Determining Optimal Cut-Off Value For Ultrasound-Measured Median Nerve Cross-Sectional Area For Diagnosis Of Carpal Tunnel Syndrome In A Sample Of Egyptian Population

Running title: Role of Median Nerve Ultrasound in Diagnosis of CTS
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ABSTRACT
Background: Carpal tunnel syndrome (CTS) is the most frequent entrapment neuropathy. Different populations have different cross-sectional area (CSA) cut-offs for carpal tunnel syndrome. This study aimed to evaluate median nerve ultrasound in Egyptian CTS patients and matched controls, correlate ultrasound with nerve conduction studies, and determine optimal CSA cut-off at the inlet for CTS screening.

Methods: This study included 35 patients with CTS and 35 age and sex-matched healthy control. The median nerve conduction studies (NCS) and the median nerve CSA using ultrasound (US) at different locations, including the carpal tunnel inlet, were measured in all participants. The receiver operator characteristic (ROC) curve analysis was performed to detect the sensitivity and specificity of nerve US-measured CSA for diagnosis of CTS.

Results: There was a significant difference in the median nerve CSA at the inlet and outlet between the CTS and control group. A significant correlation was found between the inlet and outlet CSA and the cMAP of the median nerve. The optimal cut-off CSA of the median nerve for anticipation of compression is ≥ 8.8 mm² at the inlet and ≥ 8.4 mm² at the outlet.

Conclusion: Ultrasound can be used as a screening tool for diagnosing CTS by measuring the median nerve CSA. This study proposed cut-off values for median nerve CSA at the inlet and outlet cut-off values of ≥8.8 mm² and ≥8.4 mm², respectively. Further research with larger sample sizes and a unified US protocol is warranted to confirm the current findings.

Keywords: Carpal Tunnel Syndrome; Nerve ultrasound; Nerve conduction study; Cross-sectional area; Cut-off value.

Clinical trial registration: This study was part of a master thesis with ClinicalTrials.gov Identifier: NCT04092140, registered on 17 September 2019; https://classic.clinicaltrials.gov/ct2/show/NCT04092140

Introduction
Carpal tunnel syndrome (CTS) is a type of entrapment neuropathy that is caused by compression of the median nerve at the wrist [1]. Its frequency is estimated to range from 0.2 to 4% of the general population, making CTS the most prevalent peripheral neuropathy [2, 3]. Diverse aetiologies for CTS have been documented, encompassing tumors within the tunnel or trauma that induce compression of the median nerve. Frequently, the early symptoms of this disorder—weakness, tingling, and numbness—are identified as the cause of hand muscle atrophy. Nerve conduction studies (NCS) are commonly employed in cases where the requisite equipment is accessible to validate the diagnosis of CTS [5]. Nevertheless, nerve ultrasonography (US) is gaining traction as a substitute, contingent upon the reference standard [4-6].
In 1988, Fornage and Rifkin historically delineated the initial revelation of pathological US results in CTS, facilitating the development of novel diagnostic methodologies. An elevated wrist-to-forearm swelling ratio, hypoechogenicity, altered fascicular structure, decreased slippage, and
enhanced vascularity are observed in the majority of symptomatic individuals, along with an expanded median nerve cross-sectional area (CSA) proximal to the flexor retinaculum [7]. The median nerve CSA at the pisiform tunnel inlet was reported to have the highest sensitivity and specificity [8].

According to a recent guideline, the US enhances diagnostic accuracy but should not substitute electrodiagnostic testing in diagnosing CTS, particularly in complex cases [9, 10]. However, median nerve cross-sectional area enlargement and Doppler-detected hypervascularity correlate with clinical and electrophysiological CTS severity [11, 12]. Recent applications of neuromuscular US include presurgical detection of anatomical variations causing CTS symptoms to guide surgical strategy and prevent complications. Several studies link atypical CTS to thrombosis, persistent median artery, or bifid median nerve [13-15]. The ability of nerve US to predict surgical and nonsurgical CTS outcomes has shown mixed results. Median nerve cross-sectional area and CTS severity demonstrate a nonlinear relationship. Thus, other US biomarkers, like the Doppler signal, may better predict outcomes [16]. The US can also guide corticosteroid injections and monitor treatment response. Sufficient evidence proposes US incorporation into a new CTS diagnosis paradigm [17].

Controversy exists regarding the utility of neuromuscular US for follow-up after carpal tunnel release. Some studies show clinical and electrophysiological improvement correlates with a substantial decrease in median nerve cross-sectional area [18-21]. However, others did not confirm these findings [22]. Nevertheless, nerve US appears helpful in identifying potential postoperative causes of persistent symptoms like inadequate release, traumatic neuroma, fibrosis, or hematoma [23, 24].

Prior studies have examined the diagnostic utility of median nerve US in CTS; however, reported median nerve CSA cut-off values have varied [4, 9, 25-28]. Therefore, this study aimed to evaluate median nerve ultrasound in Egyptian CTS patients and matched controls, correlate ultrasound with nerve conduction studies, and determine optimal CSA cut-off at the inlet for CTS screening.

**Material And Methods**

**Study Design, Setting, and Ethical Approval:**

This prospective, case-control study was conducted in the Neuromuscular ultrasonography unit of the Department of Neurology at the Neurology, Psychiatry, and Neurosurgery Hospital, Assiut University.

This study was approved by the Assiut University Faculty of Medicine local ethical committee (IRB: 17100905) and registered on ClinicalTrials.gov (NCT04092140). Per the World Medical Association Declaration of Helsinki 1964, all participants gave written informed consent.

**Participants and Data Collection:**

This study included 35 patients with CTS and 35 age and sex-matched healthy controls who were 18 years and older, both males and females.

The CTS group addressed all these criteria [1]: (1) paraesthesia in the median nerve distribution; (2) hand pain that wakes the patient from sleep; (3) hand paraesthesia eased by shaking or holding it in a dependent position; and (4) positive Phalen's test. Exclusion criteria: patients with disorders that could lead to CTS, such as diabetes mellitus, rheumatoid arthritis, pregnancy, acromegaly, or hypothyroidism; (3) patients with different neuropathies, such as autoimmune, diabetic, nutritional, or posttraumatic.

The control group included people attending the neurological outpatient clinic for other causes not affecting the peripheral nerves, such as headaches. The controls were subject to the identical exclusion criteria applied to the patients.

**Assessment of Participants:**

Each patient underwent complete history taking with a comprehensive general and neurological examination. All participants...
A total of 35 patients with CTS and 35 age and sex-matched healthy controls were included in this study.

Table (1) shows no significant differences between CTS and control groups regarding age and gender. However, CTS is more prevalent among females with a male-to-female ratio = 1: 4. CTS is graded into mild, moderate, and severe CTS according to nerve conduction studies, as shown in Table (1).

Table (2) summarizes the NCS results of the CTS and control groups. There was a significant difference between patients with CTS and the control group in all neurophysiological parameters except MCV and the F wave latency.

Table (3) shows significant differences with increased nerve CSA among patients with CTS compared with the control group (Figure 1), except for the forearm/inlet. However, there was no significant difference in the CSA between mild (0.136± 0.03), moderate (0.138± 0.04), and severe CTS (0.153± 0.04) with a p-value of 0.39.

Table (4) illustrates the accuracy of the cut-off values of the median nerve CSA measured by ultrasound for diagnosis of CTS using the ROC curve analysis. The optimal accuracy for the median nerve CSA for CTS diagnosis at the inlet (AUC 0.971) and outlet (AUC 0.896) with an optimal cut-off value of ≥ 0.088 cm² (97.1 % sensitivity and 85.7 % specificity) and ≥ 0.084 cm² (88.6 % sensitivity and 51.4 % specificity), respectively (Figure 2).

Table (5) illustrates the correlation between the median nerve CSA and NCS parameters. A negative correlation was observed between nerve CSA at the inlet (p = 0.025) and the outlet (p = 0.045) with the cMAP. However, The MDL was positively correlated with the Forearm/inlet Ratio (P= > 0.0001) and Forearm/outlet Ratio (P= 0.005).
### Table 1: Sociodemographic Data of CTS and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>CTS (n = 35)</th>
<th>Control (n = 35)</th>
<th>t value or X²</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.69±9.91</td>
<td>35.06±11.70</td>
<td>-1.400</td>
<td>0.166</td>
</tr>
<tr>
<td>Gender</td>
<td>7 (20%)/ 28 (80%)</td>
<td>13 (37.1%)/22 (62.9%)</td>
<td>2.52</td>
<td>0.112</td>
</tr>
<tr>
<td>Severity of CTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mild CTS</td>
<td>13 (37.1%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Moderate CTS</td>
<td>10 (28.6%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Severe CTS</td>
<td>12 (34.3%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CTS:** Carpal Tunnel Syndrome; **n:** Number

### Table 2: Nerve conduction study between CTS Patients and Control groups

<table>
<thead>
<tr>
<th>Median Parameters</th>
<th>CTS Group (n= 35)</th>
<th>Control Group (n= 35)</th>
<th>Percentage of Change</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DML (ms)</td>
<td>6.48±1.18</td>
<td>3.85±0.136</td>
<td>68.3%</td>
<td>-13.11</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>cAMP (mV)</td>
<td>5.59±1.54</td>
<td>15.07±0.89</td>
<td>62.7%</td>
<td>31.53</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>MCV (m/s)</td>
<td>57.16±8.8</td>
<td>53.91±4.13</td>
<td>6%</td>
<td>-1.97</td>
<td>&lt; 0.054</td>
</tr>
<tr>
<td>SNAP (ms)</td>
<td>4.28±1.59</td>
<td>2.996±0.088</td>
<td>43%</td>
<td>-4.73</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>F wave (ms)</td>
<td>27.59±2.76</td>
<td>27.24±1.16</td>
<td>1.34%</td>
<td>-0.70</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD). **P value** was significant if < 0.05. All data were compared by independent **t****-****test.

**n:** number; **CSA:** cross-sectional area; **CTS:** carpal tunnel syndrome; **ms:** millisecond; **mV:** millivolt; **m/s:** meter/ second; **NCS:** Nerve conduction study; **DML:** distal motor latency; **cMAP:** compound motor amplitude potential; **SNAP:** sensory nerve amplitude potential; **MCV:** motor conduction velocity, **MHQ:** Michigan hand questionnaire.

### Table 3: Measured Dimensions by Ultrasound in Patients with CTS

<table>
<thead>
<tr>
<th>Median Nerve CSA (cm²)</th>
<th>CTS Group (n= 35)</th>
<th>Control Group (n= 35)</th>
<th>Percentage of Change</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-forearm</td>
<td>0.10 ± 0.05</td>
<td>0.06 ± 0.003</td>
<td>161.6%</td>
<td>-5.50</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pronator quadrates</td>
<td>0.11 ± 0.03</td>
<td>0.06 ± 0.002</td>
<td>167%</td>
<td>-8.04</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pronator teres</td>
<td>0.10 ± 0.03</td>
<td>0.06 ± 0.002</td>
<td>159.7%</td>
<td>-7.76</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Outlet</td>
<td>0.13 ± 0.04</td>
<td>0.05 ± 0.044</td>
<td>230%</td>
<td>-7.74</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Inlet</td>
<td>0.14 ± 0.03</td>
<td>0.09 ± 0.002</td>
<td>186.2%</td>
<td>-10.23</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Forearm/inlet ratio</td>
<td>0.73 ± 0.24</td>
<td>0.71 ± 0.03</td>
<td>15.6%</td>
<td>-0.53</td>
<td>0.59</td>
</tr>
<tr>
<td>Forearm/outlet ratio</td>
<td>0.83 ± 0.31</td>
<td>0.98 ± 0.15</td>
<td>15.3%</td>
<td>5.46</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Data expressed as mean (SD). **P value** was significant if < 0.05. All data were compared by Student **t****-****test.

**n:** number; **CSA:** cross-sectional area; **CTS:** carpal tunnel syndrome; **cm²:** centimetre square.
Table 4: Accuracy of Ultrasound Dimensions of the Median Nerve in Diagnosis of CTS

<table>
<thead>
<tr>
<th>Indices</th>
<th>Outlet</th>
<th>Inlet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>88.6 %</td>
<td>97.1 %</td>
</tr>
<tr>
<td>Specificity</td>
<td>51.4 %</td>
<td>85.7 %</td>
</tr>
<tr>
<td>Accuracy</td>
<td>89.6 %</td>
<td>97.1 %</td>
</tr>
<tr>
<td>Cut-off point (cm²)</td>
<td>≥ 8.4</td>
<td>≥ 8.8</td>
</tr>
<tr>
<td>Area under curve</td>
<td>0.896</td>
<td>0.971</td>
</tr>
<tr>
<td>95% Confidence Interval</td>
<td>(0.822- 0.969)</td>
<td>(0.927 - 1.000)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*P value was significant if < 0.05. CSA: cross-sectional area; CTS: carpal tunnel syndrome.*

Table 5: Correlation Between the Percentage of Change of US vs. NCS Parameters

<table>
<thead>
<tr>
<th>Median N</th>
<th>Inlet</th>
<th>Outlet</th>
<th>Forearm/ Inlet Ratio</th>
<th>Forearm/ Outlet Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DML</td>
<td>r</td>
<td>0.137</td>
<td>0.128</td>
<td>0.624**</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.434</td>
<td>0.462</td>
<td>&gt; 0.0001</td>
</tr>
<tr>
<td>cMAP</td>
<td>r</td>
<td>-0.379*</td>
<td>-0.342*</td>
<td>-0.300</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.025</td>
<td>0.045</td>
<td>0.080</td>
</tr>
<tr>
<td>MCV</td>
<td>r</td>
<td>-0.030</td>
<td>-0.220</td>
<td>-0.039</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.866</td>
<td>0.204</td>
<td>0.826</td>
</tr>
<tr>
<td>SNAP</td>
<td>r</td>
<td>-0.181</td>
<td>-0.172</td>
<td>-0.113</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.298</td>
<td>0.323</td>
<td>0.519</td>
</tr>
<tr>
<td>F wave</td>
<td>r</td>
<td>-0.048</td>
<td>0.013</td>
<td>-0.083</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.784</td>
<td>0.941</td>
<td>0.636</td>
</tr>
<tr>
<td>MHQ</td>
<td>r</td>
<td>0.092</td>
<td>0.155</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>0.597</td>
<td>0.373</td>
<td>0.639</td>
</tr>
</tbody>
</table>

*P value was significant if < 0.05. Data was done by Pearson correlation.*

r: correlation coefficient; DML: distal motor latency; cMAP: compound motor amplitude potential; SNAP: sensory nerve amplitude potential; MCV: motor conduction velocity; MHQ: Michigan hand questionnaire.

Figure 1. Ultrasound images comparing the cross-sectional area (CSA) of the median nerve at the carpal tunnel inlet in (a) a patient with carpal tunnel syndrome showing increased CSA (0.134 cm²) versus (b) a healthy control showing normal CSA (0.045 cm²). The black arrows indicate the CSA of the median nerve at the inlet.
Abd El Maged et al.,

**Figure 2.** Receiver operating characteristic (ROC) curves evaluating the accuracy of median nerve ultrasound dimensions for diagnosing carpal tunnel syndrome. (a) ROC curve analysis at the inlet of the carpal tunnel shows an area under the curve (AUC) of 0.971 (95% CI, 0.927-1.000). (b) ROC analysis at the outlet of the carpal tunnel with a slightly lower AUC of 0.896 (95% CI, 0.822-0.969).

**DISCUSSION**

This study aimed to evaluate median nerve ultrasound in Egyptian CTS patients and matched controls, correlate ultrasound with nerve conduction studies, and determine optimal CSA cut-off at the inlet for CTS screening. The key findings demonstrate significant differences between groups in median nerve size at the carpal tunnel inlet and outlet. Nerve CSA correlated with nerve conduction amplitudes and distal motor latency. Additionally, using ROC analysis, this study suggested cut-off values for median nerve CSA at inlet and outlet cut-off values of ≥8.8 mm² and ≥8.4 mm², respectively, to anticipate median nerve compression.

In the current study, CTS was prevalent among females with a male-to-female ratio (1:4), which agrees with the literature [25, 31, 32]. This finding could be attributed to women having smaller wrist sizes, causing smaller carpal tunnels. Additionally, hormonal changes in women impact tenosynovial tissue in the tunnel [31].

In this study, patients with CTS had a significantly higher CSA of the median nerve at different locations than the control group except for the forearm/inlet ratio (0.59), with the percentage of change being higher at the carpal tunnel inlet and outlet. This finding agrees with the previous studies [1, 11, 12, 25, 33], which reported that the median nerve CSA in all patients with CTS was significantly increased compared with controls. Most articles describing ultrasound for CTS have focused on the increased CSA of the median nerve at the wrist [12]. This finding signifies that the US could be a screening tool for diagnosing CTS, differentiating affected from non-affected median nerve. Moreover, this study did not find any statistical difference in the CSA between different severities of CTS, which agrees with previous findings [25, 27, 34].

The current study found that ultrasound measurements of the median nerve CSA at the outlet and inlet had high overall accuracy (89.6% and 97.1%, respectively) in diagnosing CTS. Cut-off values above which compression is anticipated were ≥8.4mm² and ≥8.8mm² at the outlet and inlet, respectively. The CSA at the carpal tunnel inlet (at the level of the pisiform) is considered the most sensitive and specific ultrasound finding for CTS diagnosis [9]. So, the comparison with other studies focused on inlet CSA. The current study found high
accuracy in diagnosing CTS with a slightly lower CSA cut-off value at the inlet than values reported in two previous Egyptian studies - 9.5 mm² by El Sadek and colleagues with 100% sensitivity and specificity [25] and 10 mm² by Sonbol and colleagues with 93.3% sensitivity and 98.3% specificity [27].

Moreover, other previous studies have reported higher cut-off values for median nerve CSA at the inlet, ranging from 10-12 mm². Reported sensitivity ranged from 67-83%, and specificity ranged from 63-97% [1, 35-38]. For example, Sarraf et al. found 10.5 mm² to have 80% sensitivity and 76% specificity [37], while Kwon et al. found 10.7 mm² to have 66% sensitivity and 63% specificity [1]. The variability in optimal CSA cut-offs highlights that each center should establish its reference using a standardized ultrasound protocol to diagnose CTS, as the cut-off may differ among populations [25]. These differences are likely due to variations in patient and control selection methods and measurement techniques across studies [28].

This study found a significant mild to moderate correlation between ultrasound and electrophysiological findings of the median nerve, with the forearm/ inlet ratio and forearm/ outlet ratio positively correlated with the DML. Also, the CSA at the inlet and the outlet negatively correlated with the cMAP. The current findings confirm and reproduce the reported results of the median nerve CSA at the tunnel inlet (pisiform bone), which has the highest sensitivity and specificity for diagnosis [8]. These findings further support the growing interest in ultrasound as an alternative diagnostic test for CTS [5].

The correlation between NCS and ultrasound-measured nerve CSA confirms the potential of using this painless, non-invasive ultrasound parameter as an optimal screening tool for diagnosing CTS. Although electrophysiological testing remains irreplaceable, especially in complex cases, nerve CSA enlargement and Doppler-detected hypervascularity on ultrasound closely reflect CTS’s clinical and neurophysiological severity. Thus, by combining anatomical and functional assessments, the future of CTS evaluation promises enhanced precision in an efficient and patient-friendly manner [12].

The Study Limitations:
This study has some limitations. Firstly, the sample size is relatively small. Secondly, it is a single-centre study. Thirdly, there is a lack of assessment of echogenicity and median nerve vascularity that could help determine the severity of CTS if applied.

Conclusion:
This study confirmed that ultrasound can be used as a screening tool for diagnosing CTS by measuring the median nerve CSA. Also, the study proposed cut-off values for median nerve CSA at inlet and outlet cut-off values of ≥8.8 mm² and ≥8.4 mm², respectively, to anticipate median nerve compression. Further prospective multicentre studies with larger sample sizes and standardized US protocols are needed to replicate the current findings before routine use in clinical practice.

Declarations
Ethical Approval and Consent to Participate:
This study was approved by the Assiut University Faculty of Medicine local ethical committee (IRB: 17100905) and registered on ClinicalTrials.gov (NCT04092140). Written informed consent was obtained from all participants in compliance with the World Medical Association Declaration of Helsinki 1964.

Consent for Publication is Not applicable.
Availability of Data and Materials:
The data set of this work is available and can be requested from the corresponding author.

Declaration of Conflicting Interests:
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Authorship Contribution:
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