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Neurophysiological Findings in Patients with Carpal Tunnel Syndrome by Nerve Conduction Study in Comparing with Ultrasound study

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Abstract:-
Carpal Tunnel Syndrome (CTS) is the most common entrapment problem of upper limb compressive neuropathy. Clinically, the patient presented with pain and parasthesia in median nerve distribution sites and sometimes all the hand and even the pain may affect the forearm and arm, in severe cases thenar muscles atrophy. The signs and symptoms occur due to compression of median nerve at wrist as a result of increase the carpal tunnel pressure by any condition that can increase the pressure within tunnel.
The aim of the study is to assess the correlation of CTS severity by nerve conduction study and it's correlation with US results and their relation with other risk factor such as duration of disease and body mass index.
The study was conducted in Merjan Medical City, in the period from January 2013 to December 2014. And included 94 patients group (164 hands) with signs and symptoms of CTS as well as positive NCS with age ranged from 20-70 years. The study also includes control group 64 persons (128 hands) which were matched age, gender and BMI as patients group.
Results: there were significant differences in NCS of median nerve both sensory and motor parameters between patients and control groups. The patients group divided according to NCS as 73 (45%) had mild, 63(38%) had moderate, and 28(17%) had severe CTS. There were significant difference among group severity of disease and increase BMI. There was a high significant difference in the duration of disease and disease severity. There was significant relationship between dominant hands and disease severity. There is significant correlation between age and severity of disease determined by NCS. There was significant relationship between onset of symptom (day and night and night alone) and the severity of CTS by NCS, in mild CTS 75.0% night symptoms, while in severe CTS 71.4% day and night symptoms.
Keywords: Carpal Tunnel syndrome, Severity, NCS and US .

Introduction

Carpal tunnel syndrome (CTS) is an entrapment neuropathy involving the median nerve within its fibro-osseous tunnel at the wrist. It is a common type of neuropathic wrist pain, neurologic symptoms and functional limitation of the wrist and hand. It is considered the most common nerve compression disorder that affects a large part of the population [1].

By far the most widespread peripheral nerve compressive disorder in the United States is CTS that has strongly affected health care expenditures in terms of both dollars and productivity. This illness is likely to affect 3% to 6% of United States adults, with women affected 3 times as many as men, in general those between the ages of 40 and 60 years [2].

Carpal tunnel syndrome is characterised by numbness, tingling or pain in the allocation sites of the median nerve (the thumb, index, and middle fingers, and the lateral half of ring finger) and sometimes affected the whole hand that is frequently worse at night and causes wakening from sleep. Pain may become more persistent, and may radiate to the forearm, elbow, arm and shoulder. Weakness may be noted in hand grip and opposition of the thumb [3].

Infact more than half of CTS cases are idiopathic and the other cases can develop from many orthopaedic and metabolic diseases.

The most prominent risk factors are female gender, obesity, diabetes mellitus, rheumatoid arthritis, and hypothyroidism, trauma, as occupational risk factor as repeated maneuvers, and pregnancy are other important risk factors associated with increased frequency of CTS [4].

Diagnosis, usually based on clinical examination, is supported with nerve conduction study (NCS) and imaging techniques.

Nerve conduction study is considered to be the gold standard in the identification of CTS as it is an objective test that gives details on the physiological fitness of the median nerve (MN) runs across the carpal tunnel [5]. The usefulness of NCS includes objective confirmation of nerve involvement, grading of severity, and ruling out of polyneuropathy [6, 7].

Electrodiagnostic studies (EDX) are useful in making the decision for surgical decompression and in differentiating less distinctive cases such as entrapment of other nerves, cervical radiculopathy, demyelinating disease, diabetes or peripheral neuritis which could be confused with CTS. Although EDX are highly specific but, they have a considerable false-negative rate of 10–20% [8].

In the last 20 years, neuromuscular sonography has been introduced into electrodiagnostic laboratories as a complement to nerve conduction studies for the diagnosis of a variety of nerve and muscle situation and the most frequently studied condition is CTS (9).

Ultrasonography (US) is a simple, non-invasive and valuable tool. It provides further approach and used in the identification of CTS and other entrapment syndromes. The US finding showed correlations with clinical symptoms and high association with NCS in defining CTS severity and for confirming the diagnosis of CTS as it can identify the median nerve compression characteristics by median nerve morphology measurement depend on the results of median nerve cross-sectional area (CSA) (10).

The objectives of study are to:-

1. To determine sonographic criteria (cut off point for cross sectional area (CSA) of median nerve for the diagnosis of CTS in our local population, and to finding the diagnostic accuracy of enlarge median nerve cross-sectional area measured by ultrasound.
2. Assessing severity of CTS by US and finding the correlation with NCS severity.
3. Finding the effect of age, symptoms, duration of disease, body mass index, occupation and US findings of cross sectional area (CSA) of median nerve at pisiform level on the severity of disease.

Materials and Methods

This is a case-control study which included 150 subjects (100 patients and 50 controls). The study was conducted in Rheumatology and Rehabilitation Unit and Unit of Neurophysiology at Merjan Medical City in AL-Hilla Governorate through the period from January. 2013. till December. 2014

Patients group selected represents carpal tunnel syndrome (CTS) without any apparently secondary systemic disease were obtainable the choice to share in the study, which required a referral that indicated a diagnosis of CTS or primary symptoms of carpal tunnel syndrome. This study was approved by the local research ethics committee.

In this case control study there are (158) participants in this study 94 patients (164 wrist) with CTS (83 female and 11 male), their age range from (20 to 70 years old) with signs and symptoms of CTS either unilaterally or bilaterally and 64 apparently healthy volunteers.

The electrophysiological study carried out in the neurophysiology department in Merjan Medical City using Nihon Kohden machine (Japan). The study included motor and sensory of median and ulnar nerve conduction tests by standard techniques according to the practice parameters for the electrodiagnosis of CTS of the American Association of Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation.

If the results of NCS were positive, those cases were classified as electrophysiologically confirmed CTS. Patients were classified as having mild, moderate, and severe CTS according to the MN conduction velocity (m/s).

The electrophysiological abnormalities were classified into three grades according to Stevens' classification as follows):

Mild; prolonged median sensory distal latency,

Moderate; prolonged median sensory and motor distal latency, and

Severe; indicated prolonged median motor and sensory distal latencies, with either an absent SNAP or low-amplitude or absent thenar compound muscle action potential by Stevens *et al*., [11].

Then the patients with positive NCS undergo ultrasound study to the median nerve in the wrist at two levels to determine CSA at site of its entrance to the tunnel and within tunnel.

The control group with negative NCS and without signs and symptoms of CTS undergo US study too.

During ultrasonography examination, the participants sat facing the examiner with the forearm supinated and resting on a flat surface. The wrist and fingers were evaluated in a neutral and relaxed position. The transducer was placed directly without additional pressure on the patient's skin with gel.

All participants were examined using high-resolution real-time sonography of the carpal tunnel with 11MHz linear array transducer (GE, Voluson E6-2014).

The complete course of the median nerve in the carpal tunnel was assessed in both the sagittal and transverse planes. The cross-sectional area (CSA) of the median nerve in square millimeters (mm^2) was measured proximal to the entrance of median nerve to carpal tunnel at the radio carpal joint(distal radius) and inside the carpal tunnel at the level of the pisiform which is the area of maximal swelling, no measurements were taken at carpal tunnel outlet.

The CSA of the median nerve was calculated by direct methods as proposed by Duncan *et al*., (12) which was measured automatically by tracing the internal margin of the epineurium of median nerve (echogenic border) repeated 2-3 times, assuming that it has an elliptical shape boundary of the nerve. In this case, we are simply measuring the largest section of nerve identified in the region of the carpal tunnel and just proximal to it.

Cutoff value for diagnosis of CTS was considered 10 mm^2 of CSA of median nerve at inlet. It is classified according to the following scale:

Mild: if median nerve CSA ranges 10-13 mm^2;
Moderate: if median nerve CSA >13-15 mm^2; and
Severe: if median nerve CSA >15 mm^2 by Karadag *et al*.,(13).

3.4 Statistical Analysis

Statistical analysis was carried out in this study using SPSS (Statistical Package for Social Science; Version20) program.

This case control study involves arithmetic mean and the standard deviation of distribution of each set of the data is calculated for each of the studied variables. Independent t-test was used to estimation differences between control and patient groups in continuous variables. As well one-way ANOVA test was used to estimate the differences of means among severity groups. Chi square test was used for estimate differences between groups in categorical variables. Correlation between calculated parameters and other clinical parameters were analyzed by Pearson's correlation analysis. The binary logistic regression analysis is used to decide the odds ratio as a measure of the association between variables with CTS as dependant variable. Receiver operating characteristic (ROC) curves were generated to investigate the accuracy of ultrasound as compared with NCS.

Results are reported as (mean ±SD) unless otherwise indicated. P<0.05 was considered statistically significant.

Results:-

The results of sensory nerve conduction study of median nerve for patients with CTS show that there are statistically significant differences between hands with CTS and control in sensory latency , amplitude and conduction velocity (p<0.01) as shown in table (1)

Table (1): The electrophysiological study of median nerve (sensory part) in patients and control groups

Variable	Patient (164 hands)	Control (128 hands0	P value
Distal sensory latency (DSL) (ms)	**3.035±1.2212**	**2.145±.2906**	**P< 0.01****
Amplitude (SNAP) µv	**22.14±18.52**	**45.22±19.06**	**P< 0.01****
Conduction velocity(m/s)	**28.80±17.51**	**48.30±6.10**	**P< 0.01****

**p value < 0.01 is highly significant

The results of motor nerve conduction study of median nerve for patients with CTS show that there are statistically significant differences between hands with CTS and control in motor latency , amplitude , conduction velocity and F wave (p<0.01), as shown in Table (2)

Table (2): The electrophysiological study of median nerve (motor part) in patients and control groups

Variable	Patient 164 hands	Control 128 hands	P value
Distal Motor Latency (DML) (ms)	4.45±1.82	2.78±0.36	P< 0.01**
Amplitude(CMAP) (mv)	8.99±3.29	11.00±2.10	P< 0.01**
Conduction velocity (m/s)	53.93±6.48	56.96±6.39	P< 0.01**
FW	26.83±5.65	24.25±1.81	P< 0.01**

**p value < 0.01 is highly significant

FW: F wave latency

Out of 164 hands with CTS, 73 (45%) had mild, 63(38%) had moderate, and 28(17%) had severe CTS according to NCS, as shown in Figure (1).

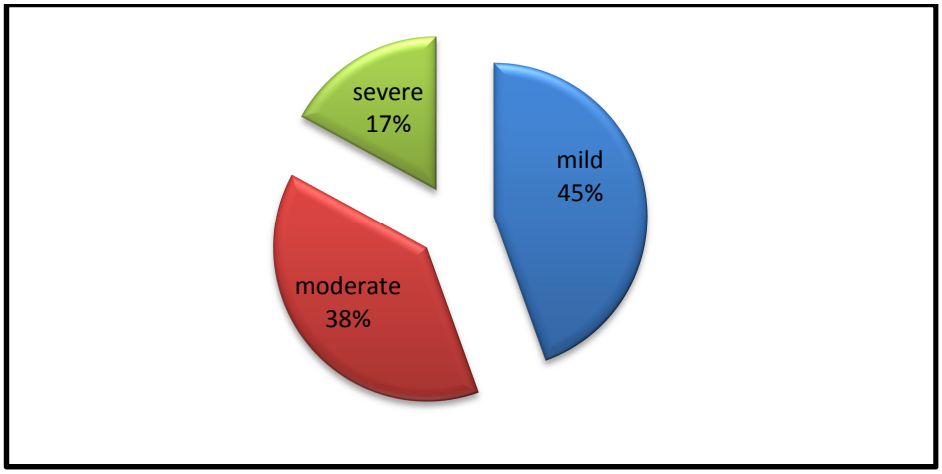


Figure (1): Demonstrate the percentage of the diseased wrists according to the severity of the CTS determined by NCS

The relation between BMI and severity of CTS are shown in table (3). Most patients with mild, moderate and severe are obese (P<0.05).

Table (3): Severity of carpal tunnel syndrome and body mass index in patient group

severity by NCS	BMI		
	normal (18.5-24.9)	Preobese (25 -29.9)	obese ≥30
mild	6.0%	40.3%	53.7%
moderate	4.9%	24.6%	70.5%
severe	17.4%	8.7%	73.9%
P value	P<0.05*		

BMI: body mass index

NCS: nerve conduction study

*p value < 0.05 is significant.

The duration of CTS in patients was variable and range from (3-150 months). The relation between duration per months of disease and severity grade (mild, moderate and severe) of CTS, are shown in Table (4). There was a high significant difference in the duration between three groups studies (P<0.01).

Table (4): Severity of carpal tunnel syndrome and duration of disease in patients group

Severity	Duration (months) Mean ± SD	P value
Mild	16.81 ± 12.43	**P < 0.01 ****
Moderate	32.34 ± 18.32	
Severe	51.92 ± 23.22	

**p value < 0.01 is highly significant

The relation between the severity of CTS and affected dominant hand, as shown in Table (5) there is significant relationship and most of dominant hands moderately and severely affected.

Table (5) severity of carpal tunnel syndrome and dominant hands

Affected hand	No. & percentage	Severiy			Total
		Mild	moderate	severe	
Dominant	Count %	28 (38.4)	38 (60.3)	17 (60.7)	83 (50.6)
Non dominant	Count %	45 (61.6)	25 (39.7)	11 (39.3)	81 (49.4)
Total	count	73	63	28	164
P value	**P <0.05***				

*p value < 0.05 is significant.

In this study there is significant correlation between age and severity of disease determined by NCS (P<0.01) as in table (6).

Table (6) severity of carpal tunnel syndrome with age mean

SEVERIY	No.	Mean ± SD
Mild	73	40.53±9.57
Moderate	63	42.61±9.79
Severe	28	49.71±11.23
P value	**P<0.01****	

**p value < 0.01 is highly significant

No: number of hands with CTS

The outcome data of this result how significant relationship between onset of symptom (day and night and night alone) and the severity of CTS by NCS, in mild CTS 75.0% night symptoms, while in severe CTS 71.4% day and night symptoms as in **figure (2)**

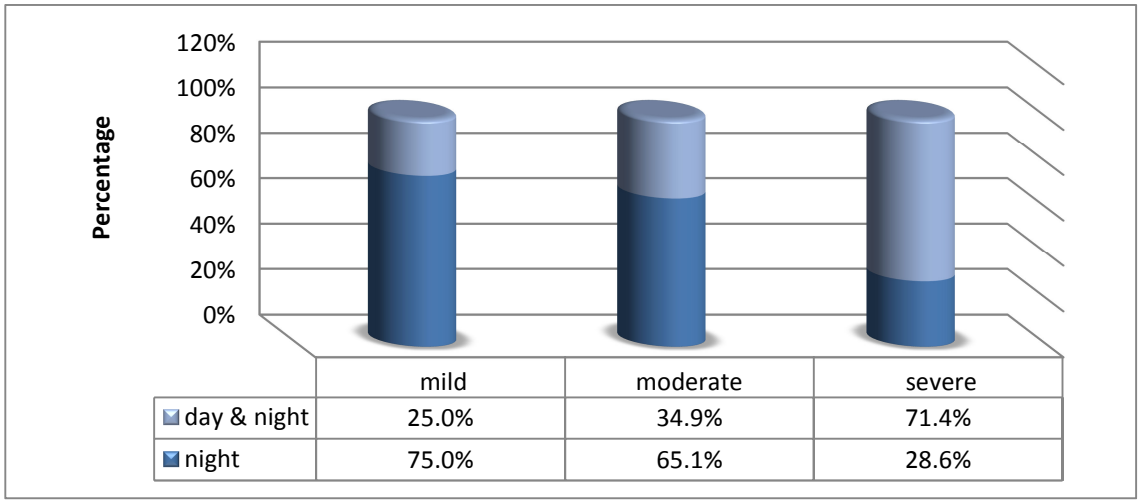


Figure (2) severity of carpal tunnel syndrome with the distribution of symptom between day and night

Ultrasonic measurements of cross section area (CSA) of the median nerve (MN) for patient and control groups, showed that the mean CSA of median nerve in pretunnel and intratunnel in CTS patients was significantly greater than that of the control group's CSA (P< 0.01), as shown in Table (7).

Table (7): Pretunnel and Intratunnel cross sectional area of the of patients and controls

CSA	Patient (164 hands)	Control (128hands)	P value
Pretunnel mm^2	11.96±3.195	7.13±1.74	P< 0.01**
Intratunnel mm^2	12.50±3.25	7.31±1.77	P< 0.01**

**p value < 0.01 is highly significant

CSA: Cross Section Area of the median nerve.

Severity of CTS by ultrasound results according to intratunnel cross sectional area scale pointed that out of 164 hands with CTS, 68(41%) had mild, 42(26%) had moderate, 27(17%) severe CTS and 27 (16%) negative result according to ultrasound, as shown in Figure (3).

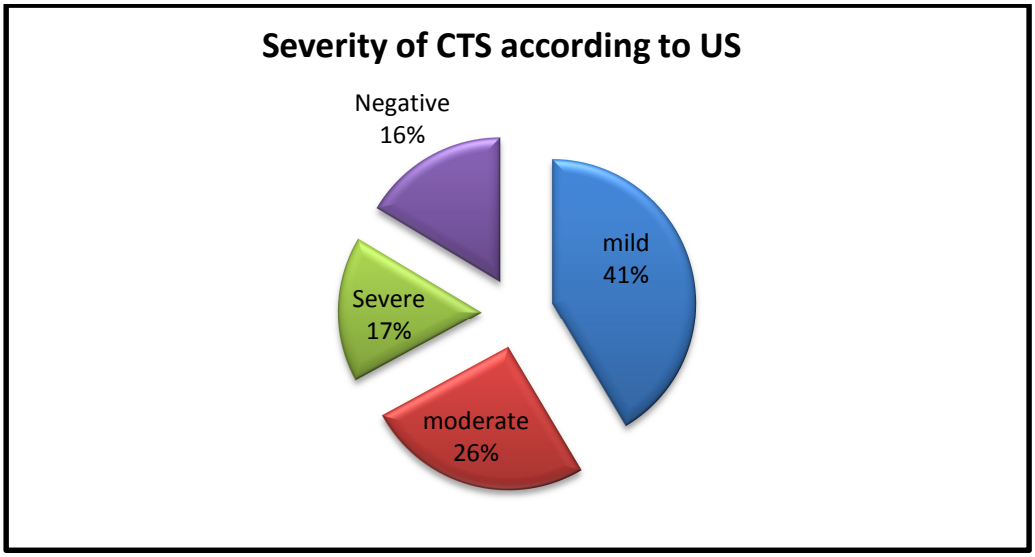


Figure (3): Demonstrate the percentage of the diseased hands according to the severity of the carpal tunnel syndrome determined by ultrasound

Severity of cross section area of median nerve at tunnel inlet by ultrasound in comparing with severity of nerve conduction study showed that that the mean CSA of the MN was calculated in patients with mild, moderate, and in patients with severe CTS, compared to CSA for the negative group, as shown in Table (8). Each of these subgroups, CSA shows significant difference from the median nerve CSA of the control group.

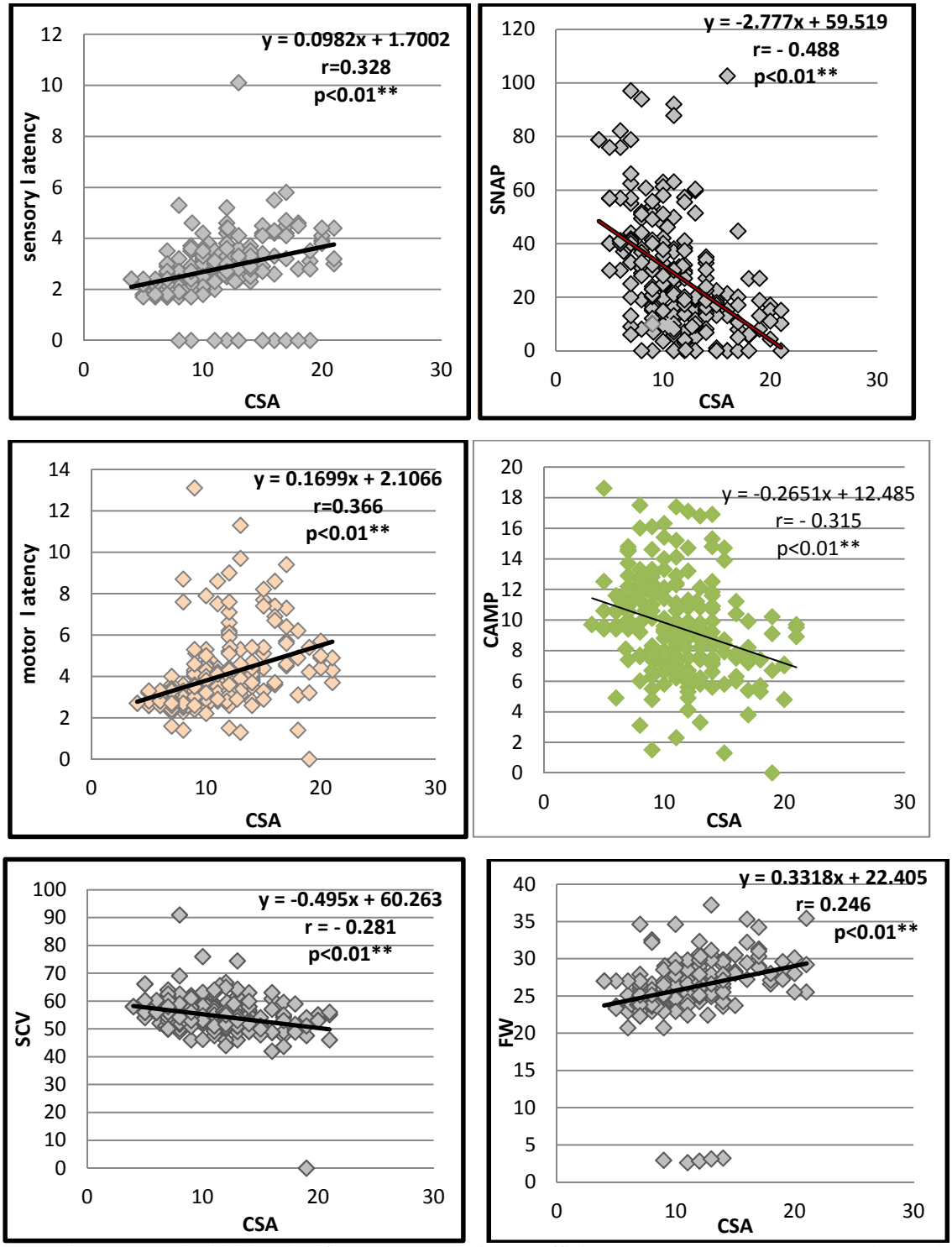
Table (8): The cross sectional area of the median nerve for the different severities of carpal tunnel syndrome according to nerve conduction study versus those with normal at nerve conducting testing

severity NCS	CSA (Mean ± SD) mm^2	P value
Mild	11.41±2.81	P < 0.01**
Moderate	12.95±3.19	
Severe	14.36±3.47	
Control	7.31±1.77	

**p value < 0.01 is highly significant
CSA: Cross Section Area of the median nerve.
CTS: Carpal Tunnel Syndrome.
NCS: nerve conduction study

Correlation between CSA and Nerve Conduction Study of median nerve (sensory and motor part), showed that there was a significant positive correlation between CSA and sensory latency ($p<0.01$), while there was a significant negative correlation between CSA and sensory amplitude ($p<0.01$), as shown in Figure (4).

In motor part, there were a significant positive correlation between CSA and motor latency and F wave ($p<0.01$) .While there were a significant negative correlation between CSA and motor amplitude and sensory conduction velocity ($p<0.01$)



**p value < 0.01 is highly significant, r correlation coefficient, SNAP, CAMP compound muscle action potential, SCV sensory conduction velocity, FW F wave latency

Figure (4): Correlation between CSA and nerve conduction study of median nerve (sensory and motor part)

The severity of CTS by nerve conduction study comparing with severity by ultrasound, According to the results of the disease severity obtained by NCS comparing to those by ultrasound there was significant differences among all groups severity by NCS comparing with US (P < 0.009), as shown in Table (9).That most of mild cases by NCS are mostly mild (47.9%), moderate (23.3%) and even negative(21.9%) by US. In moderate cases by NCS most of cases are between mild (42.9%) and moderate (25.4%) by US and in severe cases by NCS most of cases are between severe (35.7%) and moderate (32.1%) by US.

Table (9) Severity of carpal tunnel syndrome by nerve Conduction Study comparing with severity by ultrasound

Severity by NCS	Severity by US				
	Negative	Mild	Moderate	Severe	Total
Mild	16(21.9%)	35(47.9%)	17(23.3%)	5(6.8%)	73
Moderate	8(12.7%)	27(42.9%)	16(25.4%)	12(19.0%)	63
Severe	3(10.7%)	6(21.4%)	9(32.1%)	10(35.7%)	28
P Value	< 0.009**				

**p value < 0.009 is highly significant, NCS: Nerve Conduction Study, US: ultrasound

The severity of CTS and BMI according to ultrasound scale and related cross sectional areas, pointed that the relation between BMI and severity of CTS according to US CSA of MN are shown in Table (10). There was no significant relation between the mean of CSA of each severity group and BMI (P>0.05) while there was a significant difference in CSA and obesity between patients subgroups and control group (P< 0.01).

Table (10): Severity of carpal tunnel syndrome by ultrasound and their cross sectional areas in relation to body mass index in patient and control groups

severity of the CTS by ultrasound scale	NO. of hands	CSA/mm^2			P value
		normal (18.5-24.9) Kg/m^2	**Pre obese (25-29.9)** Kg/m^2	**Obese ≥30** Kg/m^2	
Mild	68	11.31±0.63	11.02±0.69	11.06±0.89	**P>0.05**
Moderate	42	13.00±0.01	14.30±0.48	13.86±0.93	**P>0.05**
Severe	27	18.00±1.71	19.00±2.12	17.90±1.64	**P>0.05**
Negative	27	8.33±1.15	8.34±1.23	8.25±0.75	**P>0.05**
Control	128	7.71±1.71	7.36±1.73	7.31±1.83	**P>0.05**
P value		**P< 0.01****	**P< 0.01****	**P< 0.01****	

CSA: cross sectional area,

BMI: body mass index

**p value < 0.01 is highly significant

The relation between duration of disease and severity of CTS regarding to US are shown in Table (11). There was a high significant difference in duration per months of disease among three group (P<0.01).

Table (11): Severity of CTS according to US and duration of disease in patient group

Severity	Duration (months) Mean ± SD	P value
Mild	26.51 ±21.27	P < 0.01 **
Moderate	27.47 ±16.06	
Severe	41.81 ±29.18	
Negative	24.00 ±12.17	

**p value < 0.01 is significant

Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of ultrasound for the diagnosis of carpal tunnel syndrome: From the statistical point of view the sensitivity and specificity were calculated for mean values of CSA at the carpal tunnel inlet and at 10mm^2 as cut off value as in Table (12), The sensitivity is of (83.53%), a specificity is of (92.19%), P value < 0.001, a PPV is of (93.19%), a NPV is of (81.37%) and an accuracy is of (87.32%).

Table (12): The Sensitivity and Specificity of Ultrasound findings compared to nerve conduction study

**p value < 0.01 is highly significant

NCS examination		positive	negative	Total
		No. of Wrists in patients with CTS	No. of wrists in control	
US examination	Positive	137	10	147
	Negative	27	118	145
Total		164	128	292
Accuracy		=((137+118)/292)×100	=87.32%	
Sensitivity		=(137/(164))×100	=83.53%	
Specificity		=(118/(128)×100%	= 92.19%	
PPV		=(137/(147)×100%	= 93.19%	
NPV		=(118/(145)×100%	= 81.37%	
P value		P< 0.01**		

The ROC curve has been done to determine the accuracy of ultrasound in diagnosis of CTS by Comparing NCS with Ultrasound results, as in Figure (5). The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease. Accuracy is measured by the area under the ROC curve at 10 mm^2 diameter which represents the best cutoff value. An area of one represents a perfect test; an area of 0.5 represents a worthless test. Table (13) Shows that the area under the curve is 0.879 that means the ultrasound has been succeed to detect CTS.

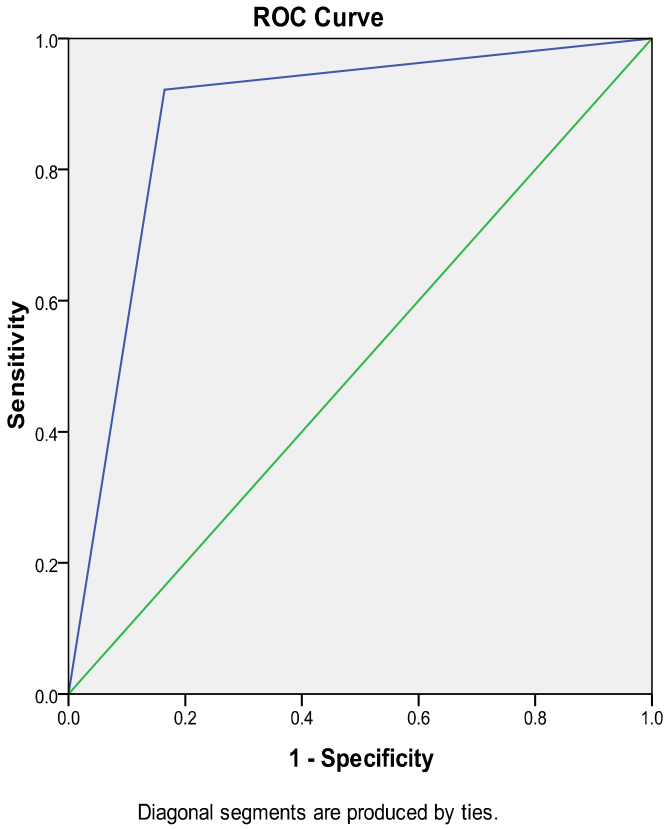


Figure (5): ROC curve of ultrasonographic measurements. ROC: receiver operating characteristic, CSA: cross sectional area at tunnel inlet in patient with CTS.

Table (13): Area under the curve for detecting accuracy of ultrasound comparing by NCS

Area	Std. Error	P value	95% CI	
			Lower Bound	Upper Bound
0.879	0.026	0.001**	0.828	0.929

**p value < 0.001 is highly significant

Discussion

The results of this research pointed that there were significant differences in median NCS parameters both sensory and motor parts including (distal sensory latency (DSL), sensory nerve action potential (SNAP) and sensory conduction velocity (SCV) (P< 0.01), as shown in Table (1) and (distal motor latency (DML), compound muscle action potential (CMAP), motor conduction velocity (MCV) and F wave) is (P< 0.01) , as shown in Table (2) between wrists with CTS and wrists in control group.

Our results are compatible with the finding of other several authors who reported that there was significant differences in median NCS parameters both sensory and motor parts [14, 15, 16].

Ibrahim *et al.*,[14] were demonstrated that the diagnostic criteria for CTS in nerve conduction studies include prolonged median nerve sensory and motor latencies in addition to delayed or diminished sensory and motor conduction velocities whereas, Kennedy *et al.*, [17] found that median F-wave latency and distal motor latency get prolonged with severe median nerve compression.

The changes in MN NCS parameters include prolonged motor and sensory latencies of the median nerve, and reduced sensory and motor conduction velocities are accepted as diagnostic criteria for CTS. These changes occurred in entrapment neuropathies. The motor distal latency and SCV reflect the function of large myelinated fibers such as the A-α and A-β fibers [18].

Nerve conduction velocity is commonly thought to be a sensitive indicator of the severity of demyelination and ischemia at entrapment point. As conduction velocity measurements can identify subclinical lesions, it is of particular value in initial diagnosis. However, in segment nerve injuries where nerve component is compressed locally, electrophysiological findings may not necessarily reflect the disease state entirely [19].

Our result from this study is that the 94(164 hands) patients are presented with symptoms and signs of CTS and in different stages of severity by electrodiagnostic study divided into mild(45%), moderate(38%) and severe. Most our patients had mild CTS followed by moderate and severe (17%), as shown in Figure (1).

Such findings were in consistent with other studies as [20,21]. And inconsistent with [19,22 ,23].

Iranmanesh *et al*., [23] found that most of cases had moderated CTS and less cases of mild and severe, respectively, while Mohamed *et al*., [22] found that most cases were having severe CTS followed by moderate and less mild cases.

The relation between BMI and severity of CTS shows that there are significant differences among patient groups ($P<0.05$), as in Table (3). Most patients with mild, moderate and severe are obese.

However, results are also reported by Harris-Adamson *et al*., [24].And disagrees with Moghtaderi *et al*.,and Sharifi-Mollayousefi *et al.,* [25,26] who found that there was no significant difference between the three grade severity subgroups and BMI.

Kouyoumdjian *et al*., [27] said that there was a correlation between BMI and median sensory latency severity in CTS population. Higher BMI increases the risk of developing CTS but could not increase its severity. Whereas Boz *et al*., [28] mentioned not only a relationship between a higher BMI and CTS development but also a statistically significant difference among severity subgroups.

The relationship between obesity and CTS suggested that the increased interstitial pressure is not the main reason for impairment of the MN. It does not exclude transient mechanical forces as a factor, but the mechanism appears to be different from typical CTS where high pressures and synovial thickening are usually demonstrated.

The conclusion is that this is related to a metabolic change. An association between obesity and impaired glucose metabolism is the most likely pathophysiology to explain the occurrence of median nerve impairment among obese individuals [29].

This study reveals that there was a significant association between the severity of CTS with duration of disease and the study found that the highest duration of illness in patients with severe CTS ($P<0.01$), as shown in Table (4).

This result is in consistent with El Miedany *et al*., [16] who found that the severity of CTS increase with duration of disease.

Also, it disagrees with Hardoim *et al*., [30] Who found that CTS symptomatology duration (months or years) is variable, and it is not strictly related to the electrophysiological median nerve severity.

The present study found that there is a significant correlation between CTS severity and dominant hand and most of dominant hands showed moderate and severity grade CTS subgroups ($P <0.05$), as shown in Table (5). This result disagrees with Padua *et al*., [31]

The study found that the dominant hand affected first followed by non dominant this occurred perhaps due to over use in already affected hand leading to increase pressure within tunnel and mechanical compression on MN leading to increase pathological changes and permanent damage on the nerve and the severity of the disease increased.

Result of this work shows that there is a significant relationship between age and severity grade of CTS subgroups by NCS and so, CTS severity increased with increasing the age($P<0.01$), as shown in Table (6)

And this data is in good agreements with Sharifi-Mollayousefi *et al.,* , Miwa T and Miwa H, Ali *et al*., [26,32 ,33]Whereas, others found that Age had no influence on the severity of the disease as Roll *et al*., and Yazdanpanah *et al.,* [34,35]

Sharifi-Mollayousefi *et al.,* [26] found that age was significantly higher in the severe subgroup compared to the mild subgroup among all patients and in the moderate subgroup compared to the mild subgroup among males.

Ali *et al.,* [33] found that patients with higher grades of CTS were of higher age.

Patients with older age group presented with milder clinical expression and more likely to have electro-diagnostically severe CTS, elderly patients, who have severe nerve entrapment with relatively fewer symptoms because there is a reduced pain sensitivity with age, which is possibly due to a reduction of the nerve membrane excitability as an age related factor. The older patient may delay looking for management at an earlier and less severe stage of the compression [36].

This search shows a significant relationship between onset of symptom (day and night and night alone) and the severity of CTS by NCS as in Figure (2). Most of our patients are suffering from mild, moderate and less severe CTS. This means that the early disease is presented with high degree of intermittent parasthesia and pain especially at night due to increase intratunnel pressure and transient ischemia leading to interruption of sleep

making patient seek for medical advice due intolerable these symptoms and to prevent the progression of demyelination to axonal damage. In severe cases, these symptoms become constant and accompany the patients most the day and night and may associate with muscle atrophy.

Our findings are consistent with Alfonso *et al*., and Ali *et al.*, [37, 33] who demonstrated that the symptom onset in the early stage is mainly nocturnal paraesthesias. And inconsistently, it disagrees with Chan *et al.,* [38] Who found that there was no correlation between nerve conduction results and the severity of CTS sensory symptoms and this may be explained as that NCS explores large myelinated Ab-fibers but not small myelinated Ad-fibers, which may contribute to pain and paresthesia, and unmyelinated C-fibers that mediate pain [39].

The results are in consistent with the previous studies of ultrasound in CTS by showing enlargement of MN CSA in CTS hands. There were significant differences in median nerve CSA between CTS and healthy volunteer's hands at two levels measured proximal to the tunnel inlet and at the Inlet ($P<0.01$) as in Table (7).

The results of CSA pretunnel agrees with Chan *et al.,* and Roll *et al.*, (40,34).And disagrees with Yazdchi *et al*., and Mohamed *et al.,* (41,42).

Roll *et al*., (34) demonstrated that there was a moderately to strong correlation of the cross-sectional area measurement immediately proximal to the carpal tunnel at the radial-carpal joint that may provide relevant diagnostic information.

While our results of CSA intratunnel (at of pisiform level) agree with Chan *et al*., , Ajeena *et al*., and Mohamed *et al*.(40,43,42) And disagrees with Yazdchi *et al*., (41).

Chan *et al*., (40) found that median nerve CSA was significantly larger in CTS hands compared to controls, at all 3 levels proximal to the carpal tunnel, at the tunnel inlet and at the tunnel outlet.

Yazdchi *et al*.,(41) found that there was no significant difference in MN CSA between patients with mild CTS and control at the pretunnel and intratunnel level.

Mohamed *et al.,* (42) agree with our results on CSA intratunnel but the study disagrees with them at pretunnel. They demonstrated that most of hands with CTS. The mean CSA pretunnel was not considerably different in the patients with CTS when compared to healthy controls although the mean CSA intratunnel was considerably increased in the patients when compared to healthy controls.

In CTS MN, swelling occurs as a result of chronic focal compression of the median nerve that can cause morphological alterations. Enlargement has been postulated as a result of edema, damming of axoplasm and collagen deposition and the demyelination caused by mechanical stress and ischemia that deforms the myelin sheath (44)

The pretunnel CSA enlargement is that the majority of the patients develop proximal nerve enlargement due to the pressure gradient being directed towards proximal. This swelling of the median nerve is possibly due to ballooning of the nerve at the site of least resistance and this increase in pressure also may be transmitted to the distal carpal outlet, which may explain isolated distal enlargement of the median nerve at the tunnel outlet (45).

According to severity scale of CSA of intratunnel in CTS hands at cut off $10mm^2$, our results of patients' hands at intratunnel CSA are determined by US classified CTS as mild (41%), moderate (26%), severe (17%) and negative result (16%) as shown in Figure (3).

Our results are in accordance with the finding of Karadag *et al*.,(13), they demonstrated that the cross-sectional area of the median nerve at tunnel inlet had been used in US to classify the severity of CTS as normal, mild, moderate and severe and normal.

While it is inconsistent with Rao *et al.*,(19) who found that most cases of CTS ultrasound findings at tunnel inlet are moderate.

The explanation of why MN CSA is tended to be locally thickened or enlarged on US in CTS due to pathophysiological processes basing on the cascade of the biological response to compression in peripheral nerves including endoneurial edema, demyelination, inflammation, distal axonal degeneration, fibrosis, growth of new axons, remyelination, and thickening of the perineurium and endothelium. The grade of axonal degeneration is associated with the amount of endoneurial edema (46).

Our result showed that the CSA of the MN at tunnel inlet were 11.41 ± 2.81 mm^2, 12.95 ± 3.19 mm^2, 14.36 ± 3.47 mm^2 in patients with mild, moderate and severe CTS, respectively and patient groups differed significantly from control group (7.31 ± 1.77 mm^2) and also there is significant difference between each subgroup and other. This confirm the findings of previous research indicating the cross-sectional area of the median nerve at the pisiform is strongly correlated with electrodiagnostic testing ($P < 0.01$) as in Table (8).

The result of this study agrees with Karadağ *et al* ., , Yazdchi *et al*., and Kataruka *et al*.,(13,41,47).And disagrees with Rao *et al.*, and Mhoon *et al*.,(19,48).

Mhoon *et al*., (48) found that there was no correlation between NCS severity and CSA of MN by US, While Rao *et al.*, (19) found that there was no statistically significant correlation between US finding and

neurophysiological grading severity (P > 0.05). But the greater the severity of neurophysiological findings, the greater is the median nerve CSA

Hence, the explanation of this correlation is that CTS is correlated with axonal loss due to a decrease in intraneural vascular flowed by chronic compression and increasing in water content subsequent nerve swelling. Therefore, there may be a positive correlation between median nerve CSA and electrophysiological severity (49).

Our results show that there was a significant positive correlation between CSA and sensory latency and there was a significant negative correlation between CSA and sensory amplitude. While in motor part, there was a significant positive correlation between CSA and motor latency and F wave and there was a significant negative correlation between CSA and motor amplitude and conduction velocity (**P<0.01**), as in Figure (4).

The finding of this study consistent with those of Chan *et al*., , Tsai *et al.*, , El Miedany *et al*., (40,50,16) they found that there is considerable correlation between conduction abnormalities of the median nerve detected by electrodiagnostic tests and measurement of its cross-sectional area (CSA) by ultrasonography. And it is inconsistent with Werner *et al.,* and Kataruka *et al.,* (29,47).

Chan *et al*., (40) reported that there was a correlation between median nerve CSA at the tunnel inlet and median DML. As prolonged, median DML is a marker of focal nerve demyelination across the carpal tunnel. This provides a biological basis for the ultrasonographic finding in CTS.

As a general guide, for MN CSA, positively, correlates with distal motor latency and distal sensory latency of the MN is that is suspiciously an enlargement of the median nerve that damages the myelin and results in the slowing of nerve conduction velocity. In contrast, the MN CSA, negatively, correlates with the amplitude of the median CMAP and median SNAP, suggesting that median nerve swelling contributes to axonal degeneration of the median nerve in CTS. Thus, larger CSA points to more median nerve damage (50).

According to the results of the disease severity obtained by NCS comparing to those by ultrasound there was significant differences among all groups severity by NCS comparing with US and P value < 0.009, as shown in Table (9).That most of mild cases by NCS are mostly mild, moderate and even negative by US. In moderate cases by NCS most of cases are between mild and moderate by US and in severe cases by NCS most of cases are between severe and moderate by US.

This result is consistent with Kim *et al.,* (1) found that mild CTS cannot show abnormal findings on US study in (22.4%) of patients with mild CTS to electrophysiological study and ultrasonic measurement is helpful to diagnose severe CTS patients with no response to electrophysiological studies while it is inconsistent with Rao *et al.*, (19).

The results of the Study demonstrate that there was no significant relationship among severity groups of CTS according to US and related finding of CSA of MN according to BMI, while there was a significant relation of CSA between patients at each subgroups severity and control group in US according to BMI, as in shown in Table (10). This may contributed to that the nerve may required more time for changes to be appear by US examination or the increase in MN CSA may occure as a result of compression by obesity or other factors. The nerve swelling in compressive neuropathies leads to intraneural edema, which increases the median nerve CSA. The increase in water content responsible for nerve swelling seems to be directly correlated to the cascade of events that ultimately leads to axon loss (19).

This result is consistent with Werner *et al.,* and Su *et al*., (29, 52). While it is inconsistent with Roll *et al.,* and Castro *et al*., (34,53).

Roll *et al.,* (34) found that the reason of median nerve CSA enlargement and obesity is not clear, but it could be caused by either the enlarged nerves that are a pathologic result of an increased BMI or the nerve is naturally larger because of the increased overall anthropometric composition of the individual.

Castro *et al*., (53) studied the correlation of CTS severity; BMI and MNA measured by US and found that there was a significant relationship.

The current study showed that there was a significant relation between the duration of disease and severity of CTS according to US. The patients with long duration of illness had the largest CSA on US (highest degree of severity according to scale) (P < 0.01), as in Table (11).The obtained values of duration of disease and US findings are in consistent with values obtained by (16) whom pointed that the median nerve CSA was significantly correlated with duration of symptom and the MN CSA that is increase with the increase of duration of disease which can be contributed to persistent edema and increased interstitial pressure finally leading to increase axonal transport and intraneural blood flow subsequently fibroblastic activity and scar formation in and about the nerve.

In this study, our aim from using of wrist US is to detect any increase in CSA of MN at tunnel inlet at cut off value 10 mm^2 as pathologic. And so by our results of intratunnel CSA, a high sensitivity and specificity

were calculated for mean values of CSA at the carpal tunnel inlet ($P < 0.01$), as shown in Table (12). This is consistent with other studies (54,55).

Boutte *et al*., and Zidan *et al*., (54,55) found that the sensitivity of a large CSA in the median nerve for the diagnosis of CTS was 70%.

The ROC curve has been done to determine the accuracy of ultrasound against the NCS in diagnosis of CTS Figure (5), the Accuracy is measured by the area under the ROC curve ($P < 0.001$), as in Table (13) which shows that the area under the curve is 0.879, indicating a sensitivity and specificity of 83.53% and 92.19%, respectively, at cut off value of 10.0 mm^2, that means the wrist sonography has been succeed to detect CTS.

This fact is supported by Chan *et al*., , Paliwal *et al*., and Kim *et al*.,(40,56,1).

Chan and his co-workers (40) found by using ROC curves to determine optimal discriminatory, threshold values for CSA at the tunnel inlet with a threshold of 10 mm^2 which gave a good diagnostic accuracy with a sensitivity and specificity of 63.0% and 88.5%, respectively.

Paliwal *et al*., (56) pointed that ROC analysis for inlet CSA showed an area under the curve of 0.933 with the best sensitivity (65%) and specificity (100%) at 10 mm^2.

Furthermore, explanations for the usage of ultrasonography versus to NCS saying that there is no competition between NCS and USG, but both of them are complementary to each other rather than replacing one with the other. Unlike NCS, it can only demonstrates median nerve lesions/compression and not explore for other causes of upper limbs paraesthesiae (57).

However, Sonography sensitivity is less, but it is quite specific and correlating somewhat with NCS results. It is an efficient morphological instrument to express other pathology e.g. synovitis which can contribute to the development of CTS where the MN is normal in appearance on US, suspicion of origin of symptoms that could be shifted to include the more proximal nerves, to search for a space-occupying lesion such as a cyst thus facilitated planning of treatment, grading severity of CTS by US which is important in management of patients especially when deciding for surgical decompression and can be used as screening test to differentiate normal from mild or severe cases by detecting any enlargement in MN CSA. The NCS can determine if the lesion is solitary or one of multiple lesions mononeuropathy multiplex, multiple entrapment neuropathies), or a feature of a polyneuropathy (demyelinating neuropathy) (58).

Conclusion

Ultrasonographic measurements of the cross sectional area (CSA) of the median nerve at tunnel inlet offer relatively high diagnostic accuracy for CTS and ultrasonographic study could be considered as a complimentary diagnostic modality for the assessment of CTS. In addition to diagnosis of CTS, US measurements of the MN could also give information about severity of CTS, structural anomalies or space occupying lesion locally.A positive correlation exists between US findings and all the conventional measures of CTS severity by NCS. Obesity considered as an important risk factor associated with CTS and the severity of disease by NCS amplify with increasing BMI. But not with US finding.

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