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Ultrasonographic assessment of carpal tunnel syndrome severity: A systematic review and meta-analysis

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Abstract

OBJECTIVE: To investigate the overall estimates of cross-sectional areas (CSA) of the median nerve measured by ultrasonography in accordance with the electrodiagnostic classification of carpal tunnel syndrome (CTS) severity.

DESIGN: MEDLINE (PubMed), EMBASE (Ovid), and Web of Science were searched for studies reporting the median nerve CSA measured by ultrasonography for mild, moderate and severe CTS based on electrodiagnostic study. CSA values measured at the carpal tunnel inlet were included in the analyses.

RESULTS: Overall, 866 citations were retrieved and checked for eligibility. Finally, 16 articles were included for meta-analysis. These studies included a total sample of 2,292 wrists including 776 mild, 823 moderate and 693 severe CTS. The pooled analysis revealed a mean CSA of 11.64 mm^2 (95% CI: 11.23-12.05 mm^2; P< 0.001) for mild CTS; a mean CSA of 13.74 mm2 (95% CI: 12.59-14.89 mm^2; P< 0.001) for moderate CTS; and, a mean CSA of 16.80 mm2 (95% CI: 14.50-19.1 mm^2; P< 0.001) for severe CTS.

CONCLUSION: This is the first meta-analysis that provides the pooled median nerve CSA values in accordance with the electrodiagnostic classification of CTS severity. The values obtained in this study have clinical utility in ultrasonographic assessment of patients with CTS.

Keywords: Carpal Tunnel Syndrome; Ultrasonography; Electrodiagnosis; Diagnosis; Review; Meta-Analysis.

Introduction

Carpal tunnel syndrome (CTS) is the most common peripheral compression neuropathy of the median nerve in the upper limb. Depending on the criteria used for diagnosis, the prevalence has been reported to vary from 3% to 6% in the general population. There is a 3:1 female predominance with a mean age of onset in the early 40s. [1-3] The classic presentation is numbness and pain in the first three radial digits and the radial side of the forth finger corresponding to the innervation of the median nerve in the hand. The diagnosis is based primarily on clinical features, but electrodiagnostic studies are widely used to confirm the diagnosis and determine the stage of severity. [4, 5]

During the past decade, high-frequency ultrasonography is extensively being used in the field of neuro- musculoskeletal medicine. One major application is evaluation of peripheral nerve entrapments in the upper and lower limbs. The most reliable ultrasonographic indicator of peripheral nerve entrapment neuropathy is enlargement of the nerve cross-sectional area (CSA). [6] Many studies have compared the diagnostic yields of ultrasonography versus electrodiagnostic studies in patients with CTS. There is now mounting evidence that ultrasonography can be used as an alternative to electrodiagnostic studies in the diagnosis of CTS. [7, 8] A median nerve CSA $\geq$10 mm^2 at the level of the pisiform bone is the most consistent parameter for diagnosis of CTS by ultrasonography. The diagnostic sensitivity has been estimated to be as high as 97% using this parameter. [9, 10] Several studies have attempted to discover whether the CSA of the median nerve is useful for predicting the severity of median neuropathy as determined by nerve conduction studies or not. In recent years, increasing numbers of authors have provided data on the mean CSA of the median nerve in accordance with electrophysiological grading of CTS severity.

However, the existing published data need to be consolidated into a full meta-analysis to determine the overall estimate of median nerve CSAs for mild, moderate and severe CTS.

The purpose of this study was to conduct a meta-analysis on high-quality research to determine the overall estimates of median nerve CSA at carpal tunnel inlet for mild, moderate and severe CTS as defined by the electrodiagnostic studies.

Materials and methods

This systematic review was conducted in accordance with the Cochrane Collaboration guidelines [11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement (Supplemental Digital Content 1, http://links.lww.com/PHM/A709). [12] This study was exempt from ethical approval since it was a secondary analysis of a publicly available datasets.

Sources and search strategy

In December 2017, two authors (PR and SR) independently conducted a systematic search of MEDLINE (PubMed), EMBASE (Ovid), and Web of Science to identify relevant publications from the inception of the databases to 1 December 2017 without any restrictions. The following text words, Medical Subject Headings (MeSH) terms and Boolean operators were used: "carpal tunnel or carpal tunnel syndrome or median nerve", "electrodiagnostic or electrophysiologic or electrodiagnostically or electromyography or nerve conduction or neurophysiologic", and "ultrasound or ultrasonography or ultrasonographic, sonography or sonographic or sonographically". The search was conducted without any language restriction.

Inclusion and exclusion criteria

The titles and abstracts of all collected studies were reviewed for relevance by the same authors (PR and SR). Disagreements were resolved through discussion to a third author (AB) when necessary. The criteria for study inclusion in this systematic review were as following: i) Study performing both high-frequency ultrasonography and electrodiagnostic study of the median nerve in patients with CTS; ii) Study reporting the median nerve CSA for mild, moderate and severe CTS in accordance with electrodiagnostic studies; iii) Clearly described electrodiagnostic grading scale for defining the severity of CTS, and, iv) Study published in full-text. We did not include case reports, case series, letters, review articles, technical reports and conference abstracts in this systematic review. The primary reason for not including some relevant articles was lack of describing a valid electrodiagnostic criteria for defining mild, moderate and severe CTS. The eligible studies that met the inclusion criteria were imported into EndNote® software version X7 (Thomson Reuters, Carlsbad, CA).

Quality assessment

We evaluated the scientific quality of the studies using the "STrengthening the Reporting of Observational Studies in Epidemiology" (STROBE) tool [(13)] (see Supplementary Checklist, Supplemental Digital Content 2, http://links.lww.com/PHM/A710). The STROBE is a standard international checklist for quality assessment of the observational studies including cohort studies, case-control studies, and cross-sectional studies. This tool evaluates components of the study design, methods for selecting participants, data collection, methods for measuring exposure and outcome variables, statistical methods, potential bias and methods to control for confounding. Studies with STROBE score <8 were not included in the meta-analysis. Two

authors (PR and AA) performed the quality assessment separately and disagreements were resolved through discussion.

Data extraction and outcome measures

After enrollment of the eligible studies, one author (SR) extracted data from each article including the name of the first author, year of publication, number of patients, number of median nerves examined (number of wrists), mean age of the studied sample, gender ratio, and mean ± standard deviation (SD) of the median nerve CSA corresponding to mild, moderate and severe CTS. The extracted data were summarized into standard data tables designed for this review. For studies that reported various median nerve CSA measurements at different anatomical sites, we only included the median nerve CSAs measured at the level of pisiform bone (carpal tunnel inlet) in this analyses.

As no generally accepted electrophysiological scale for grading the severity of CTS has been reached yet, studies included in the present review applied four different grading scales. These scales are derived from the publications by Steven [(14)], Padua et al [(15)], Bland [(16)] and Sucher. [(17)] The details of these grading schemes are given in table 1. The Steven and Sucher scales use three grades as "mild", "moderate" and "severe", with a relatively similar electrophysiological criteria. The Padua and the Bland scales divide the mild and the severe grades into more subgroups, and use five and six grades, respectively. In order to conduct the met-analysis, we grouped the Bland and the Padua scales into three grades as following:

Mild CTS: Bland grade 1 (very mild) and grade 2 (mild); Padua grade 1 (minimal) and grade 2 (mild).

Moderate CTS: Bland grade 3 (moderate); and Padua grade 3 (moderate).

Severe CTS: Bland grade 4 (severe), grade 5 (very severe) and grade 6 (extremely severe); and Padua grade 4 (severe) and grade 5 (extreme).

Data synthesis

The pooled means of CSA in mild, moderate and severe CTS and their 95 % confidence intervals (CI) were evaluated using random-effects models. The pooled CSAs were synthesized by considering the means of each study weighted by its sample size (number of wrists) for mild, moderate and severe CTS. Chi-squared tests and I-squared statistics were used to evaluate the heterogeneity between the studies. In the Chi-squared test, when the p value of Cochran's Q was lower than 0.1, the heterogeneity was considered. [18, 19] The results of I-squared test were interpreted as following: (i) 0-40 % might not be important, (ii) 30-60% might represent moderate heterogeneity, (iii) 50-90% might represent substantial heterogeneity, and (iv) 75-100 % might indicate considerable heterogeneity. [11, 19] When heterogeneity between studies was detected, a leave-one-out sensitivity analysis was conducted by sequentially removing one study at a time and recalculating the results to assess the consistency of the results. To assess the publication bias, Funnel plots, Begg's test, and Egger's regression model were used. [20, 21] When publication bias was detected, trim and fill method was used to adjust the results. All statistical analysis were performed using Comprehensive Meta-Analysis Software version 3 (Biostat Inc., Englewood, New Jersey, USA).

Results

Eligibility of studies

A total of 866 citations were identified by our initial search. Of these, 842 studies were excluded based on the title and abstract screening as they were irrelevant studies, duplicates, case reports, case series, letters, review articles, conference abstracts, and technical reports. Twenty four relevant studies were selected and their full texts were obtained for further assessments. On further scrutiny, eight studies were excluded from the meta-analysis primarily because of not describing a definite electrodiagnostic grading scale for defining mild, moderate and severe CTS. Finally, 16 studies with appropriate quality met the inclusion criteria for this meta-analysis. [22-37] No additional citations were identified in searching the reference lists of the included studies. A summary of the searching strategy and selection process is illustrated in Figure 1.

The included studies were all written in English language and were published from 2004 to 2017. They were all cross-sectional studies. These studies included a total sample of 2,292 wrists including 776 mild, 823 moderate and 693 severe CTS. Table 2 demonstrates the main characteristics of the 16 included studies.

Quantitative Synthesis

Heterogeneity was observed across the studies in means of CSA in all groups of mild, moderate and severe CTS. The details of heterogeneity analysis (I-square statistics) are described in table 3. Accordingly, the random-effect models were used to pool the data. The pooled analysis revealed a mean CSA of 11.64 mm^2 (95% CI: 11.23-12.05 mm^2; P< 0.001) for mild CTS (figure 2); a mean CSA of 13.74 mm^2 (95% CI: 12.59-14.89 mm^2; P< 0.001) for moderate CTS (figure

3); and, a mean CSA of 16.80 mm^2 (95% CI: 14.50-19.1 mm^2; P< 0.001) for severe CTS (figure 4). Among the included studies in the meta-analysis, 12 studies [22-29, 31, 33, 35, 36] reported the median nerve CSA for normal healthy volunteers/control subjects. The pooled analysis revealed a mean CSA of 8.21 mm^2 (95% CI: 8.03-8.38 mm^2; P< 0.001) for normal median nerves.

Sensitivity analysis

To evaluate the consistency of the results, a leave-one-out sensitivity analysis was performed by sequentially excluding one study at a time and recalculating the pooled means repeatedly. The sensitivity analysis revealed no significant change in the pooled means of CSA in all three severity grades of CTS when all studies were excluded one by one. This indicated the robustness and stability of the results.

Publication bias analysis

The results of Funnel plots, Begg's test, and Eggers tests revealed publication bias in the means of CSAs in moderate and severe CTS (table 4). To address the issue of publication bias, we performed trim and fill analysis to adjust the means of CSAs in moderate and severe CTS. The adjusted means for moderate and severe CTS were 13.43 mm^2 (95% CI: 11.68 -15.17 mm^2) and 16.36 mm^2 (95% CI: 13.52-19.2 mm^2), respectively.

Discussion

One of the main reasons for carrying out electrodiagnostic study in CTS is to assess the severity of the median neuropathy at the wrist. Many electrophysiological grading schemes exist for describing the severity of the CTS. These methods generally rely on measuring the degree of nerve conduction slowing across the carpal tunnel or determining whether or not sensory or motor action potentials are present. However, most available grading schemes are arbitrary in

nature. [17] The variety of grading schemes means there is no universally accepted electrophysiological scale for grading the severity of CTS. The most commonly used scales are derived from the publications by Steven [14], Padua et al [15] and Bland [16] (table 1). Steven's used three grades as "mild", "moderate", and "severe"; but did not specify latency levels within each grade. Padua et al. suggested a five-grading scheme very similar to that of Steven's scale, the difference being that it divides mild CTS into "minimal" and "mild" subdivisions, and severe CTS into "severe" and "extreme" subdivisions. They did not specify latency levels within each grade as well. Finally, Bland used six grades and determined specific latency cut-offs for each grade (table 1). These scales can be mapped onto each other to some extent, with Bland providing the greatest number of subdivisions, then Padua and then Stevens. In 2013, Sucher [17] proposed a new grading scheme based on a combination of the ranking criteria used in prior publications by Bland, Stevens and Padua. This scheme uses three grades as mild, moderate and severe, and is suggested to be a non-arbitrary means of determining CTS severity. Although there are only slight variations between these grading scales, the controversy about classifying patients into mild, moderate, and severe CTS is probably the most important challenge for the research of CTS severity in general. However, in order to conduct the present meta-analysis, we grouped the Bland grades 1 and 2 (very mild, mild) and Padua grades 1 and 2 (minimal, mild) into "mild CTS". Similarly, we grouped the Bland grades 4, 5 and 6 (severe, very severe, and extremely severe) and Padua grades 4 and 5 (severe, extreme) into "severe CTS".

In this systematic review and meta-analysis, we incorporated 16 studies assessing the median nerve CSA at the carpal tunnel inlet in accordance with the electrophysiological classifications of CTS severity. Based on findings of this study, the pooled results of the exiting literature for

median nerve CSA was 11.64 mm^2 for mild, 13.74 mm^2 (adjusted: 13.43 mm^2) for moderate, and 16.80 mm^2 (adjusted: 16.36 mm^2) for severe CTS. To our knowledge, this is the first meta-analysis that provides the pooled median nerve CSA values in accordance with the electrodiagnostic classification of CTS severity. The values obtained in this study have clinical utility in ultrasonographic assessment of patients with CTS.

Increased nerve CSA is an important diagnostic finding in compression neuropathies. [6] Prolonged compression of the nerve will result in changes in the neural microcirculation, and render the nerve susceptible to ischemia. Nerve ischemia is responsible for blood vessel endothelial permeability abnormalities, which can lead to intra-neural edema. With increased compression, there will be intrafascicular edema, fibrous tissue proliferation, and higher proportion of extracellular water contents in the affected nerve. These structural changes result in swelling of the nerve, which is reflected by increased nerve CSA in ultrasound examination. [6, 8, 9] The associations between CTS severity and median nerve CSA have been demonstrated in several studies. In a study on 106 patients with moderate to severe CTS, Phongamwong et al. [36] reported a significant positive correlation (r=0.56) between CTS severity and median nerve CSA measured at carpal tunnel inlet. Using receiver operator characteristics analysis, they showed that a cut-off value of 14 mm^2 for median nerve CSA has 91.4% specificity and 42.3% sensitivity to rule in moderate to severe CTS. This cut-off value is very close to the pooled estimates of 13.74 mm^2 for moderate CTS obtained in our meta-analysis. Padua et al. [38] made a similar observation and reported a correlation coefficient of 0.80 between median nerve CSA and electrodiagnostic classification of CTS severity. In another study Karadağ et al. [24] evaluated the agreements between the two methods of electrodiagnostic studies and ultrasonography in classification of CTS severity. They showed a good agreement (Cohen's kappa coefficient = 0.619) between these

two methods in classifying CTS as mild, moderate and severe. Despite these promising reports, a number of authors including Moran et al. [39] and Mhoon et al. [40] have found no significant correlation between the values of the median nerve CSA and electrodiagnostic severity scales.

Ultrasonographic measurement of the median nerve CSA can be performed at the carpal tunnel inlet (the level of scaphoid-pisiform), or at the level of carpal tunnel outlet (the level of hamate-trapezium). All studies included in this meta-analysis performed ultrasound measurements at the carpal tunnel inlet. Measurement of median nerve CSA at the carpal tunnel inlet is reportedly more sensitive for diagnosis of CTS. [9, 10] Additionally, it has been shown that measurement of the median nerve CSA at the carpal tunnel inlet has a better inter-reader reliability than the measurements at the carpal tunnel outlet. [39, 41] The poor inter-reader reliability at the carpal tunnel outlet may be explained by difficulty in visualizing the median nerve at this level, as the nerve moves more dorsally and is covered by a thick palmar skin. ([9, 37] However, it should be acknowledged that the ultrasonographic assessment of median nerve is highly dependent upon the skill and expertise of the practitioner. The way that the operator performs the ultrasound examination may greatly affect the values of measured CSAs. Considerable expertise are required to perform ultrasonographic assessment of the median nerve for diagnosis of CTS.

Ultrasonography represents an emerging diagnostic technique to assess median neuropathy at wrist; it is an alternative to more traditional electrodiagnostic study. However, each technique has some advantages and some shortcomings. Ultrasonography provides real-time imaging of the carpal tunnel and allows dynamic evaluation of the median nerve and the surrounding structures. Imaging can be used for evaluating anatomic variations or possible compressing masses that may be responsible for median nerve compression. Furthermore, ultrasonography is non-invasive and

requires a shorter examination time and lower costs than electrodiagnostic studies. [9] On the other hand, electrodiagnostic studies are more powerful in the assessment of differential diagnosis in individuals with symptoms that suggest CTS. For example, CTS often occurs in the context of a generalized peripheral polyneuropathy, for example in the setting of diabetes mellitus. Electrodiagnostic study is able to provide a more accurate assessment of the extent to which the symptoms may be due to a focal median mononeuropathy versus a generalized peripheral polyneuropathy in such a common situation. The same comment is also applicable for a C6-C7 radiculopathy that may appear clinically similar to CTS. At present time, the issue of which technique should be used as initial screening remains a matter of debate. As an example, Wong et al. [41] and Goldberg et al. [42] proposed diagnostic approaches that involved ultrasonography as the initial screening test for patients suspected with CTS, and secondary electrodiagnostic studies performed only when the ultrasonography results were negative. On the other hand, some authors [43] offered a counterproposal that clinicians should start the screening with nerve conduction study of the median nerve, instead of ultrasonography, because electrodiagnostic study is suggested to be more sensitive for diagnosis of median neuropathy at wrist. [44, 45] Despite these debates there is a broad consensus about the value of ultrasonography in providing complementary information regarding the nerve anatomy and the neighboring structures within the carpal tunnel.

Study limitations

In the present systematic-review, a rigorous literature search was carried out to consolidate the results of all relevant, high-quality studies. However, this study has a number of limitations. First, a number of relevant studies were not included in this meta-analysis mainly because their

electrodiagnostic criteria for CTS classification was not well-described. The second limitation was lack of temperature control in a number of included studies. It is well-established that temperature can have a significant effects on neural conduction parameters. [46] Finally, considering the electrodiagnostic studies as the reference method for determination of CTS severity has a limitation as this test may be associated with some false-positive and false-negative results. [47] The possibility of false positive and false negative results were neglected in almost all included studies.

Conclusions

In conclusion, the present meta-analysis synthesized the results of previous studies to provide the overall estimates of median nerve CSA in accordance with the electrodiagnostic classifications of CTS severity. The pooled results showed a median nerve CSA of 11.64 mm^2 for mild, 13.74 mm^2 (adjusted: 13.43 mm^2) for moderate, and 16.80 mm^2 (adjusted: 16.36 mm^2) for severe CTS. These values are of importance for the assessment of patients with CTS using ultrasonography.

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Figure legends

Figure 1. Flow diagram for inclusion of the studies in the meta-analysis.

Figure 2: The forest plot of mean cross-sectional areas for mild CTS.

Figure 3: The forest plot of mean cross-sectional areas for moderate CTS.

Figure 4: The forest plot of mean cross-sectional areas for severe CTS.

Figure 1

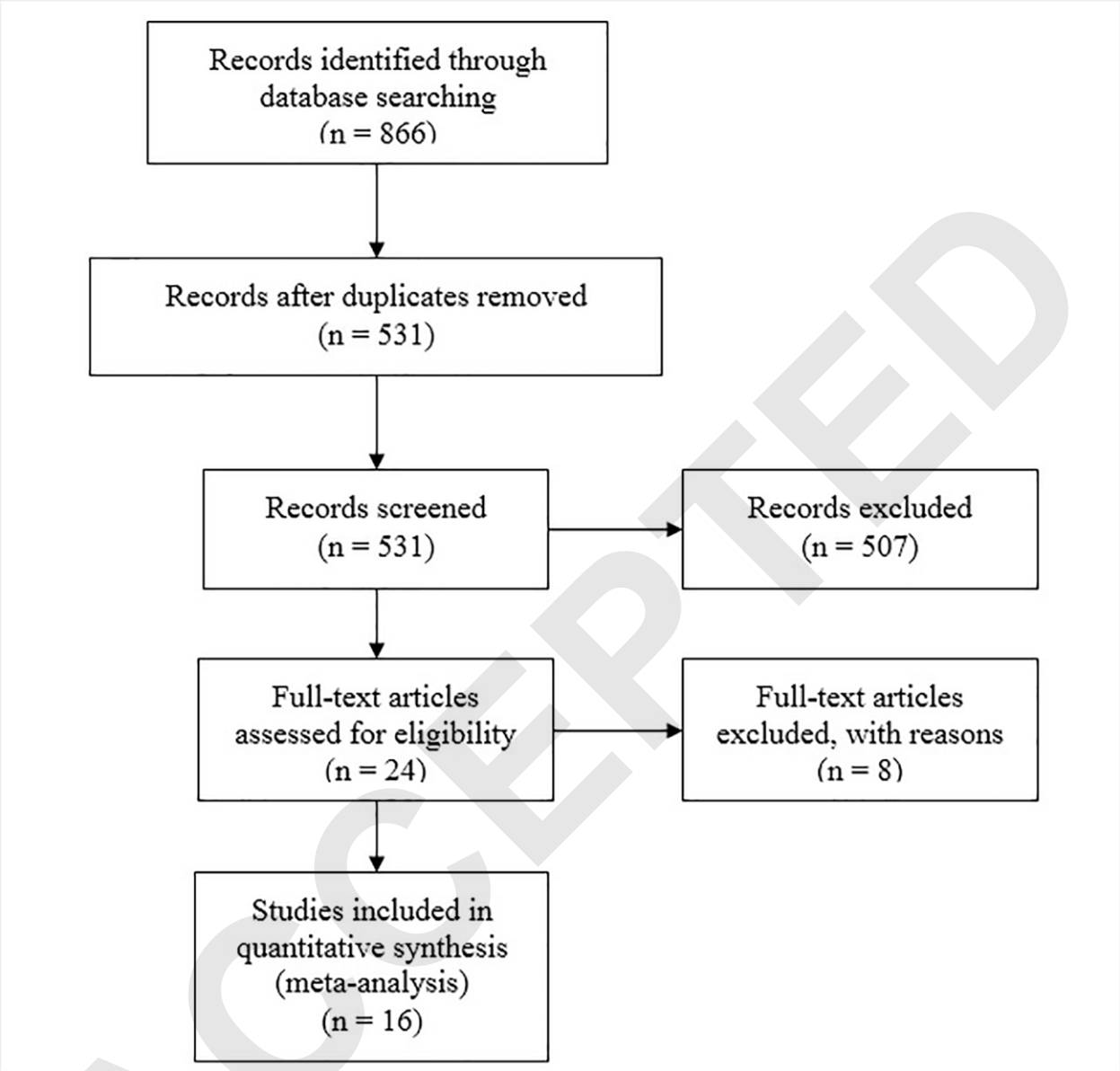
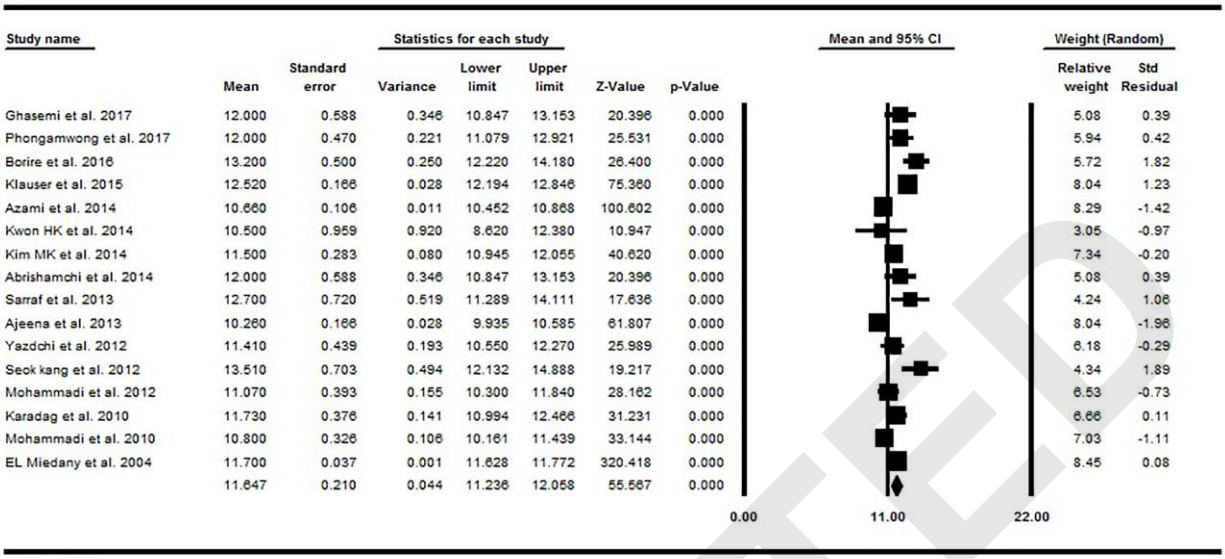
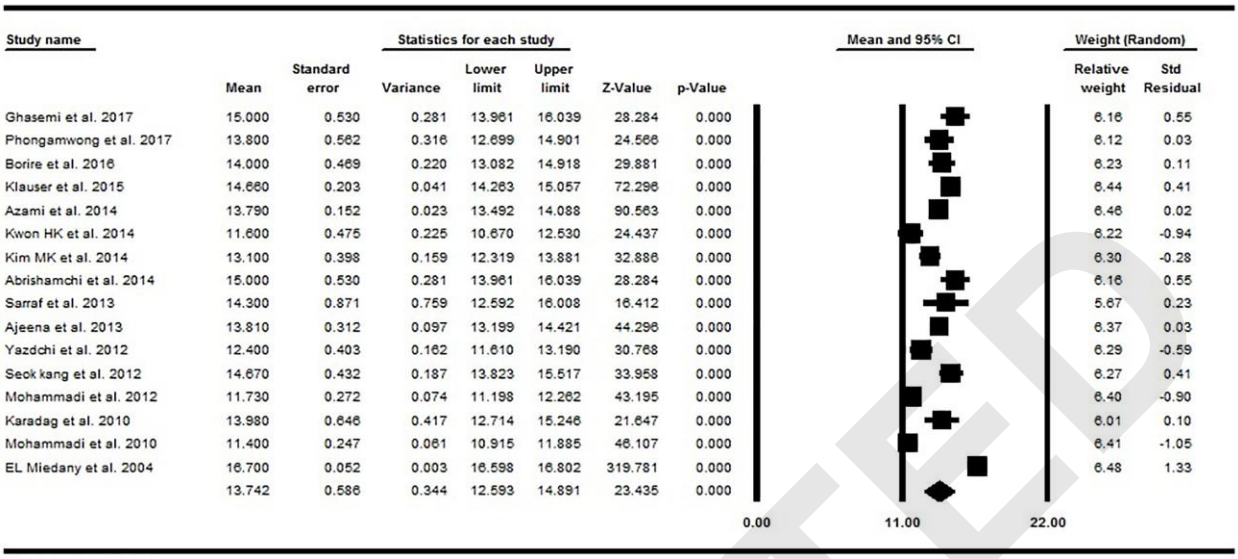


Figure 2



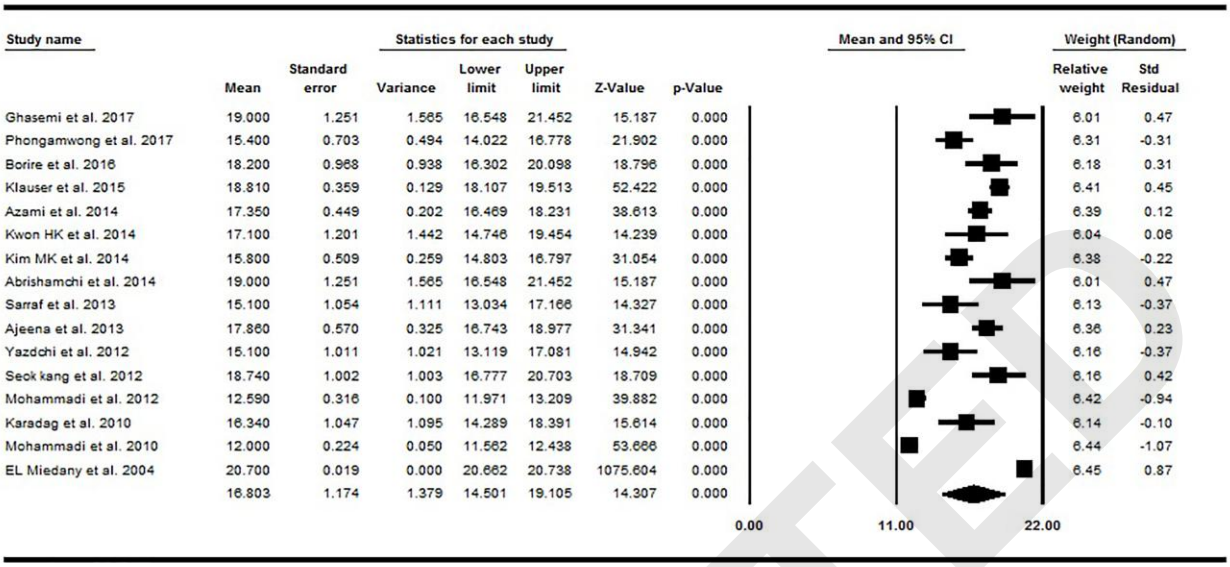
Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
Ghasemi et al. 2017	12.000	0.588	0.346	10.847	13.153	20.396	0.000	5.08	0.39
Phongamwong et al. 2017	12.000	0.470	0.221	11.079	12.921	25.531	0.000	5.94	0.42
Borire et al. 2016	13.200	0.500	0.250	12.220	14.180	26.400	0.000	5.72	1.82
Klauser et al. 2015	12.520	0.166	0.028	12.194	12.846	75.360	0.000	8.04	1.23
Azami et al. 2014	10.660	0.106	0.011	10.452	10.868	100.602	0.000	8.29	-1.42
Kwon HK et al. 2014	10.500	0.959	0.920	8.620	12.380	10.947	0.000	3.05	-0.97
Kim MK et al. 2014	11.500	0.283	0.080	10.945	12.055	40.620	0.000	7.34	-0.20
Abrishamchi et al. 2014	12.000	0.588	0.346	10.847	13.153	20.396	0.000	5.08	0.39
Sarraf et al. 2013	12.700	0.720	0.519	11.289	14.111	17.636	0.000	4.24	1.06
Ajeena et al. 2013	10.260	0.166	0.028	9.935	10.585	61.807	0.000	8.04	-1.96
Yazdchi et al. 2012	11.410	0.439	0.193	10.550	12.270	25.989	0.000	6.18	-0.29
Seok kang et al. 2012	13.510	0.703	0.494	12.132	14.888	19.217	0.000	4.34	1.89
Mohammadi et al. 2012	11.070	0.393	0.155	10.300	11.840	28.162	0.000	6.53	-0.73
Karadag et al. 2010	11.730	0.376	0.141	10.994	12.466	31.231	0.000	6.66	0.11
Mohammadi et al. 2010	10.800	0.326	0.106	10.161	11.439	33.144	0.000	7.03	-1.11
EL Miedany et al. 2004	11.700	0.037	0.001	11.628	11.772	320.418	0.000	8.45	0.08
	11.647	0.210	0.044	11.236	12.058	55.567	0.000		

Figure 3



Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
Ghasemi et al. 2017	15.000	0.530	0.281	13.961	16.039	28.284	0.000	6.16	0.55
Phongamwong et al. 2017	13.800	0.562	0.316	12.699	14.901	24.566	0.000	6.12	0.03
Borire et al. 2016	14.000	0.469	0.220	13.082	14.918	29.881	0.000	6.23	0.11
Klauser et al. 2015	14.660	0.203	0.041	14.263	15.057	72.296	0.000	6.44	0.41
Azami et al. 2014	13.790	0.152	0.023	13.492	14.088	90.563	0.000	6.46	0.02
Kwon HK et al. 2014	11.600	0.475	0.225	10.670	12.530	24.437	0.000	6.22	-0.94
Kim MK et al. 2014	13.100	0.398	0.159	12.319	13.881	32.886	0.000	6.30	-0.28
Abrishamchi et al. 2014	15.000	0.530	0.281	13.961	16.039	28.284	0.000	6.16	0.55
Sarraf et al. 2013	14.300	0.871	0.759	12.592	16.008	16.412	0.000	5.67	0.23
Ajeena et al. 2013	13.810	0.312	0.097	13.199	14.421	44.296	0.000	6.37	0.03
Yazdchi et al. 2012	12.400	0.403	0.162	11.610	13.190	30.768	0.000	6.29	-0.59
Seok kang et al. 2012	14.670	0.432	0.187	13.823	15.517	33.958	0.000	6.27	0.41
Mohammadi et al. 2012	11.730	0.272	0.074	11.198	12.262	43.195	0.000	6.40	-0.90
Karadag et al. 2010	13.980	0.646	0.417	12.714	15.246	21.647	0.000	6.01	0.10
Mohammadi et al. 2010	11.400	0.247	0.061	10.915	11.885	46.107	0.000	6.41	-1.05
EL Miedany et al. 2004	16.700	0.052	0.003	16.598	16.802	319.781	0.000	6.48	1.33
	13.742	0.586	0.344	12.593	14.891	23.435	0.000		

Figure 4



Study name	Mean	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std Residual
Ghasemi et al. 2017	19.000	1.251	1.565	16.548	21.452	15.187	0.000	6.01	0.47
Phongamwong et al. 2017	15.400	0.703	0.494	14.022	16.778	21.902	0.000	6.31	-0.31
Borire et al. 2016	18.200	0.968	0.938	16.302	20.098	18.796	0.000	6.18	0.31
Klauser et al. 2015	18.810	0.359	0.129	18.107	19.513	52.422	0.000	6.41	0.45
Azami et al. 2014	17.350	0.449	0.202	16.469	18.231	38.613	0.000	6.39	0.12
Kwon HK et al. 2014	17.100	1.201	1.442	14.746	19.454	14.239	0.000	6.04	0.06
Kim MK et al. 2014	15.800	0.509	0.259	14.803	16.797	31.054	0.000	6.38	-0.22
Abrishamchi et al. 2014	19.000	1.251	1.565	16.548	21.452	15.187	0.000	6.01	0.47
Sarraf et al. 2013	15.100	1.054	1.111	13.034	17.166	14.327	0.000	6.13	-0.37
Ajeena et al. 2013	17.860	0.570	0.325	16.743	18.977	31.341	0.000	6.36	0.23
Yazdchi et al. 2012	15.100	1.011	1.021	13.119	17.081	14.942	0.000	6.16	-0.37
Seok kang et al. 2012	18.740	1.002	1.003	16.777	20.703	18.709	0.000	6.16	0.42
Mohammadi et al. 2012	12.590	0.316	0.100	11.971	13.209	39.882	0.000	6.42	-0.94
Karadag et al. 2010	16.340	1.047	1.095	14.289	18.391	15.614	0.000	6.14	-0.10
Mohammadi et al. 2010	12.000	0.224	0.050	11.562	12.438	53.666	0.000	6.44	-1.07
EL Miedany et al. 2004	20.700	0.019	0.000	20.662	20.738	1075.604	0.000	6.45	0.87
	16.803	1.174	1.379	14.501	19.105	14.307	0.000		

Table 1. Electrophysiological grading scales for the severity of carpal tunnel syndrome.

Steven classification: [14] **Mild:** Prolonged DSL or MNL ± SNAP amplitude below the lower limit of normal. **Moderate:** Abnormal median DSL as above, and prolonged median DML. **Severe:** Prolonged median DSL and DML with either an absent SNAP or mixed nerve action potentials, or low amplitude or absent thenar CMAP. Evidence of membrane instability, reduced recruitment, and motor unit potential changes in EMG.
Padua classification: [15] **Minimal (grade 1):** Abnormal segmental or comparative tests only. **Mild (grade 2):** Slowing of digit/wrist sensory nerve conduction velocity with normal DML. **Moderate (grade 3):** Slowing of digit/wrist sensory nerve conduction velocity with abnormal DML. **Severe (grade 4):** Absence of SNAP and abnormal DML. **Extreme (grade 5):** Absent SNAP and CMAP.
Bland classification: [16] **Very mild (grade 1):** CTS demonstrable only with most sensitive tests. **Mild (grade 2):** Slow of digit/wrist sensory nerve conduction velocity with normal DML. **Moderate (grade 3):** SNAP amplitude preserved with DML < 6.5 ms. **Severe (grade 4):** SNAP amplitude absent but CMAP amplitude preserved, DML < 6.5 ms. **Very severe (grade 5):** DML > 6.5 ms with recordable CMAP amplitude. **Extremely severe (grade 6):** Absent SNAP and CMAP.
Sucher classification: [17] **Mild:** Prolonged DSL and/or median MNL, and; Normal or minimally prolonged DML, and;

Amplitudes of all responses within normal range, and; No CB or mild CB, and; No thenar EMG abnormalities.

Moderate: Prolonged DSL, MNL, and DML, and; Amplitudes of all tested responses may be diminished, typically a relative decrease, and; CB may be present, and; Minor thenar EMG abnormalities may be present.

Severe: Unobtainable median SNAP (or low amplitude and very prolonged DSL), and; Low-amplitude or unobtainable median mixed nerve response and, if present, very prolonged MNL, and; Low-amplitude or unobtainable median CMAP and, if present, very prolonged DML, and; CB may be present and pronounced, and; Thenar EMG abnormalities often present.

Abbreviations: DSL: distal sensory latency; MNL: mixed nerve latency; SNAP: sensory nerve action potential; DML: distal motor latency CMAP: compound muscle action potential; EMG: electromyography; CB: conduction block.

Table 2: Characteristics of the included studies.

Author, year	Number of patients	Number of wrists	Age (years)	Gender (F:M)	Number of mild CTS	Number of moderate CTS	Number of severe CTS	Location of CSA Measurement	Mean ± SD CSA (mm^2)		
									Mild CTS	Moderate CTS	Severe CTS
EL Miedany et al.,2004	78	90	44.9 ± 6.16	51:27	30	33	27	Inlet	11.7± 0.2	16.7 ± 0.3	20.7 ± 0.1
Mohammadi et al., 2010	82	132	43.6 ± 9	74:8	34	53	45	Inlet	10.8 ± 1.9	11.4 ±1.8	12.0 ± 1.5
Karadag et al.,2010	NA	50	43.3 ± 11	NA	24	18	8	Inlet	11.73 ± 1.84	13.98 ± 2.74	16.34 ± 2.96
Mohammadi et al.,2012	60	90	45.2	52:8	28	33	29	Inlet	11.07 ± 2.0	11.73 ± 1.56	12.59 ± 1.7

									8		
Kang et al.,2012	110	110	NA	100:10	28	46	36	Inlet	13.51 ± 3.72	14.67 ± ± 2.93	18.74 ± 6.01
Yazdchi et al.,2012	90	155	48.52 ± 12.17	68:22	34	99	22	Inlet	11.41 ± 2.56	12.40 ± ± 4.01	15.10 ± 4.74
								Outlet	10.47 ± 2.20	11.25 ± ± 3.29	13.86 ± 4.04
Ajeena et al.,2013	35	63	41.5 ± 6.5	35:00	25	27	11	Inlet	10.26 ± 0.83	13.81 ± ± 1.62	17.86 ± 1.89
Sarraf et al.,2013	38	71	47.1 ±	NA	21	37	13	Inlet	12.7 ±	14.3 ± 5.3	15.1 ±

			10.9						3.3		3.8
Abrishamchi et al., 2014	52	81	51.8 ± 10.8	45:7	26	32	23	Inlet	12.0 ± 3.0	15.0 ± 3.0	19.0 ± 6.0
Kim et al., 2014	NA	246	53.0	NA	66	91	89	Inlet	11.5 ± 2.3	13.1 ± 3.8	15.8 ± 4.8
Kwon et al.,2014	50	92	55.6 ± 8.1	45:5	23	30	39	Inlet	10.5 ± 4.6	11.6 ± 2.6	17.1 ± 7.5
Azami et al.,2014	90	120	56.8 ± 10.6	83:7	57	29	34	Inlet	10.66 ± 0.8	13.79 ± ± 0.82	17.35 ± 2.62
								Outlet	9.38 ± 1.43	11.80 ± ± 0.91	13.46 ± 1.87
Klauser et al.,2015	427	643	57.9 ± 14.7	325:102	272	152	219	Inlet	12.52 ± 2.74	14.66 ± ± 2.50	18.81 ± 5.31

Ghasemi et al., 2015	52	81	51.8 ± 10.8	45:7	26	32	23	Inlet	12.0 ± 3.0	15.0 ± 3.0	19.0 ± 6.0
Borire et al., 2016	NA	131	NA	NA	49	41	41	Inlet	13.2 ± 3.5	14.0 ± 3.0	18.2 ± 6.2
Phongamwong et al.,2017	106	137	53.1 ± 12.8	87:19	33	70	34	Inlet	12.0 ± 2.7	13.8 ± 4.7	15.4 ± 4.1

Note: Data are presented as numbers or mean ± standard deviation. Abbreviations: F: females; M; males; CTS: carpal tunnel syndrome; CSA: cross-sectional are; NA: not available.

Table 3 Heterogeneity in studies.

Parameters	Q	Df (Q)	P value	I^2
Mild CTS	212.76	15	0.000	92.95
Moderate CTS	1329.161	15	0.000	98.87
Severe CTS	2486.884	15	0.000	99.39

Table 4. Bias in publications.

Parameters	Egger's test			Begg's test	
	t	95 % CI	P value	Z	P value
Mild CTS	0.22	-2.87 to 2.32	0.82	0.99	0.32
Moderate CTS	4.15	-13.93 to -4.44	0.00097	1.71	0.08
Severe	2.95	-14.33 to -2.27	0.01	2.25	0.02