REVIEW

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# Association between Carpal Tunnel Cross-Sectional Area and Carpal Tunnel Syndrome: A Systematic Review and Meta-Analysis

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**SUMMARY**

**Background.** Carpal tunnel syndrome (CTS) is a prevalent peripheral compressive neuropathy. In addition to an enlargement of the median nerve cross-sectional area (CSA), the carpal tunnel CSA may be a determinant of CTS. However, the findings of studies assessing the association between carpal tunnel CSA and CTS are very limited and inconclusive.

**Purpose.** The present systematic review aimed to execute a meta-analysis of present literature to establish evidence of the association between the carpal tunnel CSA at the proximal and distal levels and CTS.

**Methods.** PICOS strategy was used to electronically search key terms in the PubMed, Cochrane Library, Embase and Wiley Online databases with no restrictions on the publication date for case-control and cohort studies. The bias risks for these studies were assessed using the Newcastle-Ottawa Scale (NOS). Meta-analysis was performed using the RevMan5 from Cochrane. A total of 13 studies comparing the association between CSA of the carpal tunnel at the proximal and distal levels and CTS between 428 CTS participants and 324 controls with a 145/249 male-to-female ratio and a mean age of 42.2 met the inclusion criteria.

**Results.** Overall, the studies were rated as acceptable quality, having scored 4, 6, 7, or 8 (out of 9 stars) on the NOS. Meta-analysis of the included studies indicated that the overall pooled mean difference of CSA of the carpal tunnel at the proximal level was higher in the CTS groups when compared with the control groups (0.79; 95% (confidence interval) CI 0.63-0.96; p = 0.003). Similarly, the overall pooled mean difference of CSA of the carpal tunnel at the distal level was higher in CTS individuals when compared with controls (0.54; 90%CI 0.32-0.76; p = 0.32).

**Conclusions.** This review found evidence that an increased CSA of the carpal tunnel at the proximal and distal levels is associated with CTS.

**KEY WORDS**

*Carpal tunnel syndrome; cross-sectional area; systematic review; meta-analysis; proximal; distal.*

## INTRODUCTION

Carpal tunnel syndrome (CTS) is one of the most common peripheral compressive neuropathy of the median nerve (MN) in the carpal tunnel at the wrist, with a reported rise in prevalence (1). CTS occurs due to localized compression of the MN within the narrow carpal tunnel space at the wrist. The occurrence of CTS may vary from 6.3% to 11.7% with an overall prevalence of 8% in the general population (2, 3), and 14.5% among specific work groups (4, 5). Previous studies showed that CTS prevalence differs greatly depending on the type of study, diagnostic standards, work groups and industries (2, 3, 6). Besides, CTS affects nearly 276 in every 100,000 individuals and its prevalence is significantly influenced by gender and age, particularly affecting adults between 40 to 60 years (7). Also, the incidence rate is higher for females who are three times more inclined to the disease compared to males, reaching a peak during menopause, that is, between 50 and 59 years (8). In males, CTS reaches a peak at around 50 to 59 years and 70 to 79 years (9). These outlooks on the prevalence of CTS make it a significant matter of concern, highlighting the need for early detection and effective management.

CTS is mostly bilateral although the suspected or confirmed symptoms may be unilateral (10). Nearly 50% of the patients presenting unilateral CTS were found to have bilateral symptoms (11). Bilateral CTS is associated with gender and age among other factors (12). Also, it is suspected to be associated with extrinsic conditions like hypothyroidism, menopause, obesity and pregnancy and neuropathic factors like diabetes, arthritis, vitamin deficiency and exposure to toxins which increases the carpal tunnel cross-sectional area (CSA) and volume of the carpal tunnel contents on either side of the MN (13). The classic sensory symptoms of CTS include unmanageable pain in the cutaneous innervation of the MN, tingling sensation, dysesthesia, or loss of sensation in the three radial fingers innervated by the MN and weakness of intrinsic muscles of the hand causing functional impairment (14, 15) and affecting the wellbeing of patients (16). The tingling sensation occurs not only in the areas innervated by the MN but also can involve the whole hand in a well-suited distribution (17). Besides, symptoms worsen at night, and insomnia is common. In progressive cases, patients can experience deterioration of the thenar area of the hand or even paralysis (18). Detection at an early stage is therefore required to reduce permanent neurological dysfunction and functional impairment (19).

The diagnosis of CTS commonly involves a preliminary process based on clinical signs and symptoms, followed by confirmation through electrophysiological findings like electrodiagnostic testing (EDT) which detects physiological dysfunctions of the MN. Although EDT can detect the severity of the MN malfunction, it cannot reveal anatomical changes in the carpal tunnel (20). Besides, EDT displays false-negative results at a rate of 5% to 10% (13), which could be due to the start of symptoms before impaired conduction of myelinated sensory nerve fibers. Alternatively, diagnosis using the ultrasound (US), a widely available non-invasive diagnostic imaging modality, not only helps to identify and assess CTS but also differentiates between primary and secondary CTS (21). However, the accuracy of the clinical assessment using the US is controversial due to the low sensitivity and high rate of false-negative and false-positive results (22). Thus, there lacks a clear specification for the diagnosis of CTS.

In recent years, various existing studies have conducted US assessments of CTS by examining the CSA of the MN. Although most studies have agreed with the presence of an enlarged CSA of the MN in CTS individuals when compared with healthy controls, there has been very limited attempt to assess the usefulness of carpal tunnel diameter, particularly the CSA of the carpal tunnel itself and its relation with the progressive development of CTS, the exception being the presence of anatomical anomalies that can lead to CTS (23, 24). The quantitative assessment of the carpal tunnel structures other than that of MN is very limited, despite being related to the functional changes that accompany idiopathic CTS (25). Besides, studies using US or magnetic resonance imaging (MRI) assessment for information on the enlargement of the CSA of the carpal tunnel in accordance with CTS diagnosis and severity are not well-documented (26). While few studies have reported an association of CTS with the CSA of the carpal tunnel as assessed through the US in patients with CTS and healthy controls (27, 28), studies focusing on MRI assessment of CTS with respect to the carpal tunnel CSA is limited (26-28). In this view, Chiotis *et al.* (28) reported an enlarged CSA in patients with CTS but offered no causation. Thus, no consensus has been reached about CTS findings on US (21) or MRI (29) with regards to an increased CSA of the carpal tunnel. Moreover, the existing published data lacks consolidated clinical evaluation or discussion of the findings to confirm the association of carpal tunnel CSA and CTS. Furthermore, a consistent overview regarding the anatomical differences reported in CSA of the carpal tunnel between CTS patients and healthy controls has not been well-established. A summary of the existing studies can potentially provide insight into a better understanding of empirical evidence on the research concern (30). Thus, the present systematic review and meta-analysis aim to evaluate evidence of an association between an enlarged carpal tunnel CSA and its role in the diagnosis of CTS, as observed in case-control and cohort studies. The primary question investigated was whether the proximal and distal carpal tunnel CSAs can be used as diagnostic indicators of CTS.

## METHODS

A systematic review of relevant existing studies was performed based on the preferred reporting items for systematic reviews and meta-analyses (PRISMA) chart. The PRISMA procedures and checklist were followed in the present study (31).

### Search strategy

The present study followed a systematic approach, where the first step included searching for information (keywords). A methodical keyword search strategy was conducted in major electronic databases like PubMed, Cochrane Library, Embase and Wiley Online focusing on articles related to the association of carpal tunnel CSA and the development of CTS. No restrictions were set on the publication date. Articles with the following MeSH terms were searched: Carpal tunnel syndrome, CTS, carpal tunnel, carpal canal, median nerve neuropathy, median nerve entrapment, median neuritis, median nerve compression, nerve compression syndrome, compressive neuropathy, carpal tunnel dimension, carpal tunnel diameter, carpal tunnel cross-sectional area, CSA, association, relationship, predict, risk factor, determinant, comparative study, cross-sectional study, cohort study, case-control study. The Boolean words "OR" and "AND" were used. The following search was carried out:
("Carpal tunnel syndrome" OR "CTS" OR "carpal tunnel" OR "carpal canal" OR "median nerve neuropathy" OR "median nerve entrapment" OR "median neuritis" OR "median nerve compression" OR "nerve compression syndrome" OR "compressive neuropathy") AND ("carpal tunnel dimension" OR "carpal tunnel diameter" OR "carpal tunnel cross-sectional area" OR "CSA") AND ("association" OR "relationship" OR "predict" OR "risk factor" OR "determinant") AND ("comparative study" OR "cross-sectional study" OR "cohort study" OR "case-control study"). The organized structure of key terms yielded 243 articles (**table I**). The reference lists of the included articles were examined and manually searched for the inclusion of additional studies on the relationship between tunnel CSA and CTS.

**Table I.** Number of hits in the search databases.

| Databases | Number of hits |
|---|---|
| PubMed | 23 |
| Cochrane Library | 30 |
| Embase | 11 |
| Wiley Online | 179 |
| **Total** | **243** |

### Eligibility (inclusion and exclusion) bases

The stepwise selection of the 243 articles obtained was based on the relevance of titles, abstracts, assessment of the main body and close examination against the following preset inclusion criteria:

1. Comparative study designs like case-control studies, cohort studies and cross-sectional studies comparing a cohort of patients with CTS to a cohort of healthy controls were considered.
2. Studies that have patients with a clinical diagnosis of CTS based on signs and symptoms, rigorous diagnostic criteria, or documented clinical findings like EDT, imaging modalities and so forth.
3. Studies assessing the association of carpal tunnel CSA with CTS on patients above 18 years of age were included.
4. Further, the search aimed for articles available in the English language.

Exclusion criteria:

1. Book chapters, systematic and literature reviews, proceedings, letters, case and technical reports, records and editorials were excluded.
2. Studies, where the subjects did not have a defined clinical diagnosis of CTS (non-specific pain of the arm or hand), were excluded.
3. Studies conducted among CTS patients without control groups were excluded.
4. Studies not assessing tunnel diameter, but only external wrist diameter were excluded.
5. Studies focusing only on the association of BMI, diabetes and other comorbidities with CTS were also excluded.
6. Studies with insufficient data sets were excluded.

### Bias assessment

Following the selection of the articles, the methodological quality of the case-control and cohort studies was assessed using the Newcastle-Ottawa Scale (NOS) in three domains such as sample selection, comparability and outcome of the study (32). This tool is the recently recommended standard checklist for assessing the bias risks and methodological quality for observational studies including, case-control, cohort and cross-sectional studies, which is also congruent with guidance from the Cochrane Handbook for Systematic Review of Interventions (33). The NOS consists of 8 items resulting in a total score of 9. Studies yielding a score between 3 to 4 (selection), 1 to 2 (comparability) and 2 to 3 (outcome) are considered high-quality studies with a low bias risk.

### Data extraction

From each study, data on the following variables were obtained: author (s) and year, study design, study population and sample size, male/female, mean age/range, *in vivo*

diagnostic tool, outcome (carpal tunnel diameter corresponding to CTS, specificity, and sensitivity) and adjustment for other confounders.

### Data analysis

To conduct the meta-analysis, all materials across the articles were pooled due to sampling considerations or missing information in a fixed-and random-effects model. Possible publication bias across the studies was detected using Egger's test and variation due to statistical heterogeneity among the studies was detected using the $I^2$ statistic. $I^2$ score > 70% was considered to be highly heterogenic (34). Results were graphically represented using forest and funnel plots. The restorations were considered as the statistical unit. Here, statistical significance was considered at $p < 0.05$. All analyses were performed using the RevMan5 statistical software from Cochrane.

## RESULTS

### Identification and characteristics of studies

Electronic searches from the databases (PubMed, Cochrane Library, Embase and Wiley Online) and manual search of reference lists identified 249 articles (**figure 1**). Among the 229 articles screened, 48 were selected for full-text assessment. A final total of 13 studies were included in this review based on the implementation of the eligibility criteria. The elucidation of the characteristics of each study is compiled in **table II**.

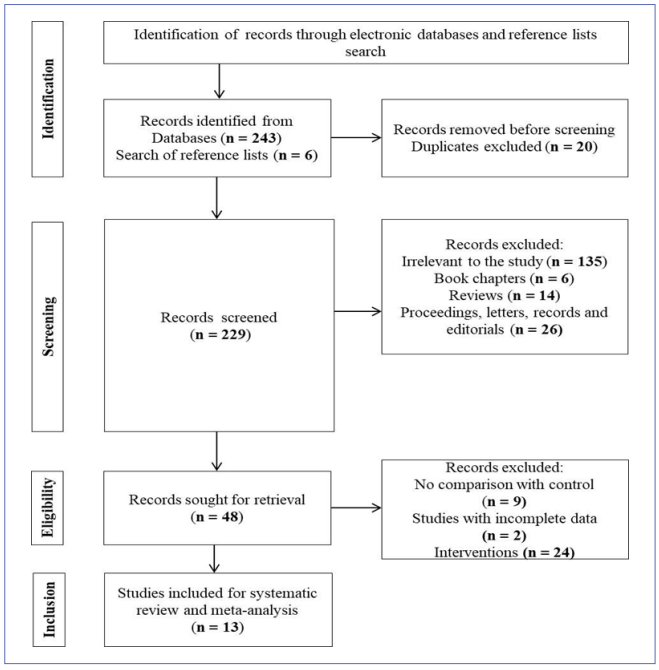


**Figure 1.** PRISMA representation for stepwise selection of articles.

Of all the 13 studies, eight were case-control (35-42), four were prospective (22, 25, 43, 44), and one was retrospective (26). Among all the included articles, 10 (24, 25, 35-42), measured the CSA of the carpal tunnel at the proximal and distal parts, three (26, 43, 44), measured the CSA of the carpal tunnel at the distal parts and one (43), measure the carpal tunnel contents (CTC)/carpal tunnel volume (CTV). All studies confirmed signs and symptoms of CTS by documented clinical findings or rigorous diagnostic criteria. Three studies used computed tomography (CT) (35-37), three used nerve conduction studies (NCS) and magnetic resonance imaging (MRI) (25, 26, 43), three used only MRI (39-41), two used EDT and US (23,42), while one study each used electromyography (EMG) and CT (38), and EDT and MRI (44), for the detection of CTS. Of all the studies, four (23, 26, 42, 44), focused on sensitivity and specificity of the clinical measurements. Four studies adjusted for confounders like gender (23, 35, 36, 41), two studies adjusted for age, height, body weight and BMI (23, 26), while seven studies reported unadjusted estimates only. The total numbers of CTS participants in the included studies were 428 with 324 controls and a 145/249 male-to-female ratio and a mean age of 42.2.

### Methodological evaluation of selected studies

The assessment of the methodological quality of the observational studies is presented in **table III**. Based on the NOS scale, three studies obtained a total score of 4 (37-39), four studies had a total score of 6 (23, 25, 26, 36), three studies obtained a total score of 7 (41, 42, 44), and three studies obtained a total score of 8 (35, 41, 43). These scores indicate overall acceptable quality of the studies being subjected to systematic review and meta-analysis. Four of the 13 studies (40, 42-44) scored a maximum rating of 4 for the selection section indicating that the participants and controls were well defined and were included based on suitable eligibility criteria, without a possibility for any bias of selection, particularly for case-control studies. The remaining nine studies could not obtain a maximum score due to either a lack of the selection criteria or insufficient information on the control groups. Besides, the studies by (23, 26, 35, 36, 41), obtained 2 ratings for the comparability section as they controlled for a range of demographics such as gender, age, weight, height and BMI. Two studies by (40, 42), scored 1 star, out of maximum 2 stars, for the comparability section as they did mention of the blinding process. However, the remaining studies scored zero for this section, as they neither controlled for any confounders nor mentioned the use of any blinding process. For the exposure section, scores varied between 1 to 3 stars. The studies scoring 3 stars (40, 42-44), employed comparable methods for selecting partic-

**Table II.** Summary of studies included for the systematic review and meta-analysis.

| Author (s), year, study design | Study population (sample size) | Male/female | Mean age/ range (years) | *In vivo* diagnostic tool | Outcome | | Adjustment for confounders |
|---|---|---|---|---|---|---|---|
| | | | | | Carpal tunnel diameter | Sensitivity and specificity | |
| Dekel *et al.* (35), case-control | Females with idiopathic CTS (n = 26) Control (n = 33) | 14/19 (control) | 39.0 (CTS) 40.5 (control) | CT | The CSAs of the carpal tunnel at the proximal and distal parts were significantly smaller in female controls compared to the male controls and significantly smaller in patients than in the controls | NR | Gender |
| Merhar *et al.* (36), case-control | Patients with CTS (n = 19) Normal volunteers (n = 13) | 4/15 (CTS) 4/9 (Control) | 47 (CTS) 43 (Control) | CT | The CSA of the carpal tunnel was larger in the CTS group than in the control groups, but this difference was not significant in males and females | NR | Gender |
| Bleecker (37), case-control | Male patients with CTS (n = 11) Controls (n = 3) | NA | 49 | CT | The carpal tunnel CSAs at the proximal part was significantly smaller in the CTS group compared to the control group | NR | Not adjusted |
| Kamil *et al.* (38), case-control | Female patients with unilateral and bilateral CTS (n = 17) Control (n =6) | NA | NM | Electromyography (EMG) and CT | The carpal tunnel CSAs at the proximal and distal levels were significantly smaller in CTS patients than in controls. | NR | Not adjusted |
| Allmann *et al.* (39), case-control | Patients with clinically diagnosed CTS (n = 19) Healthy volunteers (n = 17) | 7/12 (CTS) 5/12 (Control) | 49.7 (CTS) 43.4 (Control) | MRI | The carpal tunnel CSAs at the proximal and distal parts were significantly smaller in patients than in controls. | NR | Not adjusted |
| Cobb *et al.* (43), prospective | Patients with clinically diagnosed CTS (n = 7) and asymptomatic age-, sex-, weight- and stature-matched volunteers (n = 7) | NM | NM | Nerve conduction studies (NCS) and MRI | The carpal tunnel contents (CTC) to carpal tunnel volume (CTV) ratio was significantly higher in the CTS group than in the control group. The CSA of the carpal tunnel at the distal part was higher in the CTS group compared to the control group, the difference being statistically insignificant. | NR | Not adjusted |

| Author (s), year, study design | Study population (sample size) | Male/female | Mean age/ range (years) | *In vivo* diagnostic tool | Outcome | | Adjustment for confounders |
|---|---|---|---|---|---|---|---|
| | | | | | Carpal tunnel diameter | Sensitivity and specificity | |
| Horch *et al.* (40), case-control | Patients with clinically diagnosed CTS (n = 19) Sex- and age-matched healthy volunteers (n = 17) | 7/12 (CTS) 5/12 (control) | 49.7 (CTS) 43.4 (control) | MRI | The carpal tunnel CSAs at the levels of the pisiform and hamate were smaller in the CTS group than in volunteers. | NR | Not adjusted |
| Monagle *et al.* (41), case-control | Female patients with CTS (n = 8) Asymptomatic male and female volunteers (n = 16) | 7/9 (control) | 43 (CTS) 39 (control) | MRI | The CSAs of the carpal tunnel were significantly larger in female patients compared to female control groups, while it was significantly larger in male controls compared to male patients | NR | Gender |
| Jarvik *et al.* (44), prospective | Individuals with clinically suspected CTS who underwent MRI after diagnosis with NCS (n = 40) and sex-matched healthy controls (n = 20) | 66/54 | 42.5 | Electrodiagnostic testing (EDT) and MRI | The distal CSA of the carpal tunnel at the outlet was significantly smaller in patients with CTS compared to healthy controls | The MRI findings reported high sensitivity (96%) but low specificity (33%) | Not adjusted |
| Uchiyama *et al.* (25), prospective | Females with idiopathic CTS (n = 105) and female volunteers (n = 36) | | 59.6 (CTS) 46.2 (control) | NCS and MRI | The carpal tunnel CSAs at the level of the pisiform and hamate were larger in the CTS group than in the control; however, the differences were not significant. | NR | Not adjusted |
| Kim *et al.* (23), blinded comparison study (prospective) | Patients with CTS who underwent US after 1 week of EDT (n = 51) and normative controls (n = 24) | 9/42 | 53.8 | EDT and ultrasound (US) | Proximal CSA of the carpal tunnel was significantly larger in patients with CTS than control subjects and this difference was significant between males and females | The EDT studies had a sensitivity and a low specificity of 86.2% and 59.1% | Age, gender height, body weight, BMI |
| Dehdashti Shahrokh *et al.* (42), case-control | Patients with confirmed idiopathic CTS (n = 39) and age-matched healthy controls (n = 35) | 24/26 (CTS) 23/27 (controls) | 53.7 (CTS) 50.2 (controls) | EDT and US | The CSA of the carpal tunnel at the inlet and outlet were significantly larger in CTS patients compared to healthy controls | The sensitivities and specificities of CSA at the inlet were 92% and 96%, CSA at the outlet were 92% and 92%, and AP diameter was 64% and 58% | Not adjusted |
| Sung Park *et al.* (26), retrospective | Patients with CTS (n = 67) Healthy controls (n = 97) | 7/60 (CTS) 31/66 (control) | 61.8 | NCS and MRI | The CSA at the carpal tunnel outlet was significantly higher in the patient group compared to the control group. | Based on MRI, the CSA at the inlet revealed a sensitivity of 83.6% and specificity of 84.5% | Age, weight, height and BMI |

**Table III.** Newcastle-Ottawa scale for quality assessment of case-control and cohort studies.

| Study | Selection | | | | Comparability | Exposure | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5-6 | 7 | 8 | 9 | |
| Dekel *et al.* (35) | * | * | * | * | ** | * | - | * | 8/9 |
| Merhar *et al.* (36) | * | * | - | - | ** | * | * | - | 6/9 |
| Bleecker (37) | * | * | * | - | -- | * | - | - | 4/9 |
| Kamil *et al.* (38) | * | * | * | - | -- | * | - | - | 4/9 |
| Allmann *et al.* (39) | * | * | * | - | -- | * | - | - | 4/9 |
| Cobb *et al.* (43) | * | * | * | * | -* | * | * | * | 8/9 |
| Horch *et al.* (40) | * | * | * | * | -* | * | * | * | 8/9 |
| Monagle *et al.* (41) | * | * | * | - | ** | * | - | * | 7/9 |
| Jarvik *et al.* (44) | * | * | * | * | -- | * | * | * | 7/9 |
| Uchiyama *et al.* (25) | * | * | * | * | -- | * | - | * | 6/9 |
| Kim *et al.* (23) | * | - | - | * | ** | * | - | * | 6/9 |
| Dehdashti Shahrokh *et al.* (42) | * | * | * | * | -- | * | * | * | 7/9 |
| Sung Park *et al.* (26) | * | * | * | - | ** | * | - | - | 6/9 |

*Indicates the subsection of assessment of methodological quality criteria; scoring criteria: 1) depiction of the exposed study; 2) selection of the non-exposed study; 3) identification of exposure; 4) demonstration that outcome of interest was not present at the start of the study; 5) comparability of cohorts based on the design or analysis; 6) outcome assessment; 7) was observation period sufficient for the occurrence of outcomes; 8) adequacy of the observation period.

ipants, well-matched demographics for selecting controls and a complete response rate. In contrast, studies scoring 1 or 2 stars in the exposure section either followed different methods for recruiting participants or had poor response rates. However, no studies scored zero for this section, implying that all the researchers made efforts to carefully recruit participants to enhance the methodologic quality.

## Findings of meta-analysis

Across the 13 studies, there are varying results concerning the carpal tunnel CSA. Most (seven) of the studies suggested a significant increase in carpal tunnel CSA (23, 25, 26, 36, 41-43), in CTS patients when compared with healthy controls. Moreover, three studies (23, 35, 41), found the difference in carpal tunnel CSA to be significant based on gender. In contrast (25, 43), found no significant differences ($p > 0.05$) in carpal tunnel CSA between the CTS patients and controls.

## The CSA of the carpal tunnel at the proximal level

The pooled mean difference in a fixed-effects model from 11 studies demonstrated that the mean CSA of the carpal tunnel at the proximal level is higher in CTS patients than in individuals without CTS, the difference between the two groups being statistically significant. The pooled mean difference is 0.79 (95%CI 0.63-0.96) (**figure 2A**). The notable moderate heterogeneity in the outcomes of 11 studies

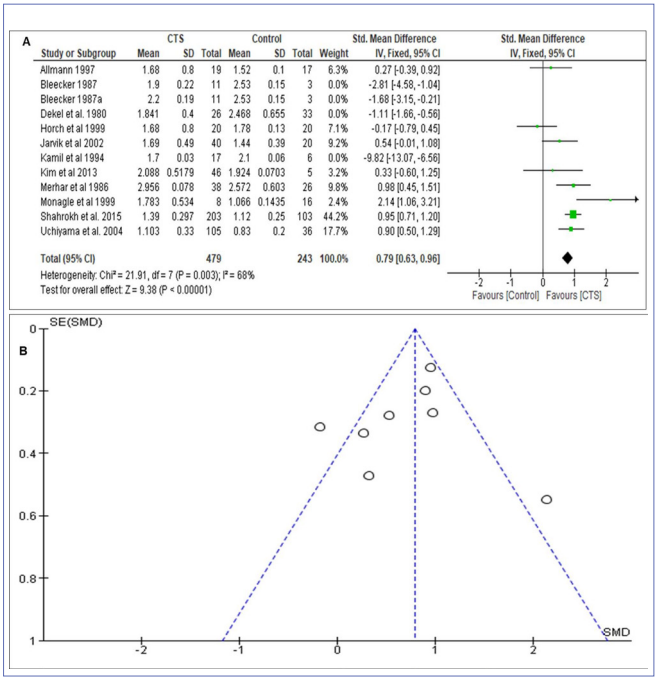


**Figure 2. (A)** A forest plot of 11 studies representing the mean difference in the cross-sectional area of the carpal tunnel at the proximal level between patients with and without carpal tunnel syndrome; **(B)** A funnel plot of log mean differences of the incidence of carpal tunnel syndrome in the studies among patients with an increased cross-sectional area of the tunnel at the proximal level.

showed Chi² = 21.91 (p = 0.003, I² = 68%), indicating that the findings were not apparently homogenous and have a slight suspicion for publication bias (**figure 2A**). The studies by (25, 42), could be considered to contribute the maximum weight to the meta-analysis for the association between increased CSA of the carpal tunnel at the proximal level and the progressive development of CTS. However, the pooled mean difference from seven studies demonstrated a positive association, while four studies demonstrated a negative association between CTS and increased CSA of the carpal tunnel at the proximal level.

## Publication bias

Three studies are located on the right of the funnel plot and their mean values are clustered near the pooled mean value. Similarly, three studies are on the left of the funnel graph and smaller-sized studies with increased or reduced mean differences appear missing. However, one study each is located outside on the right and left of the graph. The asymmetrical funnel plot reflects a slight suspicion of publication bias (**figure 2B**).

Each author's name on the left-hand side represents one study and horizontal lines represent their range of 95% confidence intervals. The green squares represent the means of each study. The area of the green squares reflects the statistical weight of individual studies as per the sample size in the meta-analysis. The vertical line indicates no effect of outcome (mean = 1). The diamond represents the overall effect (weighted average of each observation) from the meta-analysis. The right column shows the numerical value of the forest plot. CI: confidence interval; CTS: carpal tunnel syndrome; SD: standard deviation.

The graph indicates outcome effects *versus* the study size that is calculated from standard error (SE) of log (mean difference). Open circles represent each study in the present meta-analysis. The broken line represents a 95% pseudo-score confidence interval of the extent of effect in the study.

## The CSA of the carpal tunnel at the distal level

The pooled mean difference for the association between CSA of the carpal tunnel at the distal level and CTS for all the studies included in the meta-analysis is presented. The results of 13 studies have been pooled and a random-effects model was fitted to the data. The pooled mean difference (0.54; 90%CI 0.32-0.76) demonstrated that the mean CSA of the carpal tunnel at the distal level is higher in CTS patients than in individuals without CTS, the difference being statistically significant (**figure 3A**). The heterogeneity in the outcomes of 13 studies showed Chi² = 9.21 (p = 0.32, I² = 13%), indicating consistent findings and a low suspicion for publication bias (**figure 3A**). The studies by (40, 43, 44), could be considered to contribute the maximum weight to the meta-analysis for the association between increased CSA of the carpal tunnel at the distal level and the gradual development of CTS. However, eight studies demonstrated a positive association, while five studies demonstrated a negative association between CTS and increased cross-sectional area of the carpal tunnel at the distal level.

## Publication bias

Five studies are located on the right of the funnel plot and their mean values are clustered near the pooled mean value. Also, three studies are on the left of the funnel graph and smaller-sized studies with increased or reduced mean differences appear missing. The symmetrical funnel plot reflects a low suspicion of publication bias (**figure 3B**) (45).

Each author's name on the left-hand side represents one study and horizontal lines their range of 90% confidence intervals. The green squares represent the means of each study. The proportional size of the green squares reflects the statistical weight of individual studies as per the sample size in the meta-analysis. The vertical line indicates no effect of exposure (mean = 1). The diamond represents the overall effect (weighted average of each observation) from the

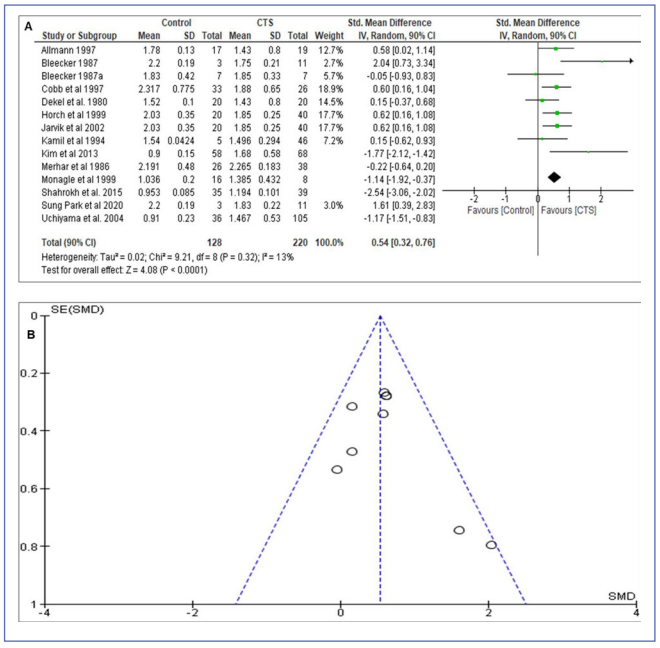


**Figure 3. (A)** A forest plot of 13 studies representing the mean difference in the cross-sectional area of the carpal tunnel at the distal level between patients with and without carpal tunnel syndrome; **(B)** A funnel plot of log mean differences of the incidence of carpal tunnel syndrome among patients with an increased cross-sectional area of the tunnel at the distal level in the studies.

meta-analysis. The right column shows the numerical value of the forest plot. CI: confidence interval; CTS: carpal tunnel syndrome; SD: standard deviation.
The graph indicates outcome effects *versus* the study size that is calculated from standard error (SE) of log (mean difference). Open circles represent each study in the present meta-analysis. The broken line represents a 90% pseudo-score confidence interval of the extent of effect in the study.

## DISCUSSION

This systematic review examined the role of carpal tunnel CSA in assessing carpal tunnel syndrome by analysing the trends observed in the contributing studies. While most of the existing studies reported on the association between CSA of MN and the diagnosis of CTS (46-48), studies comparing the CSA of the carpal tunnel at the proximal and distal levels between cohorts (participants and controls) are scarce (23). To the best of the authors' knowledge, the present study is one of the first to compare and establish the evidence associating the CSA of the carpal tunnel with CTS. The findings of the present study demonstrate that, overall, the studies which have assessed CSA of the carpal tunnel in individuals with CTS support the association between higher CSA of the carpal tunnel at the proximal and distal levels and CTS, suggesting it to be a relevant diagnostic determinant of this condition.
The level of evidence in this study was evaluated based on: 1) the consistency level of the contributing studies, 2) an assessment of the pooled mean differences, 3) the trend of the forest plot, and 4) the funnel plot shape for publication bias. Overall, the findings show consistency to some extent, and this is confirmed when different case definitions and methods of measurement of CTS are considered. In general, studies with non-conservative criteria (such as only noting symptoms) found an association more frequently and had a higher incidence than studies with a more stringent case definition (49). The most precise results were obtained when a positive NCS was combined with clinical symptoms (50). To avoid any potential heterogeneity in future observational studies and for clinical use, Barcenilla *et al.* (51) advised using a conservative case definition of CTS.
Of note, the studies by (35, 40, 43), scored 8 (out of 9) stars as per the NOS suggesting "high" methodologic quality. Besides, the studies by (41, 42, 44), scored 7 (out of 9) stars as per the NOS suggesting "moderate" methodologic quality (52). The demographics of the samples in these studies were appropriately well-matched to the control group and have relatively lesser variations compared to the demographics in the rest of the studies. Furthermore, care was taken to ensure that control groups had not been diagnosed with CTS nor accompanied by any comorbidity. However, Cobb *et al.* (43) do emphasize inadequate statistical power as a factor contributing to the risk of bias. Those studies scoring less than 4 stars in the selection section of the NOS might have some tendency for selection bias since there is an increased possibility of demographic variances between the participant and control groups. Thus, regulating these confounders is crucial to precisely provide a true association of the findings between the CTS group and the control group. In the general population, demographics such as gender and age, occupation, diseases like arthritis or diabetes mellitus and anthropometric characteristics of the hand are important determinants and may influence the development of CTS (52). The inclusion of females as participants and controls limited the generalizability of Nakamichi and Tachibana's (46) findings.
Studies receiving 3 stars in the NOS exposure section in this study may have been more robust in the sense that individuals from both the case and control groups were assumed to be included using the same method and that the CTS patients had a definitive diagnosis of the condition. However, studies with less than 3 stars in the exposure section either used different methods to include the cohorts or had low response rates. Furthermore, as four of the studies reviewed followed prospective cohort design, one followed retrospective design and the majority were case-control in nature, the level of evidence supported by this review can be categorized as 2A and 3A evidence (54). The levels of evidence also consider the methodologic quality of the studies. Based on these levels of evidence, the present review promotes grade B or C recommendations indicating that in general, clinicians should consider the evidence but should be observant of new research in this domain and thoughtful of the preferences of patients (54). From this study, clinicians could consider that an increased CSA of the carpal tunnel at the proximal level and distal level may be considered a diagnostic determinant of CSA.
Despite efforts contributed towards careful study identification and selection, data extraction and analysis of findings, some limitations to this study are present and need to be overcome by future studies. First, the preset inclusion criteria for the selection of articles included comparative (case-control and cohort) studies. This study did not attempt to assess randomized controlled trials (RCTs). There may be RCTs available that directly compare interventions or risk factors for CTS between diagnosed individuals and healthy adults. With the contributing studies being case-control and cohort in nature, the level of evidence that can be concluded from this review is limited to 2A and 3A with grade B or grade C recommendations. Second, different assessment methods for the diagnosis of

CTS are often noted as a limitation in the existing systematic reviews. In the present review, the contributing studies considered different methods for assessment of CTS which further differed between studies. Further studies should emphasize developing a clinical classification framework with a defined limit, a standardized assessment method and risk analysis of the method to promote the use of a precise and common diagnostic tool for CTS (55). Third, this review is limited by the absence of adequate sensitivity in some of the contributing studies as evident by the extensive confidence intervals. According to Abbas *et al.* (56), less stringent studies are likely to yield higher but ambiguous estimates. Since studies using a stringent case definition of CTS encountered lower prevalence rates, future prospective studies should consider this while estimating the population size. Primary studies with a stringent case definition of CTS, objective assessment methods and appropriate sensitivity would enable elimination of inconsistent findings and demonstrate a significant association between increased CSA and the incidence rate of CTS. Fourth, the role of gender in influencing the consistency of the findings cannot be excluded. Thus, more future prospective studies should explore the association of gender with anatomical variations in the carpal tunnel. Fifth, some of the contributing studies used volunteers as a control group, which is another limitation of the present study. Generally, volunteers tend to be healthier compared to the general population in terms of body weight and BMI (57). A further limitation of this study was that except for four studies, nine studies did not include well-matched demographics of the control group with that of the test group. The study by Uchiyama *et al.* (25) noted 13 years of differences in the mean age of the participant and control groups, which might lead to bias and identify age-based changes related to the development of CTS against CTS-related changes.

## CONCLUSIONS

In conclusion, the contributing studies provide evidence of an association between increased CSA of the carpal tunnel and the development of CTS. Overall, the reviewed studies suggest that there is an increased CSA of the carpal tunnel at the proximal and distal levels evident in the group of CTS patients when compared with control groups. Based on the evidence established in this review, further high-quality studies must be conducted to accurately establish the role of CSA of the carpal tunnel in the development of CTS. Well-designed RCTs and prospective cohort studies would be appropriate to evaluate the risk and further develop this evidence base.

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None.

## DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

## CONTRIBUTIONS

MRD, AKB, SGK, SAJ: conceptualization, supervision. MRD: methodology, investigation, writing – review & editing. SAJ, SGK: statistical inferences.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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