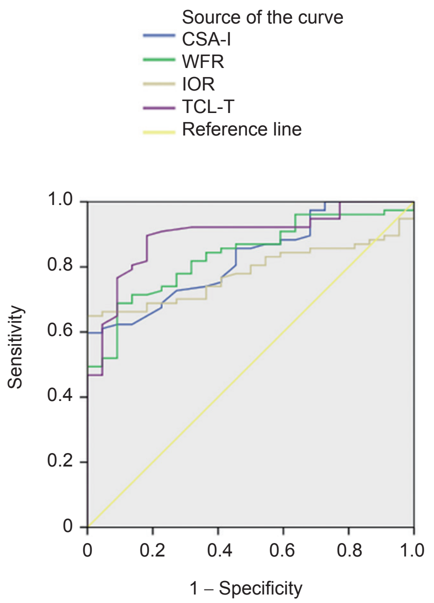


**Figure 2 Receiver operating characteristic curves were used to determine the cut-off values for the cross-sectional areas (CSA) of the median nerve at the tunnel inlet (CSA-I), wrist-to-forearm ratio (WFR), inlet-to-outlet ratio (IOR), and transverse carpal ligament thickness (TCL-T) for the carpal tunnel syndrome group.**
The area under the curve of the measurements indicates the efficacy of diagnosing carpal tunnel syndrome.

CSA-I cut-off values for diagnosing CTS, ranging from 9 to 15 mm$^2$ with 57–98% sensitivity and 51–100% specificity. Tai et al. (2012) performed a meta-analysis and reported that a CSA-I ≥ 9 mm$^2$ is the best single diagnostic criterion. The data from the present study showed a cut-off value of 9.05 mm$^2$ with 85.7% sensitivity and 55% specificity. Another potentially useful measurement is the wrist-to-forearm ratio. Hobson-Webb et al. (2008) indicated that a wrist-to-forearm ratio ≥ 1.4 gave 100% sensitivity for diagnosing CTS, while using only the median nerve area at the wrist resulted in a sensitivity of 45–93%. Lange (2013) indicated that the optimal cut-off value for the wrist-to-forearm ratio for CTS was 1.6. In the present study, there was a significant difference between the wrist-to-forearm ratio in the CTS and control groups. The cut-off value was 1.41 with 81.8% sensitivity and 68.2% specificity.

The above measurements of the median nerve area may only represent the effects of one lesion of the median nerve at the wrist. However, a previous study reported that both swollen and compressed nerve can be observed at the carpal tunnel (Hobson-Webb et al., 2012). We hypothesized that the ratio of the swollen and compressed site values provides a better alternative for diagnosing and grading the severity of CTS. The ratio of the CSA-I and CSA-O (inlet-to-outlet ratio) was calculated in the present study to assess the changes in the median nerve at the wrist. The area under the curve for the inlet-to-outlet ratio was 0.782 at a cut-off value of 1.14 with 77.9% sensitivity and 55.5% specificity.

Appropriately grading the severity of CTS is important for treatment planning and follow-up. Many researchers have classified CTS severity based on the clinical features and

**Table 5 Sensitivity and specificity of the IOR cut-off values for discriminating between the different CST grades**

| Group | IOR | | *P* value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| | < 1.29 | > 1.29 | | | |
| Mild CTS (*n* = 11) | 8* | 3* | 0.00 | 64.7 | 72.7 |
| Moderate and severe CTS (*n* = 66) | 18* | 48* | | | |
| | < 1.52 | > 1.52 | | | |
| Moderate CTS (*n* = 51) | 32* | 19* | 0.00 | 80 | 64.7 |
| Severe CTS (*n* = 15) | 3* | 12* | | | |

IOR: Inlet-to-outlet ratio; CTS: carpal tunnel syndrome; *: the number of patients. The statistical analysis was performed using chi-square tests.

electrophysiological findings (Ghasemi-Rad et al., 2014). Recent studies suggested that the CSA-I can be used for grading the severity of CTS (Karadag et al., 2010). However, Mhoon et al. (2012) reported that although median nerve ultrasound is a highly sensitive screening tool for electrodiagnostic abnormality, it cannot determine CST severity. El et al. (2004) found that the CSA-I cut-off value between control and mild was 10.03 mm$^2$, between mild and moderate was, 13.03 mm$^2$, and between moderate and severe was 15.02 mm$^2$. In the present study, based on the statistical analysis of 77 cases of CTS, the CSA was 9.53 ± 1.64 mm$^2$ in the mild group, 12.88 ± 4.57 mm$^2$ in the moderate group, and 15.21 ± 5.98 mm$^2$ in the severe group. No significant differences in CSA-I were found between the moderate and severe groups. These results were similar to those from a previous study (Mohammadi et al., 2012). The small sample size used in the present study is one limitation, and future work increasing the sample size would be appropriate. Despite this limitation, the inlet-to-outlet ratio found here was significantly different among the groups. The results showed that 1.29 (64.7% sensitivity, 80% specificity) and 1.52 (72.7% sensitivity, 64.7% specificity) were the best cut-off values to discriminate between CTS grades. The inlet-to-outlet ratio was calculated from the CSA-I and CSA-O data, which represent the swollen and compressed areas of the median nerve at the carpal tunnel. Buchberger et al. (1991) reported observing swollen and compressed nerve at the carpal tunnel. However, the authors of that article were not blinded to the groups, which could affect the results, and the number of repeated measurements that were made is unknown. The inlet-to-outlet ratio is relatively low sensitivity and specificity for use in grading the severity of CTS.

Part of the variability in the data is likely caused by inter-patient variations, the experience of the ultrasonographer, the quality of the device, and the methods used for the ultrasonographic measurements. Still, ultrasonography of the median nerve may eventually be a useful method for diagnosing and grading CTS. In addition, the morphological changes in the median nerve assessed by ultrasonography could be useful for understanding peripheral nerve regeneration.

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**Author contributions:** *LZ and AR worte the paper, provided the data, conducted experiments and performed data analysis. FP and LC conceived and designed this study, and provided technical support. CY and TBW provided technical support and revised the paper. All authors approved the final version of the paper.*

**Conflicts of interest:** *None declared.*

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