Comparison of Interpolation Methods in the Diagnosis of Carpal Tunnel Syndrome

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Background: Diagnosis of carpal tunnel syndrome is based on clinical symptoms, examination findings, and electrodiagnostic studies. For carpal tunnel syndrome, the most useful part is nerve conduction studies. However, nerve conduction study can result in ambiguous or false negative results, particularly for mild carpal tunnel syndrome. Increasing the number of nerve conduction study tests improves accuracy, but also increases time, cost, and discomfort. To improve accuracy without additional testing, the Terminal Latency index and Residual Latency are additional calculations using the minimum number of tests. Recently, the median sensory-ulnar motor latency difference was devised as another way to improve diagnostic accuracy for mild carpal tunnel syndrome.

Aims: Median sensory-ulnar motor latency difference, Terminal Latency index and Residual Latency were compared for diagnostic accuracy by severity.

Study Design: Diagnostic accuracy study.

Methods: A total of 657 subjects were retrospectively enrolled. The carpal tunnel syndrome group consisted of 546 subjects with carpal tunnel syndrome by nerve conduction study (all severities). The control group consisted of 121 subjects with no hand symptoms and normal nerve conduction study. All statistical analyses were performed using SAS. Means were compared using the one-way ANOVA test with the Bonferroni adjustment. Sensitivity, specificity, positive predictive value and negative predictive value were compared including Receiver Operating Characteristic curve analysis.

Results: For mild carpal tunnel syndrome, median sensory-ulnar motor latency difference showed the higher specificity and positive predictive value rates (0.967 and 0.957, respectively) than Terminal Latency index (0.603 and 0.769, respectively) and Residual Latency (0.818 and 0.858, respectively). The area under the Receiver Operating Characteristic was highest for the median sensory-ulnar motor latency difference (0.889), followed by the Residual Latency (0.829), and the Terminal Latency index last (0.762). Differences were statistically significant (median sensory-ulnar motor latency difference is the most accurate). For moderate carpal tunnel syndrome, sensitivity and specificity rates of Residual Latency (0.989 and 1.000) and Terminal Latency index (0.983 and 0.975) were higher than median sensory-ulnar motor latency difference (0.866 and 0.958). Differences in area under the Receiver Operating Characteristic curve were not significantly significant, but median sensory-ulnar motor latency difference sensitivity was lower. For severe carpal tunnel syndrome, Residual Latency yielded 1.000 sensitivity, specificity, positive predictive value, negative predictive value and area beneath Receiver Operating Characteristic Curve. Differences in area under the Receiver Operating Characteristic curve were not significantly significant.

Conclusion: Median sensory-ulnar motor latency difference is the best calculated parameter for diagnosing mild carpal tunnel syndrome. It requires just a simple calculation and no additional testing. Residual Latency and Terminal Latency index are also useful in diagnosing mild to moderate carpal tunnel syndrome.

Keywords: Carpal tunnel syndrome, diagnosis, interpolation, nerve conduction

Carpal Tunnel Syndrome (CTS) is a complex syndrome caused by compression of median nerve beneath the transverse carpal ligament (1). CTS is characterized by paresthesia, pain, atrophy, weakness and sensory abnormalities in the median nerve innervation (2).

Early diagnosis of CTS increases the chance of successful treatment. Diagnosis of CTS is based on clinical symptoms, physical examination findings, and electrodiagnostic (EDX) tests, primarily nerve conduction studies (NCS). Clinical tests can identify probable cases. EDX findings improve diagnosis (3). EDX tests are used to confirm the diagnosis of CTS and exclude other possible causes, including cervical radiculopathy (CRP) or peripheral neuropathy (4).

However, several studies show that routine EDX tests have limited sensitivity and specificity for mild CTS (4-9). An expensive, uncomfortable test with inaccurate results is not helpful. Therefore, additional calculations utilizing the minimum number of tests to improve accuracy are crucial. These tests have included the terminal latency index (TLI) and residual latency (RL),and studies have shown they improve CTS diagnostic accuracy (3, 10-12). A more recent technique, median sensory latency-ulnar motor latency difference (MSUMLD) was shown to be useful in a previous small study (13). The 3 techniques have never been directly compared.

The aim of this study is to compare diagnosis accuracy of all of these methods in large study involving patients with CTS of all severities.

MATERIALS AND METHODS

Study population

This diagnostic accuracy study was conducted retrospectively (flowchart, Fig1). A total of 657 subjects were enrolled between January 2012 and December 2013. The CTS group consisted of 546 subjects with clinical symptoms and findings of CTS (e.g., numbness, tingling, paresthesia, pain or sensory deficits in the median nerve distribution, weakness of abductor pollicis brevis (APB) muscle and a positive Tinel's test), and abnormal NCS. The control group consisted of 121 subjects with clinical symptoms of CRP (neck pain but no hand symptoms) and normal NCS. Patients

FIG. 1. Flowchart of this study.

with hand symptoms and normal NCS were not included in either group. One hand of each subject was examined (14).

Exclusion criteria were a history of wrist fracture, previous median nerve surgery or injury, diabetes, chronic renal failure, gout, rheumatoid arthritis, thyroid disease, other systemic diseases associated with polyneuropathy, and plexopathy. The study protocol was approved by the school of medicine ethics committee.

Nerve conduction studies

Routine EDX tests including sensory and motor NCS for the median and ulnar nerves were performed using a Viasys Medelec Synergy EMG device. Skin temperature was maintained at 32.0 C; room temperature between 22.0 and 25.0 C. Filter bandwidth were 20 Hz-2 kHz for sensory NCS and 10 Hz- 10 kHz for motor NCS. Sweep speed was 1 msecs/division for sensory NCS and 5 msecs/division for motor NCS. Sensitivity was 20 µV/division for both types of NCS and increased if needed. Cup electrodes (AgCl) with 8 mm in diameter were used. Distance between the recording electrodes was 3-5 cm.

Distance between stimulator electrodes was 3 cm. Stimulation intensity was 10-30 mA for sensory NCS and 10-50 mA for motor NCS. Duration was 0.1-0.2 msecs for sensory NCS and 0.1-0.5 msecs for motor NCS. Supramaximal stimulation was achieved by adjusting the duration and intensity of the stimulus.

Median sensory NCS, digit II (finger)-wrist median and palm-wrist sensory nerve conduction velocities were orthodromically recorded with surface stimulation from digit II and mid palm. Latencies of the sensory nerve action potentials were measured from onset to initial negative peak.

The median motor compound muscle action potential (CMAP) was recorded with the active recording electrode placed over the midpoint of APB muscle and reference electrode distally over the thumb. The belly-tendon principle was followed and the ground electrode was placed between the stimulating and recording electrodes. Median motor distal latency (mMDL) was measured from the stimulus onset to the initial CMAP response. Median motor nerve conduction velocity (mMNCV) was determined by dividing the distance between the stimulation points by the difference in conduction times.

For the ulnar motor CMAP, the active recording electrode was placed over the belly of the abductor digiti minimi (ADM) midway between the distal wrist crease and the base of digit V. The reference electrode was placed on the proximal phalanx of the digit V. Electrical stimulation of the ulnar nerve was done proximal to the active recording electrode at the wrist crease just lateral to the flexor carpi ulnaris tendon. Ulnar motor distal latency was measured from the stimulus onset to the initial ADM CMAP deflection.

TLI was calculated with Equation 1 and RL with Equation 2. MSUMLD was a simple subtraction (13). TLI = terminal distance / (mMNCV × mMDL)

RL = mMDL − (distal distance (mm) / mMNCV)

EDX data were compared with normal reference values and categorized by our laboratories grading system (15):

• extreme CTS (absence of motor and sensory potentials)

• severe CTS (absence of sensory response and abnormal mMDL)
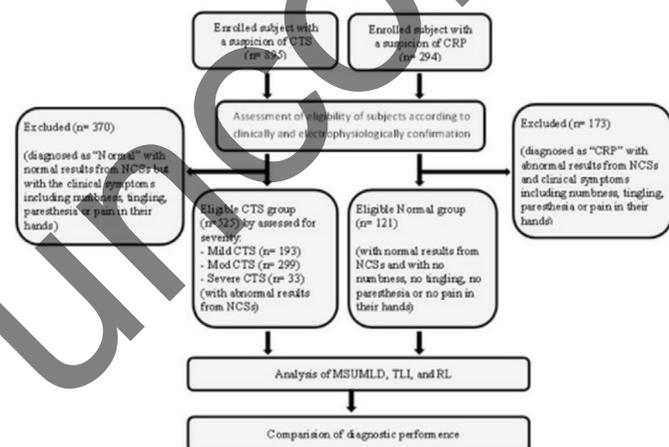
• moderate CTS (abnormal sensory conduction combined with mMDL abnormalities)

• mild CTS (abnormal median sensory conduction only)

• normal requires all findings in the normal range.

In extreme CTS, median sensory and motor latencies could not be obtained and hence not included in parameter analysis. The MSUMLD requires a median sensory response and hence could not be determined in severe cases.

Statistical analysis

All statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC). Data were reported as means ± standard deviation (SD). Means were compared using one-way ANOVA test with the Bonferroni adjustment. For the statistical significance, the probability level of 5% ($p < 0.05$) was required. The sensitivity and specificity were compared using Receiver Operating Characteristic (ROC) curve analysis.

RESULTS

The control and the CTS groups characteristics

According to the standards for the reporting of diagnostic accuracy studies (STARD) (16), the characteristics of the control and CTS groups are listed in Table 1. All data except gender were normally distributed. Distribution of the data was determined to be homogeneous using one way ANOVA test with the Bonferroni adjustment. The control group was significantly younger than the CTS group (p<.05).

Comparisons of parameters between the control and the CTS groups

Comparisons of mean values between control and all CTS groups are presented in Table 2. There was a statistically significant difference in all three parameters between the control group and all CTS groups (p<.0001).

Comparison of the sensitivity and specificity

Fig. 2 shows the lowest 1-specificity point corresponding to the highest sensitivity value of the cut-off ROC curve for each parameter (25). Comparing controls against all CTS patients (Table 3), using a cutoff value of > 0.8 msecs, the MSUMLD showed
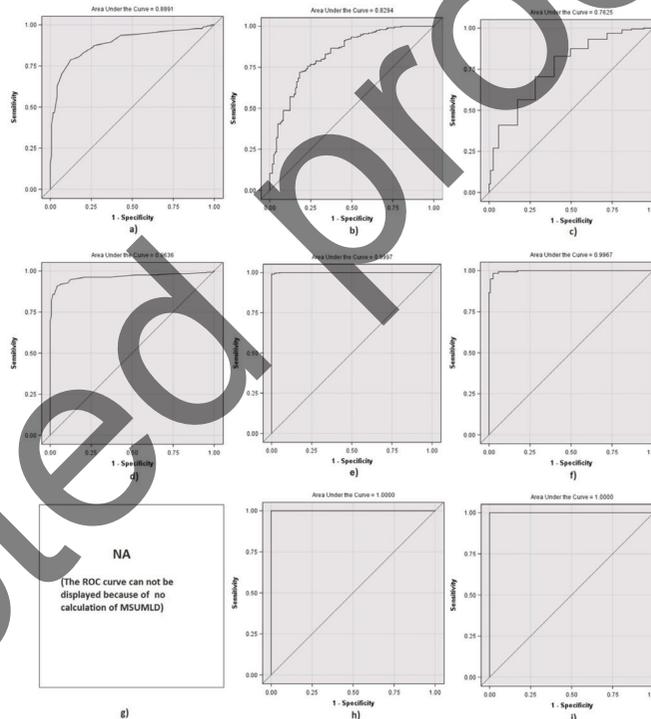
FIG. 2 a-i. The pilot of Receiver Operating Characteristic curves for each parameter a) median sensory-ulnar motor latency difference for mild carpal tunnel syndrome b) Terminal Latency index for mild carpal tunnel syndrome c) Residual Latency for mild carpal tunnel syndrome d) median sensory-ulnar motor latency difference for moderate carpal tunnel syndrome e) Terminal Latency index for moderate carpal tunnel syndrome f) Residual Latency for moderate carpal tunnel syndrome g) median sensory-ulnar motor latency difference for severe carpal tunnel syndrome h) Terminal Latency index for severe carpal tunnel syndrome, and i) Residual Latency for severe carpal tunnel syndrome.

TABLE 1. Characteristics of the control and the CTS groups

Group	n of Subject	Female / Male	Mean Age±SD	Age range
Control	121	70/51	44.9±10.7	20-66
Mild CTS	193	168/25	52.1±10.5	21-82
Moderate CTS	299	256/43	51.5±11.7	17-88
Severe CTS	33	28/5	55.2±12.3	29-78
Total	646	522/124	50.6±11.5	17-88

CTS: carpal tunnel syndrome; N: number; SD: standard deviation

TABLE 2. Comparison of the mean values between the control and three CTS groups

Parameters	Control Group (MN±SD)	CTS Group (MN±SD)					
		Mild	pa	Moderate	pb	Severe	pc
MSUMLD (msecs)	0.50±0.25	1.04±0.38	p<0.001	1.76±0.78	p<0.001	NA	
TLI (msecs)	0.30±0.03	0.27±0.02	p<0.001	0.20±0.03	p<0.001	0.15±0.04	p<0.001
RL (msecs)	2.08±0.33	2.50±0.29	p<0.001	3.70±0.69	p<0.001	5.18±1.14	p<0.001

CTS: carpal tunnel syndrome; MSUMLD: median sensory-ulnar motor latency difference; TLI: terminal latency index; RL: residual latency; MN: mean value; SD: standard deviation; pa: statistical significance value of the difference between the control and mild CTS; pb: statistical significance value of difference between the control and moderate CTS; pc: statistical significance value of difference between the control and severe CTS

sensitivity = 0.864, specificity = 0.893, positive predictor value (PPV) = 0.969, and negative predictor value (NPV) = 0.632. RL > 2.37 msecs showed sensitivity = 0.897, specificity = 0.818, PPV = 0.955, and NPV = 0.647. For TLI < 0.26 msecs, sensitivity = 0.729, specificity = 0.942, PPV = 0.983 and NPV = 0.496.

Comparing the control and mild CTS groups (Table 4), cutoff values were slightly different. MSUMLD > 1.02 msecs yielded sensitivity = 0.517, specificity = 0.967, PPV = 0.957 and NPV = 0.582. RL > 2.4 msecs, sensitivity = 0.689, specificity = 0.818, PPV = 0.858, and NPV = 0.623. For TLI < 0.29 msecs, sensitivity = 0.829, specificity = 0.603, PPV = 0.769, and NPV = 0.689. The area under the ROC was highest for the MSUMLD (0.889), followed by the RL (0.829), and the TLI last (0.762), and the differences were statistically significant (MSUMLD is the most accurate).

Comparison of the control and moderate CTS is shown in Table 5. For MSUMLD > 0.95 msecs, sensitivity = 0.866, specificity = 0.958, PPV = 0.981, NPV = 0.743, and area beneath the ROC Curve = 0.963. For RL > 2.92, sensitivity = 0.989, specificity = 1.000, PPV= 1.000, NPV = 0.975 and area beneath the ROC Curve = 0.999. For TLI <0.249, sensitivity = 0.983, specificity = 0.975, PPV = 0.989, NPV = 0.959 and area beneath ROC Curve = 0.996. Differences in area under the ROC curve were not significantly significant, but MSUMLD sensitivity was lower.

Comparing controls and severe CTS (Table 6), RL > 3.39 yielded 1.000 sensitivity, specificity, PPV,

NPV and area beneath ROC Curve. For TLI < 0.21, sensitivity = 0.969, sensitivity and PPV both = 1.000, NPV = 0.991 and area beneath the ROC curve = 1.000. Differences were not statistically significant.

TABLE 3. Comparison of the ROC parameters between the control and all CTS group

Parameters	All CTS					
	Cut-off	Sens	Spec	PPV	NPV	AUC
MSUMLD (msesc)	≥ 0.8	0.864	0.893	0.969	0.632	0.935
TLI (msecs)	≤ 0.26	0.779	0.942	0.983	0.496	0.910
RL (msecs)	≥ 2.37	0.897	0.818	0.955	0.645	0.937

CTS: carpal tunnel syndrome; MSUMLD: median sensory -ulnar motor latency difference; TLI: terminal latency index; RL: residual latency; Cut-off: cut-off value; Sens:sensitivity; Spec: specificity; PPV: positive predictive value; NPV=negative predictive value; AUC: area under curve

TABLE 4. Comparison of the ROC parameters between the control and mild CTS group

Parameters	Mild CTS					
	Cut-off	Sens	Spec	PPV	NPV	AUC
MSUMLD (msecs)	≥ 1.02	0.517	0.967	0.957	0.582	0.889
TLI (msecs)	≤ 0.29	0.829	0.603	0.769	0.689	0.762
RL (msecs)	≥ 2.4	0.689	0.818	0.858	0.623	0.829

CTS: carpal tunnel syndrome; MSUMLD : median sensory -ulnar motor latency difference; TLI: terminal latency index; RL: residual latency; Cut-off: cut-off value; Sens: sensitivity; Spec: specificity; PPV: positive predictive value; NPV:negative predictive value; AUC: area under curve

TABLE 5. Comparison of the ROC parameters between the control and moderate CTS group

Parameters	Mod CTS					
	Cut-off	Sens	Spec	PPV	NPV	AUC
MSUMLD (msecs)	≥ 0.95	0.866	0.958	0.981	0.743	0.963
TLI (msecs)	≤ 0.249	0.983	0.975	0.989	0.959	0.996
RL (msecs)	≥ 2.92	0.989	1.000	1.000	0.975	0.999

CTS: carpal tunnel syndrome; Mod:moderate; MSUMLD : median sensory -ulnar motor latency difference; TLI: terminal latency index; RL: residual latency; Cut-off: cut-off value; Sens: sensitivity; Spec: specificity; PPV:positive predictive value; NPV:negative predictive value; AUC: area under curve

TABLE 6. Comparison of the ROC parameters between the control and severe CTS group

Parameters	Severe CTS					
	Cut-off	Sens	Spec	PPV	NPV	AUC
MSUMLD (msecs)			NA			
TLI (msecs)	≤ 0.21	0.969	1.000	1.000	0.991	1.000
RL (msecs)	≥ 3.39	1.000	1.000	1.000	1.000	1.000

CTS: carpal tunnel syndrome; MSUMLD : median sensory -ulnar motor latency difference; TLI: terminal latency index; RL: residual latency; Cut-off: cut-off value; Sens: sensitivity; Spec: specificity; PPV:positive predictive value; NPV:negative predictive value; AUC: area under curve

DISCUSSION

In this study, sensitivity and specificity of TLI, RL and MSUMLD were examined. In CTS, conduction abnormalities are often limited to short segments of the carpal tunnel, so normal conduction in parts of the carpal tunnel can mask slowing in mild CTS (3,12,17). This lack of sensitivity, particularly for motor conduction, may result in failure to detect abnormalities (5, 18 21). Our results support earlier findings that sensory studies are of limited value in severe CTS because the responses are often absent (3, 22).

Previous studies showed a higher mean value of TLI in the control group than our study (12,23). This

may be due to the population size of the control group, gender, age distribution, and differences in the normal values that each laboratory uses. Our results showed similar TLI and RL in CTS compared to other studies (24,25), although one showed higher sensitivity and specificity (26). This may be due to the lack of stratification of CTS severity in some of the other studies.

MSUMLD can be a very sensitive and specific test for CTS. It is worth noting that the MSUMLD does not require mid palm stimulation, saving time and patient comfort. For MSUMLD in mild CTS, Bodofsky et al. found higher sensitivity and specificity rates than our results (13). This may be due to our larger study size, as well as the generally high sensitivity rates of other techniques in more advanced cases. All the techniques worked well for the moderate and severe cases, but they are usually not needed, as the diagnosis is straightforward in these cases. Mild CTS cases are

hard to diagnose, and MSUMLD is the most helpful in these cases. Ulnar motor latency is usually unaffected in mild CTS, while ulnar sensory latency rises (27,28). Previous studies have shown the Median and Ulnar motor latencies are significantly correlated as well as the Median and Ulnar sensory latencies in both normal and CTS, while the Median sensory and Ulnar motor are not. This can make the MSUMLD more sensitive than the (Median-Ulnar) motor or sensory latency differences.

There are some limitations to this study. For severe CTS, MSUMLD could not be compared with RL and TLI because the median sensory responses by definition could not be obtained. However, severe cases are easily diagnosed by standard criteria. There was limited information on some patients. This was a retrospective study. Diagnostic criteria were primarily EDX.

There were more female subjects in this study. However, CTS incidence is reported to be significantly higher in female population (29). Therefore, we did not need equal numbers of males and females in the control group to avoid bias. The younger control population is a limitation. Nerve conduction velocities are affected by age. There is a negative correlation between the increasing age and both NCV and amplitude per decade after the age of 20 (30). However, both median and ulnar distal latencies rise by similar degrees with increasing age, and both velocities fall to a similar degree. So a difference such as the MSUMLD should not change much with age, and this is likely also true for TLI and RL. Our normal group was referred for a clinical diagnosis of CRP and was relatively younger than the CTS group. Attempting to match the CTS group by age would have required using a much smaller normal group.

CONCLUSIONS

MSUMLD is the best calculated parameter for diagnosing mild CTS using a minimum number of tests. It requires just a simple calculation and no additional testing. RL and TLI are also useful in diagnosing mild to moderate CTS.

Conflict of interest: No conflict of interest was declared by the authors.

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