Neurological Sciences (2019) 40:1041–1047
https://doi.org/10.1007/s10072-019-03756-z

ORIGINAL ARTICLE

The controversy of the normal values of ultrasonography in carpal tunnel syndrome: diagnostic accuracy of wrist-dependent CSA revisited

Floriaan G. C. M. De Kleermaeker[1] · Jan Meulstee[1] · Wim I. M. Verhagen[1]

Received: 29 April 2018 / Accepted: 6 February 2019 / Published online: 22 February 2019

Abstract

Introduction No consensus exists about the upper limit of normal (ULN) of the cross-sectional area (CSA) of the median nerve in diagnosing carpal tunnel syndrome (CTS). Previously, we demonstrated a strong positive correlation between wrist circumference and CSA. ULN depending on wrist circumference turned out to have a low sensitivity, which was hypothesized to be caused by an age mismatch. The aim of this study was to re-evaluate the found invariance by augmentation of the healthy control group, adding older subjects, and to determine the diagnostic accuracy of the updated normal values.

Methods CSA and wrist circumference were measured in an additional 42 healthy controls in the ages of 40–60. Univariable and multivariable linear regression analyses were applied to determine predicting factors for CSA. Diagnostic accuracy was assessed in a prospective cohort of 253 patients.

Results A strong correlation was found between wrist circumference and CSA ($r = 0.61$). Wrist circumference is the most important independent predictor for ULN ($r^2 = 0.37$). We managed to simplify our newly derived regression equations, which turned out to be unrelated to age. Sensitivity of our new equations is low, but higher than a general fixed cut-off value (53.4% and 47.4%, respectively).

Discussion Wrist circumference is the most important independent predicting factor of CSA. By using our updated equations and taking wrist circumference into account, one can determine a more precise ULN for each individual, which will lead to the improvement of the diagnostic accuracy of ultrasonography (US). Sensitivity for US in diagnosing CTS remains low and it can therefore not replace EDX.

Keywords Carpal tunnel syndrome · Ultrasonography · Normal values · Cross-sectional area · Wrist circumference · Diagnosis

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, and ultrasonography (US) of the median nerve at the carpal tunnel inlet has an increasingly important role in confirming its diagnosis. Currently, there is no consensus about the upper limit of normal (ULN) of the cross-sectional area (CSA) of the median nerve at the carpal tunnel inlet. Frequently, a fixed cut-off value for the upper limit of normal of the CSA is used, varying from 8.5 to 14 mm^2 [1, 2]. Sensitivity of these fixed values varies in an extensive range from 66 to 89%, and specificity varies from 63 to 97% [3–8]. Previously, we collected values for ULN of CSA in healthy subjects for application in yet-to-be-conducted clinical studies. In this journal, we already demonstrated a statistically strong positive correlation between wrist circumference and CSA [9]. Application of the found upper limits of normal in clinically defined CTS patients showed that there is a rather small chance of finding a normal electrodiagnostic test (EDX) result in case of an abnormal US test (3.3%); at the same time, however, the sensitivity turned out to be lower (57%) than in the studies with fixed cut-off values [10]. In discussions during oral presentations, it was repeatedly suggested that had we included a relatively larger number of older healthy controls,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10072-019-03756-z) contains supplementary material, which is available to authorized users.

✉ Floriaan G. C. M. De Kleermaeker
florisdekleermaeker@gmail.com

[1] Department of Neurology, Canisius Wilhelmina Hospital, Weg door Jonkerbos 100, 6532 SZ Nijmegen, the Netherlands

the invariance might not hold true. In this case, the age mismatch between the group of patients and the healthy controls could be the explanation of the lower sensitivity. For this reason, we re-evaluated the found invariance by augmentation of the healthy controls group, adding 42 healthy subjects in the ages of 40–60. In addition, we applied the normal values derived from the augmented set to test the diagnostic accuracy in patients with clinically defined CTS and compared this to our previously reported results. Furthermore, we compared our updated normal values to a fixed cut-off value for ULN in order to determine the differences in practice.

Methods

Controls

Forty-two healthy control subjects (20 women, 22 men) in the ages of 40–60 without signs or symptoms of CTS were recruited as control subjects. They were interviewed in a standard fashion and excluded if they had a history of diabetes mellitus, rheumatoid arthritis, wrist trauma, or BMI > 35 kg/m^2. Weight and height of each participant were measured, as well as the wrist circumference. The left or right wrist was included randomly, as we previously found no differences in CSA between left and right. CSA was measured at the inlet of the carpal tunnel (Philips Diagnostic Ultrasound System model iU22, 5–17-MHz linear transducer), using the direct trace method (TM) by the same experienced electrodiagnostic technicians and according to the protocol of our previous study (Online Resource 1) [9, 10]. The mean of three separate measurements was taken as CSA. We added our newly obtained data from control subjects to those of our previous study (also including randomly left or right wrist), resulting in a total of 96 healthy controls.

Patients

CTS patients were prospectively enrolled in the study if they complained about pain and/or paresthesias in the territory innervated by the median nerve (whether or not the fifth finger was included) and if they met two or more of the following clinical CTS criteria: (1) nocturnal paresthesias, (2) aggravation of paresthesias by activities such as driving a car, riding a bike, holding a book, or holding a telephone, (3) paresthesias relieved by shaking the hand (the positive Flick sign). Exclusion criteria were defined as follows: age under 18, significant language barrier, history or clinical signs of polyneuropathy or known HNLPP (hereditary neuropathy with liability to pressure palsies), previous trauma or surgery to the wrist, history of rheumatoid arthritis, diabetes mellitus, thyroid disease, alcoholism, arthrosis of the wrist, pregnancy, or severe atrophy of the abductor pollicis brevis muscle. They underwent US and EDX according to the protocol described in our earlier study (Online Resource 1) [9, 10]. Informed consent was obtained from each patient and healthy control. Permission from the local Medical Ethics Committee was obtained.

Statistics

All statistical analyses were performed using SPSS Statistics 24.0. Baseline characteristics for healthy controls and patients were described as frequency (%), mean ± SD, and median. Group comparisons of baseline data were assessed by applying an unpaired T test for continuous variables with normal distribution and the Mann-Whitney test in case of non-normal distribution. A chi-square test was used for categorical variables. We used the Pearson r in a bivariate correlation analysis to determine the correlation between variables and univariable regression analyses to create equations for the ULN for CSA. Multivariable linear regression was performed with all significant variables (wrist circumference, weight, gender, age, BMI, and height) entered in a stepwise way in order to identify which factors independently correlated with the CSA, and this was checked for multicollinearity.

Differences in CSA between men and women were determined by applying the unpaired T test. Differences in sensitivity between the various sets of normal values were calculated using the McNemar test. $p < 0.05$ was considered to be statistically significant. Normal distribution of data was assessed visually by plotting a histogram and performing the Kolmogorov-Smirnov method. We tested for outlines using Tukey's method. The initial method used a multiplier of 1.5, but more recent studies suggested that a multiplier of 2.2 is more appropriate. Therefore, we applied a multiplier of 2.2 in our outlier calculations [11, 12].

Results

Controls

An overview of clinical features of the healthy participants is demonstrated in Table 1. A total of 21 right wrists and 21 left wrists were analyzed ("healthy controls, new") in addition to the previously analyzed 54 wrists ("healthy controls, the previous study") [9]. The features of the two groups combined are shown in the third column ("healthy controls, combined"). There were no statistically significant differences in baseline characteristics between the previous group of healthy controls and the new group of healthy controls, with the exception of age and mean CSA, which was significantly higher in the new controls. Bifid median nerves ($n = 11$, 5.8%) were excluded. In men ($n = 47$), the mean CSA was 10.2mm^2 (SD 1.9) and in women, ($n = 49$) it was 8.8 mm^2 (SD 1.9). The mean CSA for the left and right

Table 1 Characteristics of healthy controls and patients

	Healthy controls previous study[a]	Healthy controls additional[b]	*p*	Healthy controls combined[c]	Patients[d]	*p*
Participants (*n*)	54	42		96	253	
Men/women	25 (46.3%)/29 (53.7%)	22 (52.3%)/20 (47.7%)	0.554	47 (49.0%)/49 (51.0%)	51 (20.2%)/202 (79.8%)	< 0.001
Mean age (*y*, range, SD)	40.6 (18–65, 12.7)	49.7 (40–60, 6.6)	< 0.001	44.6 (18–65; 11.4)	47.1 (18–86; 10.9)	0.060
Median age (*y*)	42	49		46	48	
Left/right	27/27	21/21		48/48	104/149	
Mean length (cm, range, SD)	175.4 (153–193, 8.2)	176.4 (160–198, 10.0)	0.596	175.8 (153–198; 9.0)	167.3 (149–190; 7.9)	< 0.001
Mean weight (kg, range, SD)	76.9 (55–115, 13.5)	77.9 (55–113, 13.7)	0.756	77.3 (55–115; 13.5)	76.6 (50–137; 15.6)	0.569
Mean BMI (range, SD)	25.0 (17.9–34.6, 3.7)	25.0 (19.5–34.9, 3.5)	0.988	25 (18–35; 3.6)	27.3 (18.4–48.4; 4.9)	< 0.001
Mean circumference included wrist (cm, range, SD)	16.6 (13.0–19.8; 1.4)	17.0 (14.7–19.5; 1.4)	0.170	16.8 (13.0–19.8; 1.4)	16.6 (14.2–20.6; 1.3)	0.250
Mean CSA included wrist (mm^2, range; SD)	9.0 (5.1–14.5; 1.9)	10.1 (6.6–15.0; 2.0)	0.009	9.5 (5.1–15.0; 2.0)	13.5 (6.5–41.3; 4.4)	< 0.001

[a] Healthy controls included in our previously reported study [9]

[b] Newly added healthy controls in an age of 40–60 years in this study

[c] "Healthy controls previous study" and "healthy controls additional" combined

[d] Patients with clinically defined CTS

y years, *SD* standard deviation, *cm* centimeter, *kg* kilogram, *BMI* body mass index, *CSA* cross-sectional area, *mm* millimeter

median nerves was statistically significantly different in men and women ($p < 0.05$). Therefore, fixed ULN could be calculated for men and women separately. Our data appeared to have a Gaussian distribution (the Kolmogorov-Smirnov $p > 0.05$) and outliers were not identified. In men, the fixed ULN (mean plus 2SD) for CSA was 14.0 mm^2 (95% CI 13.5–14.4) and in women, it was 12.6mm^2 (95% CI 12.2–13.1).

We found statistically strong correlations between wrist circumference and CSA. Regression line equations between men and women showed no significant differences, so data of both genders could be pooled (data not shown). A plot of this compound regression equation (ULN = $0.88x - 2.0$), including the regression line (lower continuous line), the 95th prediction interval (red dotted lines), and the regression line indicating ULN (upper continuous line), is presented in Fig. 1. The correlation coefficient (the Pearson r) was 0.61 ($p < 0.01$); the proportion of variance explained by regression (r^2) 0.37. The ULN can be calculated by substituting wrist circumference for "x" in the equation.

The CSA of the median nerve was significantly correlated with age ($r = 0.32$), gender ($r = 0.34$), height ($r = 0.29$), weight ($r = 0.44$), and BMI ($r = 0.31$), however to a much smaller extent than wrist circumference (Table 2). Yet, after the application of a multiple regression analysis, only wrist circumference ($p < 0.01$) and gender ($p = 0.04$) appeared to have a significant independent correlation with CSA (Table 3). For wrist circumference alone, r^2 was 0.37, which slightly increased to 0.40 after the addition of gender to the model.

Patients

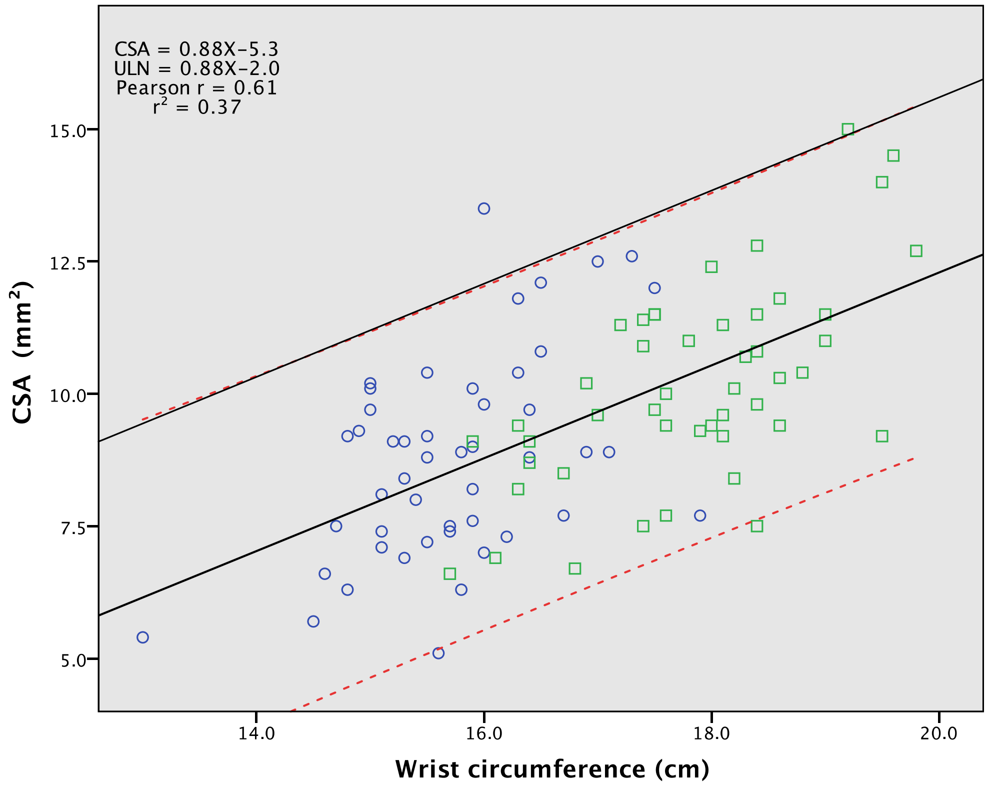
A total of 253 patients with clinically defined CTS were consecutively enrolled in our study. Characteristics of these patients are shown in Tables 1 and 4. The mean age of patients did not differ significantly from controls ($p = 0.06$). To determine the sensitivity of the updated compound equation for normal values, we applied this equation to all 253 patients. Moreover, we compared the results to those of the previous equations of normal values as well as to the fixed ULN as calculated for men and women separately (as described above).

Within the group of 253 clinically defined CTS patients, 201 (79.4%) had abnormal EDX results, supporting the diagnosis of CTS. Only 135 (53.4%) patients had abnormal US results when using the updated compound normal values, versus 144 (56.9%) patients when applying the previous normal values ($p = 0.004$). However, when using the updated normal values, US was more often abnormal compared to the application of the fixed cut-off value (53.4% versus 47.4%, $p = 0.003$). The results of US and EDX are shown in Table 5.

Discussion

Diagnostic accuracy of US depends on what is considered normal. Normal values for US differ in literature, and most common is the use of a fixed cut-off value for the CSA of the

Fig. 1 Regression analysis for ULN of the CSA depending on wrist circumference. Lower continuous line, regression line; red dotted lines, the 95th prediction interval; upper continuous line, regression line indicating ULN; blue circles, women; and green squares, men, CSA cross-sectional area, ULN upper limit of normal



median nerve at the carpal tunnel inlet [1, 2]. In an earlier study, however, we found a strong correlation between wrist circumference and CSA of the median nerve. Therefore, we suggested that normal values for each individual should be established by applying the obtained regression equations [9]. Sensitivity of our equations proved to be relatively low compared to studies with a fixed cut-off normal value, which raised the suspicion that our reference group was not representative for the group of CTS patients. This study, however, confirms that, even though we applied age-matched controls by adding an extra 42 healthy older controls, this strong correlation remains, and low sensitivity of US for diagnosing CTS persists.

We found that wrist circumference has the strongest correlation with CSA. Wrist circumference accounts for 37% of the variation in CSA, which increases with only a negligibly small amount of 3% after the addition of gender. Other parameters, such as age, height, weight, and BMI are not independently correlated to CSA. Therefore, wrist circumference turns out to be the most important independent predicting factor for CSA.

Our aim was to extend the group, adding older controls to the original group. As a consequence, the mean age of our newly added controls was significantly higher than the healthy controls in our previous study. Moreover, the mean CSA in the newly added controls was significantly higher than in the previous control group. This seems to be no surprise, as CSA is positively correlated with age. However, in the multivariable regression analysis, we showed that when taking wrist circumference into account, CSA is independent of age. In other words, a fixed cut-off value for CSA is age-dependent, yet our equations are invariant with respect to age.

The effect of these updated equations for ULN differs from those of our earlier published equations [9]. For example, the right wrist circumference for a given patient is 17 cm. The ULN, when applying the previous TM equation, for this patient would be 12.5mm^2, while using the updated equation gives a ULN of 13.0mm^2. Therefore, the ULN for US will be a little higher than previously expected, and as a consequence, sensitivity is lower. As illustrated in Table 5, the sensitivity of our new equation is only 53.4%. When using the fixed cut-off value as ULN, sensitivity will be even lower (47.4%). One can conclude that sensitivity for US is low and that it cannot replace EDX in diagnosing CTS.

In this study, we succeeded in simplifying the equations for normal values. As equations for ULN turned out not to be significantly different for the left and the right wrist, we could include them randomly in order to increase variance and to strengthen our equations. Because of this reduction in the amount of equations, it will be more convenient for clinical use, and reported equations can be applied independent of side or gender.

Our values for ULN are somewhat higher than reported in most earlier studies. We hypothesized that an important reason might be that all included control subjects were Caucasians. Although there is no specific literature about this, Caucasian people (and especially Dutch people) are taller than most other

Table 2 Correlation between CSA and patient characteristics in bivariate correlation analyses (the Pearson *r*)

	Gender	Age	Height	Weight	BMI	Wrist circumference	CSA
Gender	1						
Age	0.336**	1					
Height	0.651**	0.166	1				
Weight	0.511**	0.170	0.574**	1			
BMI	0.139	0.076	− 0.040	0.791**	1		
Wrist circumference	0.743**	0.392**	0.651**	0.800**	0.485**	1	
CSA	0.340**	0.320**	0.289**	0.442**	0.307**	0.610**	1

$^*p < 0.05$; $^{**}p < 0.01$

BMI body mass index, *CSA* cross-sectional area

racial groups and therefore have a larger wrist circumference. In fact, our results show that wrist circumference is positively correlated to height and weight. Therefore, we can assume that smaller people will have a smaller wrist circumference and consequently have a lower CSA of the median nerve. This concept is extensively supported by previous studies. Bathala et al., who determined the CSA of 100 healthy Asian volunteers, found that the mean CSA for median nerve at the wrist was clearly lower (men 7.5mm^2 ± 1.0 and women 6.8 mm^2 ± 1.0) than obtained in our healthy controls. Won et al. found slightly higher CSA in Asian controls (8.3 mm^2 ± 1.5), but still lower than in our control group. Mean height (160 cm ± 10 and 165 cm ± 9, respectively), weight (59.3 kg ± 11.3 and 63.1 kg ± 12.2), and BMI (22.95 kg/m^2 ± 3.5 and 22.90 kg/m^2 ± 3.1) in these studies were obviously lower than in our controls [13, 14]. Unfortunately, wrist circumference was not reported in these studies. Besides, in African-Caribbean and Indian population CSA has been reported to be lower than in our population (8.2 mm^2 ± 1.3 and 7.2 mm^2 ± 1.0, respectively), and it was stated that the differences in CSA between Indian and Dutch people cannot be solely attributed to differences in weight, height, and BMI [15, 16]. According to our results, this discrepancy is probably caused by differences in wrist circumference between these ethnic groups. Again, however, wrist circumference was not taken into account. In contrast to these studies, normal values reported by Cartwright et al. (American population, mean weight 73 kg, and mean height 167 cm) and Qrimli et al. (mixed ethnicities, mean BMI 25.3 kg/m^2 ± 5.3) are comparable to ours (the mean CSA is 9.8 mm^2 ± 2.4) [17, 18]. Because of these differences, it is advised in literature that reference values obtained in a specific population in a specific laboratory cannot be transferred indiscriminately to other populations; they need to be validated in this new group [16, 19]. Taking the wrist circumference into account might overcome this problem at least partly.

Other causes for differences in ULN between our study and previously reported studies can be the diversity in the way CSA is measured by US. To decrease the chance of measurement errors, we calculated the CSA as the mean of three different measurements and used the TM instead of the ellipse method (EM) in order to obtain reference values as accurately as possible. Moreover, we used a 17-MHz linear array transducer, compared to 5–12 MHz in most other studies. Thus, very precise circumscription of the median nerve is possible in order to establish the CSA.

Our study had some limitations. Firstly, the electrodiagnostic technicians who performed ultrasonography were not blinded, so they knew our controls were healthy and did not have CTS. This may have influenced the measurements, because they did not expect enlargement of the nerve.

Table 3 Multivariable regression analysis assessing significant predictors of median nerve CSA

	B (95% CI)	SE *B*	*β*	*R*	R^2
Wrist circumference	1.14** (0.78–1.45)	0.18	0.80	0.63	0.40
Gender	− 1.02* (− 1.92–0.06)	0.50	− 0.25		

Excluded non-significant variables: age, height, BMI, weight

$^*p < 0.05$; $^{**}p < 0.01$

B partial regression coefficient, *SE B* standard error partial regression coefficient, *R* multiple correlation coefficient, R^2 determination coefficient

Table 4 Characteristics of patients with clinically defined CTS

Variable	Patients (*n* = 253)
Median duration symptoms (months, range)	12 (1–240)
Atrophy m. APB	47 (18.5%)
Weakness m. APB	60 (23.7%)
Weakness m. opponens	13 (5.1%)
Sensory loss	
TPD	164 (64.8%)
MF	103 (40.7%)

APB abductor pollicis brevis, *TPD* two-point discrimination, *MF* monofilament

Table 5 Results of US and EDX applying previously obtained equations, updated compound equations, and fixed cut-off value for ULN

		Abnormal EDX	Normal EDX	Total	*p*
Abnormal US	Previous equations[a]	134	10	144 (56.9%)	0.004
	Updated compound equations[b]	127	8	135 (53.4%)	0.003
	Fixed cut-off[c]	115	5	120 (47.4%)	
Normal US	Previous equations[a]	67	42	109 (43.1%)	0.004
	Updated compound equations[b]	74	44	118 (46.6%)	0.003
	Fixed cut-off[c]	86	47	133 (52.6%)	
Total		201 (79.4%)	52 (20.6%)		

Total 253 patients included

[a] Equations derived from "healthy controls previous study"

[b] Equations derived from "healthy controls combined"

[c] Fixed ULN determined by mean CSA + 2SD (men 14.0 mm^2; women 12.6mm^2)

US ultrasonography, *EDX* electrodiagnostic test, *ULN* upper limit of normal

Secondly, in the control group, we have not performed EDX in order to monitor for subclinical neuropathy of the median nerve. However, if only the least complaints consistent with CTS were present, controls were excluded. Besides, it is known that even EDX cannot identify all patients with median nerve entrapment [20]. Thirdly, we used clinical criteria as a gold standard for CTS. In fact, this could have led to patients falsely diagnosed with CTS being included in this study, which could have negatively influenced sensitivity of US. Yet, our group of patients seems to be representative, as almost 80% had abnormal EDX, which is in accordance with previous literature [21]. The upper limit of BMI in this study was 35, so our data will not be applicable to obese patients. Moreover, our patient group contained people with sensory symptoms in the territory of the median nerve, including the fifth finger. An ulnar neuropathy may theoretically have played a role and was not strictly ruled out. However, in an earlier study, we showed that the presence of symptoms in digit 5 is often reported in CTS patients and treatment outcome does not differ from patients with classic CTS complaints [22]. Finally, it is important to realize that the low sensitivity for US found in this study is based on assessing CSA exclusively. In daily practice, this is the most common strategy. By contrast, previous studies found improvement of diagnostic accuracy by adding other parameters such as hypervascularity, hypoechogenicity, or forearm-wrist ratio [23–25]. In this study, we did not investigate if including these parameters would have increased the sensitivity of US.

Further research should be undertaken to confirm the value of measuring the wrist circumference in determining the ULN in CTS in other populations. It would be of great interest to investigate whether the interracial differences for ULN are caused by differences in wrist circumference.

In conclusion, this study confirms that normal values for the median nerve at the carpal tunnel inlet strongly depend on wrist circumference. Moreover, wrist circumference turned out to be the most important independent predicting factor the CSA. Even though we increased the mean age of our control group, sensitivity for US in diagnosing CTS remains relatively low and it therefore cannot replace EDX. Our equation for ULN proved to be unrelated to age, whereas fixed values seem to be age-dependent. By using our simplified and updated equation and taking the wrist circumference into account, one can determine a more precise ULN for each individual, which will lead to improvement of the diagnostic accuracy of US.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Cartwright MS, Hobson-Webb LD, Boon AJ, Alter KE, Hunt CH, Flores VH, Werner RA, Shook SJ, Thomas TD, Primack SJ, Walker FO, American Association of N, Electrodiagnostic M (2012) Evidence-based guideline: neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome. Muscle Nerve 46(2):287–293. https://doi.org/10.1002/mus.23389
2. Bayrak IK, Bayrak AO, Kale M, Turker H, Diren B (2008) Bifid median nerve in patients with carpal tunnel syndrome. J Ultrasound Med 27(8):1129–1136

3. Deniz FE, Oksuz E, Sarikaya B, Kurt S, Erkorkmaz U, Ulusoy H, Arslan S (2012) Comparison of the diagnostic utility of electromyography, ultrasonography, computed tomography, and magnetic resonance imaging in idiopathic carpal tunnel syndrome determined by clinical findings. Neurosurgery 70(3):610–616. https://doi.org/10.1227/NEU.0b013e318233868f
4. Fowler JR, Munsch M, Tosti R, Hagberg WC, Imbriglia JE (2014) Comparison of ultrasound and electrodiagnostic testing for diagnosis of carpal tunnel syndrome: study using a validated clinical tool as the reference standard. J Bone Joint Surg Am 96(17):e148–e1-4. https://doi.org/10.2106/JBJS.M.01250
5. Swen WA, Jacobs JW, Bussemaker FE, de Waard JW, Bijlsma JW (2001) Carpal tunnel sonography by the rheumatologist versus nerve conduction study by the neurologist. J Rheumatol 28(1): 62–69
6. Kwon BC, Jung KI, Baek GH (2008) Comparison of sonography and electrodiagnostic testing in the diagnosis of carpal tunnel syndrome. J Hand Surg Am 33(1):65–71. https://doi.org/10.1016/j.jhsa.2007.10.014
7. Visser LH, Smidt MH, Lee ML (2008) High-resolution sonography versus EMG in the diagnosis of carpal tunnel syndrome. J Neurol Neurosurg Psychiatry 79(1):63–67. https://doi.org/10.1136/jnnp.2007.115337
8. Nakamichi K, Tachibana S (2002) Ultrasonographic measurement of median nerve cross-sectional area in idiopathic carpal tunnel syndrome: diagnostic accuracy. Muscle Nerve 26(6):798–803. https://doi.org/10.1002/mus.10276
9. Claes F, Meulstee J, Claessen-Oude Luttikhuis TT, Huygen PL, Verhagen WI (2010) Usefulness of additional measurements of the median nerve with ultrasonography. Neurol Sci 31(6):721–725. https://doi.org/10.1007/s10072-010-0258-9
10. Claes F, Kasius KM, Meulstee J, Verhagen WI (2013) Comparing a new ultrasound approach with electrodiagnostic studies to confirm clinically defined carpal tunnel syndrome: a prospective, blinded study. Am J Phys Med Rehabil 92(11):1005–1011. https://doi.org/10.1097/PHM.0b013e31829b4bd8
11. Hoaglin DC, Iglewicz B (1987) Fine-tuning some resistant rules for outlier labeling. J Am Stat Assoc 82(400):1147–1149. https://doi.org/10.2307/2289392
12. Hoaglin DC, Iglewicz B, Tukey JW (1986) Performance of some resistant rules for outlier labeling. J Am Stat Assoc 81(396):991–999. https://doi.org/10.2307/2289073
13. Won SJ, Kim BJ, Park KS, Yoon JS, Choi H (2013) Reference values for nerve ultrasonography in the upper extremity. Muscle Nerve 47(6):864–871. https://doi.org/10.1002/mus.23691
14. Bathala L, Kumar P, Kumar K, Visser LH (2013) Ultrasonographic cross-sectional area normal values of the ulnar nerve along its course in the arm with electrophysiological correlations in 100 Asian subjects. Muscle Nerve 47(5):673–676. https://doi.org/10.1002/mus.23639
15. Arrigo A, Borot T, Mejdoubi M (2015) Median nerve ultrasound: normal and cut-off values in carpal tunnel syndrome in an Afro-Caribbean population. Muscle Nerve 51(2):304–305. https://doi.org/10.1002/mus.24485
16. Burg EW, Bathala L, Visser LH (2014) Difference in normal values of median nerve cross-sectional area between Dutch and Indian subjects. Muscle Nerve 50(1):129–132. https://doi.org/10.1002/mus.24124
17. Cartwright MS, Shin HW, Passmore LV, Walker FO (2009) Ultrasonographic reference values for assessing the normal median nerve in adults. J Neuroimaging 19(1):47–51. https://doi.org/10.1111/j.1552-6569.2008.00256.x
18. Qrimli M, Ebadi H, Breiner A, Siddiqui H, Alabdali M, Abraham A, Lovblom LE, Perkins BA, Bril V (2016) Reference values for ultrasonography of peripheral nerves. Muscle Nerve 53(4):538–544. https://doi.org/10.1002/mus.24888
19. Geffre A, Friedrichs K, Harr K, Concordet D, Trumel C, Braun JP (2009) Reference values: a review. Vet Clin Pathol 38(3):288–298. https://doi.org/10.1111/j.1939-165X.2009.00179.x
20. De Kleermaeker F, Meulstee J, Claes F, Kasius KM, Verhagen WIM (2017) Treatment outcome in patients with clinically defined carpal tunnel syndrome but normal electrodiagnostic test results: a randomized controlled trial. J Neurol 264(12):2394–2400. https://doi.org/10.1007/s00415-017-8637-2
21. Werner RA, Andary M (2011) Electrodiagnostic evaluation of carpal tunnel syndrome. Muscle Nerve 44(4):597–607. https://doi.org/10.1002/mus.22208
22. Claes F, Kasius KM, Meulstee J, Grotenhuis JA, Verhagen WI (2014) Treatment outcome in carpal tunnel syndrome: does distribution of sensory symptoms matter? J Neurol Sci 344(1–2):143–148. https://doi.org/10.1016/j.jns.2014.06.044
23. Rahmani M, Ghasemi Esfe AR, Vaziri-Bozorg SM, Mazloumi M, Khalilzadeh O, Kahnouji H (2011) The ultrasonographic correlates of carpal tunnel syndrome in patients with normal electrodiagnostic tests. Radiol Med 116(3):489–496. https://doi.org/10.1007/s11547-011-0632-6
24. Azman D, Hrabac P, Demarin V (2018) Use of multiple ultrasonographic parameters in confirmation of carpal tunnel syndrome. J Ultrasound Med 37(4):879–889. https://doi.org/10.1002/jum.14417
25. Hobson-Webb LD, Massey JM, Juel VC, Sanders DB (2008) The ultrasonographic wrist-to-forearm median nerve area ratio in carpal tunnel syndrome. Clin Neurophysiol 119(6):1353–1357. https://doi.org/10.1016/j.clinph.2008.01.101