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The diagnostic accuracy of high-resolution ultrasound in screening for carpal tunnel syndrome and grading its severity is moderated by age

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HIGHLIGHTS

- In patients ≥65 y with moderate and severe carpal tunnel syndrome (CTS), cross-sectional area (CSA) and CSA wrist-forearm ratio (WFR) were negatively correlated with age.
- Diagnostic yield of CSA, WFR in CTS was excellent in subjects <65 y and satisfactory in subjects ≥65 y.
- Both CSA and WFR have satisfactory accuracy in grading CTS only in patients aged <65 y.

ABSTRACT

Objective: To assess the effect of age on the accuracy of high-resolution ultrasound (HRUS) in the diagnosis and grading of carpal tunnel syndrome (CTS).
Methods: Patients with symptoms and signs of CTS (N = 527 wrists) were evaluated using electrodiagnostic studies (EDx) for CTS diagnosis and grading. Median nerve cross-sectional areas at carpal tunnel inlet (CSA) and at forearm level were measured by HRUS and the ratio of these values was calculated (WFR). Healthy controls underwent identical testing (N = 122 wrists). HRUS accuracy was assessed against the EDx standard by Receiver Operator Characteristic (ROC) curve analysis.
Results: In patients >65 y with moderate and severe CTS, disease-related increases in CSA and WFR were negatively correlated with increasing age. Subjects were grouped by age into younger (<65 y) and older (≥65 y). The c-statistics for CSA and WFR respectively were: For CTS diagnosis, younger group: 0.94 and 0.96 (excellent); older group: 0.85 and 0.86 (satisfactory). For CTS grading, younger group: differentiating mild CTS from controls: 0.90 and 0.92 (excellent); mild from moderate: 0.79 and 0.74 (satisfactory); moderate from severe: 0.82 and 0.78 (satisfactory). For CTS grading, older group: differentiating mild CTS from controls: 0.83 and 0.83 (satisfactory); mild from moderate: 0.53 and 0.61 (poor); moderate from severe: 0.65 and 0.53 (poor).
Conclusions: For subjects aged <65 y, HRUS accuracy is excellent in CTS diagnosis and satisfactory in grading. For older subjects, accuracy is satisfactory in diagnosis but not in grading.
Significance: HRUS for CTS has diagnostic limitations selectively in older individuals.

1. Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy (Latinovic et al., 2006). Although CTS is a clinical syndrome, electrodiagnostic studies (EDx) are commonly used to support diagnosis and stage CTS (Jablecki et al., 1993), with staging

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being particularly important in guiding treatment options (Bland, 2001). Recently, HRUS has emerged as an attractive, non-invasive alternative method for the diagnosis of CTS with sensitivity and specificity equivalent to EDx (Fowler et al., 2011). Cross-sectional area of the median nerve at the wrist (CSA) and wrist to forearm ratio (WFR) have both been studied for the diagnosis of CTS, yielding similar results (Mhoon et al., 2012). However, relatively few studies have considered the capability of HRUS to stage CTS severity, showing variable results, as recently reviewed (Chen et al., 2016). Specifically, in some studies, HRUS results were found to parallel EDx (El Miedany et al., 2004; Karadağ et al., 2010; Kim et al., 2014; Klauser et al., 2015; Kutlar et al., 2017; Lee et al., 2005; Lee and Kim, 2016; Padua et al., 2008; Yurdakul et al., 2016), whereas no good correlation was found in others (Kaymak et al., 2008; Mhoon et al., 2012; Mondelli et al., 2008; Moran et al., 2009). This apparent discrepancy may be at least partially due to small sample sizes and wide distribution of patients' ages.

In view of the former considerations, we conducted a large case-control study aiming to assess the accuracy of CSA and WFR in CTS diagnosis and staging with particular focus on the confounding effect of patient age.

2. Methods

2.1. Subjects

The study was conducted between February 2016 and April 2018 in two institutions in Athens, Greece. The complete study protocol was approved by the ethics committee of "Attikon" University Hospital. Written informed consent was obtained from all patients and healthy controls prior to study enrollment.

In order to be included in the study, patients were required to present typical symptoms and signs of CTS, while CTS diagnosis was confirmed by EDx studies. Patients with diabetes mellitus or previously diagnosed polyneuropathy were excluded because it is well known that these conditions generally affect nerve diameter and echogenicity and, thus, might confound the results. Also excluded were patients with ipsilateral radiculopathy proven by EDx studies or MRI of the cervical spine, or secondary CTS shown by US and/or other neuroimaging modalities. Patients and controls with bifid median nerve were also excluded because there are no generally accepted criteria for its area measurement. We also recruited and examined healthy volunteers (colleagues, relatives, and friends) without neurologic or other relevant medical conditions.

A total of 433 patients (527 wrists) and 92 healthy individuals (122 wrists) were evaluated. Baseline characteristics of the study populations are presented in Table 1.

2.2. Electrophysiology

EDx studies were conducted by Dantec Keypoint G4 apparatus. They included median, ulnar and radial nerve conduction studies in both hands (wrist temperature >32 °C). EMG study included at least one muscle from myotomes C_5 C_6 C_7 and C_8 T_1. In order to grade the severity of CTS, standard criteria were used as previously described (Werner and Andary, 2011):

Mild CTS (A): prolonged sensory median latency and normal motor latency (<4.5 ms). Patients with symptoms suggestive of CTS and abnormal comparative studies were also included in the mild CTS group.

Moderate CTS (B): prolonged sensory median latency plus prolonged motor latency (≥4.5 ms).

Severe CTS (C): abnormalities mentioned above plus absent median sensory nerve action potential or evidence of degeneration of median motor fibers (CMAP amplitude from baseline to negative peak <6 mV, the value which represented the lowest normal limit in our laboratory) and signs of denervation in the EMG study of abductor pollicis brevis (APB). In all cases of severe CTS, APB was sampled in order to achieve correct grading.

2.3. Ultrasonography

Ultrasonography was performed by certified neurosonologists blinded to EDx results with a portable Sonosite Edge machine equipped with a 6–15 MHz linear transducer. Median nerve cross-section area was measured first at the level of the pisiform bone and then 12 cm proximally at the forearm between flexor digitorum superficialis and profundus. The perimeter of the nerve was traced manually and, subsequently, the area was automatically calculated by the software of the device. Device settings were kept constant in order to make area measurements. Hyperechoic epineurium was excluded in both measurements. The ratio of the above measurements (WFR) was calculated.

2.4. Statistical analyses

Continuous variables are presented as mean ± SD (normal distribution) or as median with interquartile range (skewed distribution), while categorical variables are presented as percentages. Measurements from patients with extreme CTS (absent SNAPs

Table 1
Baseline characteristics and electrodiagnostic measurements of the study population. p-values refer to differences between patients and controls for each age group and each parameter. Statistical tests: Pearson's χ^2 for Sex, unpaired t-test for all others.

		N	Age, years Median (IQR)	Sex (F/M)	BMI, kg/m^2 Median (IQR)	Motor latency (ms)	CMAP (mV)	Sensory latency (ms)	SNAP (μV)
Overall	Controls	122	56(27)	98/24	26.95(6.66)	3.72 ± 0.03	10 ± 0.25	2.73 ± 0.02	45.95 ± 1.70
	Patients	527	56(31)	395/132	28.13(6.59)	5.65 ± 0.09	8.60 ± 0.21	3.44 ± 0.06	14 ± 0.50
			p = 0.531	p = 0.222	p = 0.012	$p = 4.9 * 10^{-15}$	$p = 6.6 * 10^{-6}$	$p = 5.6 * 10^{-8}$	$p = 1.3 * 10^{-54}$
<65 y	Controls	75	46(19)	56/19	26.07(6.82)	3.44 ± 0.04	10.81 ± 0.25	2.67 ± 0.03	51.62 ± 2.18
	Patients	353	48(13)	270/83	28.13(7.29)	4.65 ± 0.08	9.28 ± 0.28	3.58 ± 0.06	23 ± 0.62
		(150A/168B/35C)	p = 0.231	p = 0.732	p = 0.005	$p = 2.8 * 10^{-15}$	p = 0.0084	$p = 2.1 * 10^{-11}$	$p = 7.3 * 10^{-46}$
≥65 y	Controls	47	73(11)	42/5	27.58(5.59)	3.41 ± 0.06	9.20 ± 0.47	2.78 ± 0.03	25.26 ± 1.32
	Patients	174	75(11)	125/49	28.13(5.72)	5.65 ± 0.16	6.35 ± 0.26	3.84 ± 0.12	7.60 ± 0.68
		(48A/48B/78C)[†]	p = 0.190	p = 0.015	p = 0.464	$p = 7.0 * 10^{-12}$	$p = 3.3 * 10^{-6}$	$p = 6.8 * 10^{-4}$	$p = 6.7 * 10^{-20}$

N: number of wrists; IQR: interquartile range; F: Female; M: Male; BMI: Body Mass Index; CMAP: Compound Muscle Action Potential; SNAP: Sensory Nerve Action Potential.
[†] Percentage of severe CTS among patients was significantly higher in the >65 y than in the <65 age group ($p < 0.0001$, χ^2 test).

or/and absent CMAPs) were excluded only from statistical analysis involving latency. Statistical comparisons between different subgroups were performed using Pearson's χ^2 test, unpaired t-test and Mann–Whitney U test, where appropriate. All significance tests were two-sided. A p value of 0.05 or less was deemed significant.

To assess the correlation between EDx and HRUS indices, Spearman's correlation coefficients (r) were computed. Diagnostic utility of HRUS for the diagnosis and grading of CTS was also evaluated using receiver-operating characteristics (ROC) curve analysis and the c statistics (area under curve – AUC) with corresponding 95%CI (confidence intervals) were calculated as appropriate. Ideal discrimination produces a c-statistic of 1.0, whereas discrimination that is no better than chance produces a c-statistic of 0.5. Comparisons of c-statistics between different HRUS indices were performed according to de Long methodology. In order to determine the optimal cut-off points for CSA and WFR, the Youden Index was used (Rücker and Schumacher, 2010; Schisterman et al., 2005). The Youden index summarizes the performance of a diagnostic test for a dichotomous result. The index is calculated as [sensitivity + specificity – 1] for each cut-of value. The optimal cut-off value is the one that maximizes the index.

Statistical analyses were performed by Origin 8.5, SPSS 14.0 and MedCalc 14.8 software.

3. Results

3.1. Demographic data, correlations between EDx and HRUS measures

There was no difference in age and sex between the patient and control groups (Table 1). BMI was higher in patients than controls. EDx measurements in the two groups are shown in Table 1. The percentage of severe CTS among patients increased significantly with age ($p < 0.0001$).

In order to evaluate the potential impact of age on CSA and WFR measurements, Scatter plots of CSA and WFR values as a function of age were created (Figs. 1 and 2). A significant ($p < 0.01$) negative monotonic correlation between CSA and WFR with age was observed in patients aged ≥65 years with moderate and severe CTS. In contrast, age was not related to CSA or WFR measurements in healthy individuals and patients with mild CSA. Based on these observations, we dichotomized our study population in two age groups: <65 years & ≥65 years.

The correlations between EDx measurements with CSA and WFR are shown in Table 2. Both CSA and WFR were strongly correlated ($p < 0.0001$) with CMAP (negative correlation), SNAP (negative correlation), motor latency (positive correlation) and sensory latency (positive correlation). The respective scatter plots are shown in Supplementary Fig. S1. No significant correlations were found between CSA, WFR and sex ($p = 0.33$ and $p = 0.25$

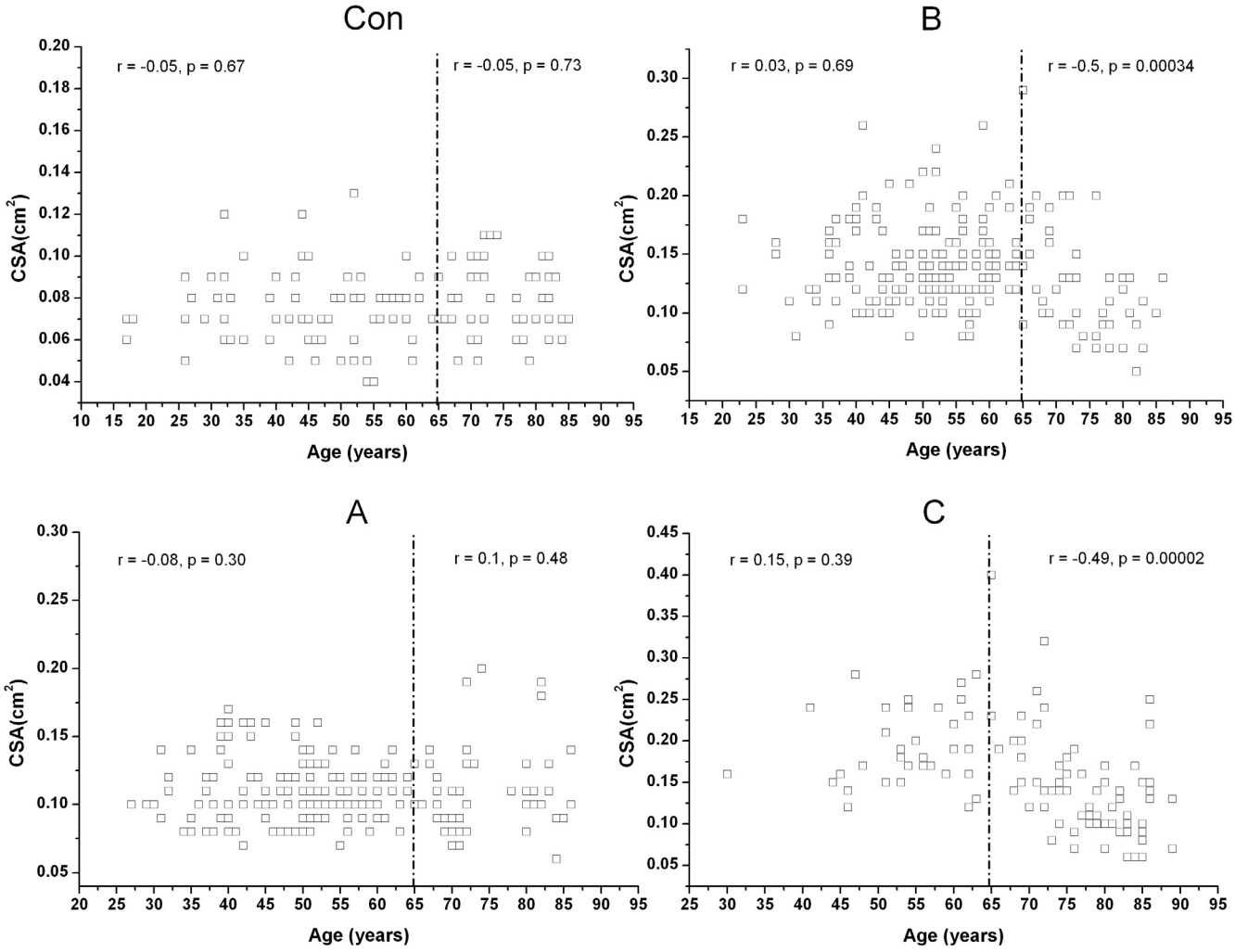

Fig. 1. Correlation between CSA and age. Scatter plots of correlation between CSA and age in controls (Con) and patients with mild (A), moderate (B) and severe (C) CTS. After the age of 65 y, a moderate negative correlation exists in moderate and severe CTS only (Spearman correlation coefficient r = −0.50 and r = −0.49 respectively).

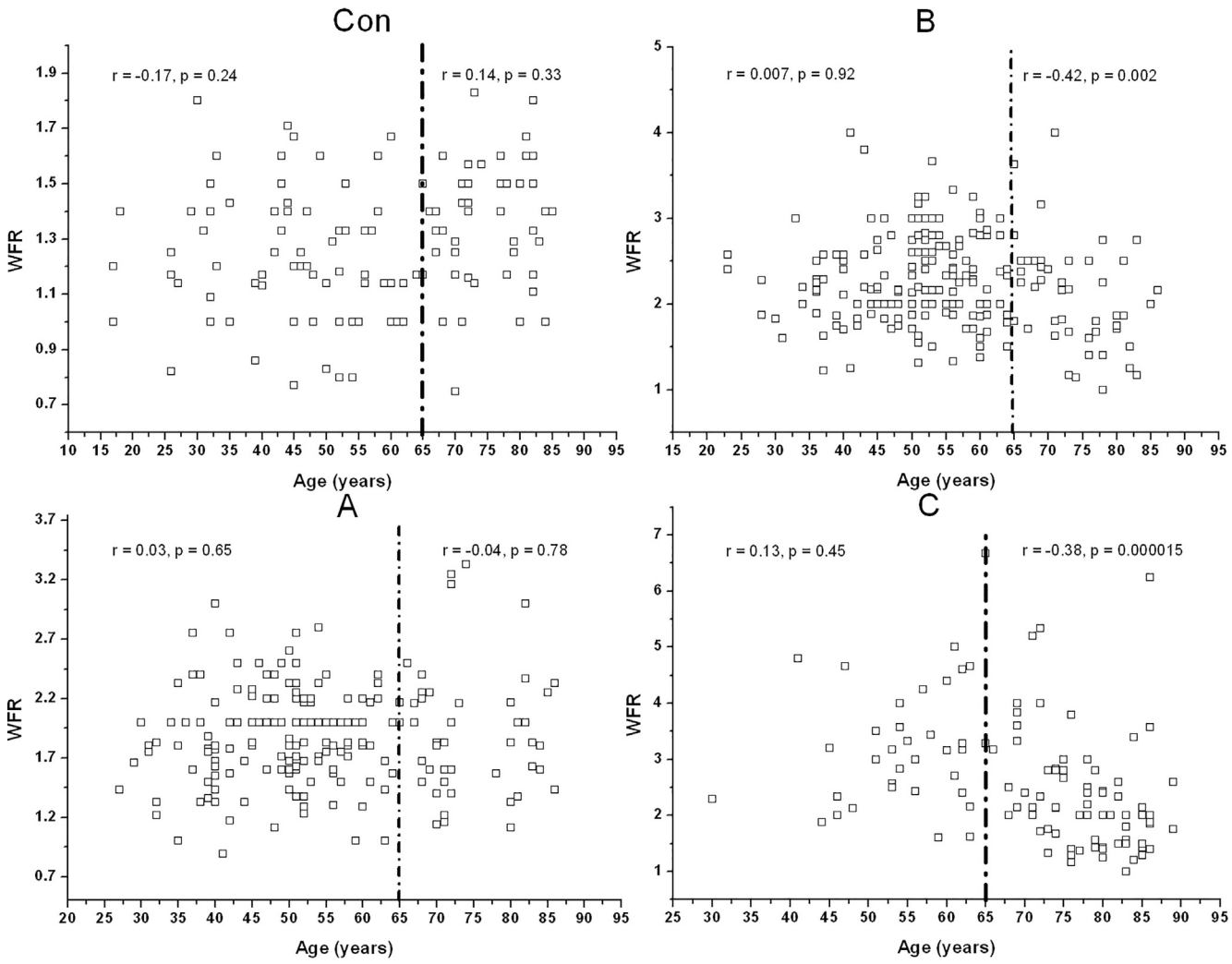

Fig. 2. Correlation between WFR and age. Scatter plots of correlation between WFR and age in controls (Con) and patients with mild (A), moderate (B) and severe (C) CTS. After the age of 65 y, a negative correlation was found only in moderate and severe CTS (Spearman correlation coefficient r = −0.42 and r = −0.38 respectively).

Table 2
Correlations between cross-sectional area of the median nerve at the wrist (CSA) and wrist to forearm ratio (WFR) with electrodiagnostic measurements.

	Motor latency, r (p value)	CMAP, r (p value)	Sensory latency, r (p value)	SNAP, r (p value)
CSA	r = 0.47 (p < 0.0001)	r = −0.31 (p < 0.0001)	r = 0.36 (p < 0.0001)	r = −0.48 (p < 0.0001)
WFR	r = 0.43 (p < 0.0001)	r = −0.30 (p < 0.0001)	r = 0.34 (p < 0.0001)	r = −0.45 (p < 0.0001)

CMAP: Compound Muscle Action Potential; SNAP: Sensory Nerve Action Potential; r: Spearman's correlation coefficient.

respectively, independent t-test) or BMI (p = 0.30 and p = 0.25 respectively, Spearman's correlation).

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.clinph.2018.12.005.

3.2. CSA and WFR as screening tests for CTS diagnosis

For the total population of patients with CTS and controls studied, ROC curve analysis showed that both WFR and CSA are excellent screening tests for CTS diagnosis with corresponding c-statistics of 0.93 and 0.91 respectively (Table 3, Fig. 3).

In the younger age group, ROC curve analysis showed that both WFR and CSA are excellent screening tests for CTS diagnosis with corresponding c-statistics of 0.96 and 0.94 respectively (Table 3, Fig. 3).

In the older age group, ROC curve analysis showed that both WFR and CSA are satisfactory screening tests for CTS diagnosis with corresponding c-statistics of 0.86 and 0.85 respectively (Table 3, Fig. 3).

The c-statistic of the CSA ROC curve was higher in younger than older patients (p for De Long statistic: 0.015). Similarly, the c-statistic of the WFR ROC curve was higher in younger than older patients (p for De Long statistic: 0.017).

3.3. Correlations between ultrasonographic (CSA, WFR) and electrodiagnostic CTS severity

In the overall study population, both CSA and WFR values were different across the subgroups stratified by CTS severity (Table 4, Fig. 4), indicating that abnormal ultrasound findings were more pronounced in patients with more severe CTS. ROC curve analysis

Table 3
Diagnostic utility of cross-sectional area of the median nerve at the wrist (CSA) and wrist to forearm ratio (WFR) for carpal tunnel syndrome (CTS) diagnosis stratified by age.

Age	CSA, c-statistic (95%CI)	Optimal cut-off value* Sensitivity (95%CI)/Specificity (95%CI)	WFR c-statistic (95%CI)	Optimal Cut-off value* Sensitivity (95%CI)/Specificity (95%CI)
Overall	0.91 (0.88–0.94)	0.09 83 (80–86)/85 (77–91)	0.93 (0.91–0.96)	1.6 82 (78–85)/94 (89–98)
<65 y	0.94 (0.92–0.97)	0.09 88 (84–91)/88 (78–94)	0.96 (0.93–0.99)	1.6 86 (82–89)/95 (87–99)
≥65 y	0.85 (0.78–0.92)	0.09 74 (67–80)/81 (67–91)	0.86 (0.79–0.94)	1.6 73 (66–79)/94 (83–99)

CI: Confidence Interval.
* Optimal cut-off values were defined on the basis of the highest Youden index.

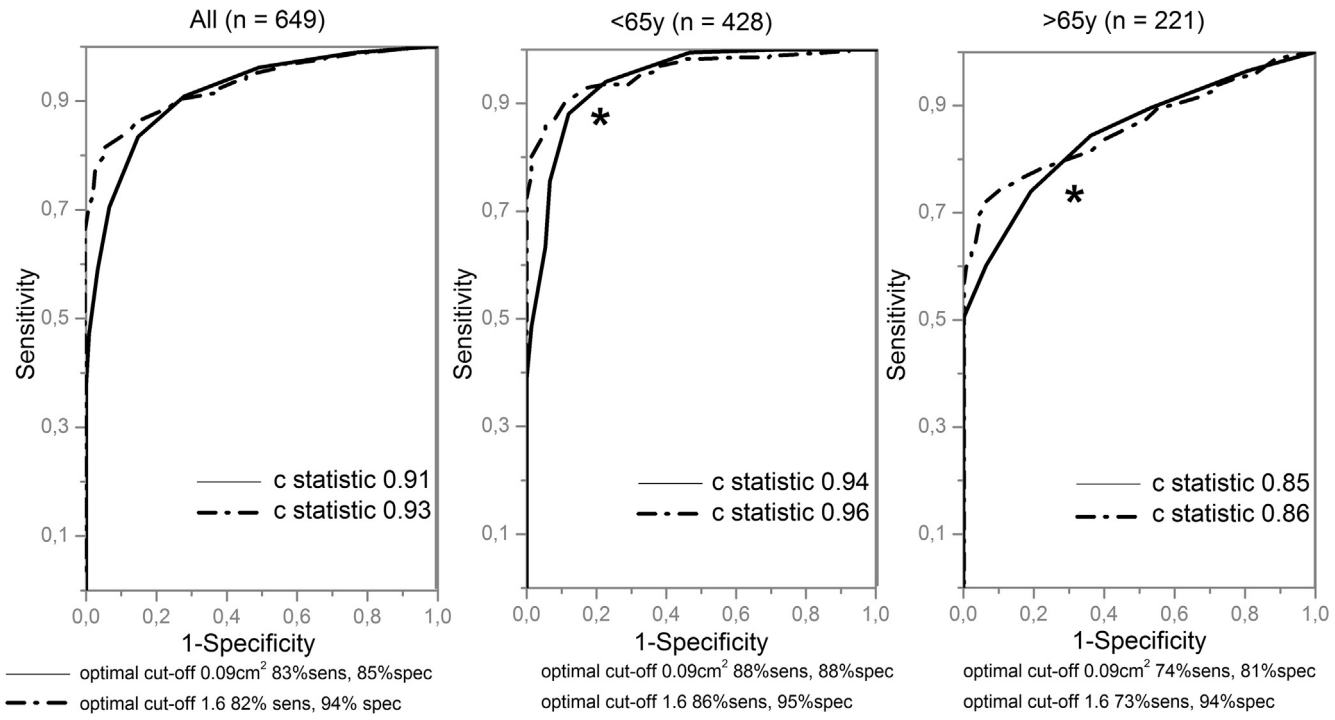

Fig. 3. CSA and WFR as screening tests for the diagnosis of CTS. ROC analysis for CSA (solid line) and WFR (dash dot) for the three age groups studied (all ages, <65 y, ≥65 y). The sensitivity and specificity of CSA and WFR as well as the optimal cut-off value for each age group are given at the bottom of the figure. There was no significant difference between the c-statistics for CSA and WFR in each one of the three age groups (De Long statistic 0.232, 0.284 and 0.643 respectively). On the other hand, c-statistics for both CSA and WFR were significantly higher in the younger than in the older age group (p = 0.015, p = 0.017 respectively, asterisk).

(Fig. 4) disclosed that CSA is a satisfactory test for differentiating patients with mild CTS from normal (Con) individuals (c-statistic: 0.88), a fair test for discriminating mild (A) from moderate (B) CTS (c-statistic: 0.73) and a poor test for differentiating between moderate and severe (C) CTS (c-statistic: 0.60). WFR was a satisfactory test for differentiating patients with mild CTS from normal individuals (c-statistic: 0.89), a fair test for discriminating mild from moderate CTS (c-statistic: 0.70) and a poor test for differentiating between moderate and severe CTS (c-statistic: 0.58).

The c-statistics of ROC curves evaluating the diagnostic utility of CSA and WFR for CTS severity grading were similar (Fig. 4; p for De Long statistics across all comparisons >0.1). On the other hand, the c-statistic of the ROC curve evaluating the diagnostic utility of CSA and WFR to differentiate controls from mild CTS was significantly higher (p for De Long statistic <0.0001) than the c-statistics of the ROC curves assessing the diagnostic utility of CSA and WFR to differentiate moderate from mild CTS and severe from moderate CTS (Fig. 5, asterisks).

3.4. Correlations between CSA, WFR and electrodiagnostic CTS severity stratified by age

3.4.1. Younger group (<65 years)

In the group of patients aged <65 years, both CSA and WFR values were markedly different across the subgroups stratified by CTS severity (Table 4, Fig. 6), indicating that abnormal ultrasound findings were more pronounced in patients with more severe CTS. ROC curve analysis (Fig. 6) showed that WFR and CSA are excellent tests to distinguish healthy individuals from mild CTS patients and satisfactory tests to distinguish patients with mild from moderate CTS and patients with moderate from severe CTS. The c-statistics of the ROC curves of CSA and WFR for grading CTS severity did not differ significantly (p for De Long statistics across all comparisons >0.1). On the other hand, the c-statistic of the ROC curve evaluating the diagnostic utility of CSA and WFR to differentiate controls from mild CTS was significantly higher than the c-statistics of the ROC curves assessing the diagnostic utility of CSA and WFR to

Table 4
Diagnostic utility of median nerve cross-sectional area at the wrist (CSA) and wrist to forearm ratio (WFR) for carpal tunnel syndrome (CTS) severity stratified by age.

	CSA (cm^2, median)	p^	c-statistic (95%CI)	Cut-off value^^ (cm^2)	Sens (95%CI) Spec (95%CI)	WFR (median)	p^	c-statistic (95%CI)	Cut-off value^^ (cm^2)	Sens (95%CI) Spec (95%CI)
Overall										
Control group	0.07					1.25				
Mild CTS (A)	0.11	$3.5 * 10^{-31}$	0.88 (0.85–0.92)	0.09	74 (67–80) 86 (79–92)	1.83	$1.5 * 10^{-32}$	0.89 (0.86–0.93)	1.6	72 (65–78) 94 (88–98)
Moderate CTS (B)	0.13	$4.3 * 10^{-16}$	0.73 (0.68–0.78)	0.11	74 (67–79) 66 (59–73)	2.2	$9.7 * 10^{-13}$	0.70 (0.65–0.75)	1.67	67 (57–76) 69 (62–75)
Severe CTS (C)	0.15	$1.6 * 10^{-3}$	0.60 (0.54–0.67)			2.4	0.024	0.58 (0.51–0.64)		
Age < 65 y										
Control group	0.07					1.2				
Mild CTS (A)	0.11	$1.2 * 10^{-22}$	0.90 (0.85–0.94)	>0.08	88 (82–93) 77 (66–86)	1.83	$6.3 * 10^{-25}$	0.92 (0.88–0.95)	>1.5	82 (75–88) 89 (80–95)
Moderate CTS (B)	0.13	$1.4 * 10^{-18}$	0.79 (0.74–0.93)	>0.11	81 (74–87) 65 (57–73)	2.33	$1.8 * 10^{-13}$	0.74 (0.69–0.79)	>1.83	83 (77–89) 52 (44–61)
Severe CTS (C)	0.18	$2.6 * 10^{-9}$	0.82 (0.76–0.87)	>0.15	77 (60–90) 74 (67–80)	3.16	$2.9 * 10^{-7}$	0.78 (0.71–0.83)	>2.8	63 (45–79) 85 (79–90)
Age ≥ 65 y										
Control group	0.08					1.30				
Mild CTS (A)	0.11	$2.6 * 10^{-9}$	0.83 (0.74–0.90)	>0.09	69 (54–81) 81 (67–91)	1.83	$1.9 * 10^{-8}$	0.83 (0.74–0.90)	>1.6	65 (50–78) 94 (83–99)
Moderate CTS (B)	0.11	0.69	0.53 (0.44–0.68)			2.16	0.11	0.61 (0.48–0.71)		
Severe CTS (C)	0.14	0.015	0.65 (0.51–0.71)			2.14	0.59	0.53 (0.45–0.66)		

Sens: Sensitivity; Spec: Specificity; CI: Confidence Interval.
^ p by Mann-Whitney U-test between Con-A, A-B and B-C.
^^ Optimal cut-off values were defined on the basis of the highest Youden index.

differentiate moderate from mild CTS and severe from moderate CTS (p for De Long statistic <0.05 for CSA and p < 0.001 for WFR; Fig. 5, asterisks).

In order to further examine whether ultrasound findings are strongly correlated with the electrodiagnostic grading of CTS, we focused on 92 patients in whom both wrists were examined and the severity of carpal tunnel between the two sides differed by one grade (i.e. Con-A, A-B, B-C). The results of the EDx and HRUS agreement are shown in Fig. 7. Ultrasound and EDx studies were in accordance in 86%, 80% and 79% of the cases in the three wrist pair groups studied. Intra-class correlation coefficient was 0.84 (95%CI 0.65–0.93), 0.75 (95%CI 0.55–0.86) and 0.74 (95%CI 0.32–0.90) respectively.

3.4.2. Older group (≥65 years)

Older patients with mild, moderate and severe carpal tunnel syndrome had very significantly higher median CSA and WFR values than controls ($p = 2.6 * 10^{-9}$ and $1.89 * 10^{-8}$ between subgroup A and Con, $p = 6 * 10^{-6}$ and $4.62 * 10^{-9}$ for comparisons between subgroup B and Con, $p = 3.45 * 10^{-13}$ and $1.63 * 10^{-12}$ for comparisons between subgroup C and Con; Fig. 8). On the other hand, older patients with moderate CTS did not differ significantly in CSA values from those with mild CTS (p = 0.691), but had lower CSA values from those with severe CTS (p = 0.015; Table 4). In other words, HRUS measures did not follow EDx grading of CTS in this age group. In addition, older patients with moderate and severe CTS had significantly lower median CSA and WFR values than the corresponding measurements in the younger group (p = 0.0005 and 0.00072 for CSA and WFR comparisons in younger and older patients with moderate CTS and $p = 6.0 * 10^{-6}$ and $3.5 * 10^{-5}$ for CSA and WFR comparisons in younger and older patients with severe CTS). Taken together these findings indicate that WFR and CSA are good screening tests for the diagnosis of CTS in older patients (Fig. 3), while their diagnostic utility for discriminating patients with CTS of different severity is poor (Table 4; Fig. 8).

4. Discussion

The first observation of this large case-control study was that the association of increases in CSA and WFR with presence and severity of CTS is consistent only for subjects aged <65. A previous study (Miwa and Miwa, 2011) has shown that in patients with severe CTS aged >80 y the median CSA is significantly reduced. The researchers hypothesized that in very elderly patients CSA may not be a reliable measurement for the evaluation of severe-grade CTS. In our dataset, in patients over 65 y with moderate and severe CTS, disease-related increases in CSA and WFR were negatively

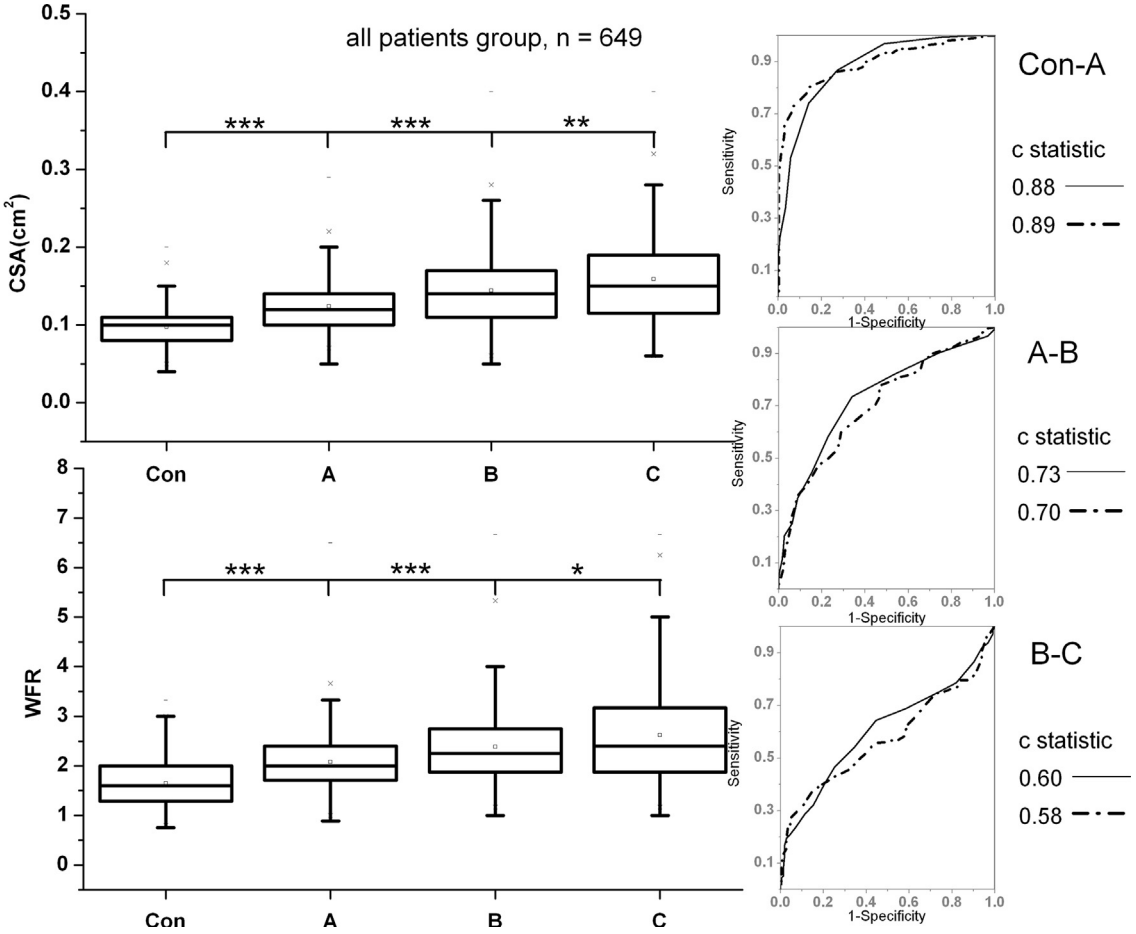

Fig. 4. CSA and WFR by CTS severity, irrespectively of age (Control = Con, mild = A, moderate = B, severe = C). Left: Box charts of CSA and WFR values for different grades of CTS severity. Both CSA and WFR measurements were significantly different between patients with different grades ($^{*}p < 0.05$, $^{**}p < 0.0001$, $^{***}p < 0.00001$). Right: ROC analysis for CSA (solid line) and WFR (dash dot) shows that CSA and WFR are good screening tests for discriminating mild CTS from control (Con-A), fair screening tests for discriminating mild from moderate CTS (A-B) and poor screening tests for discriminating moderate from severe CTS (B-C).

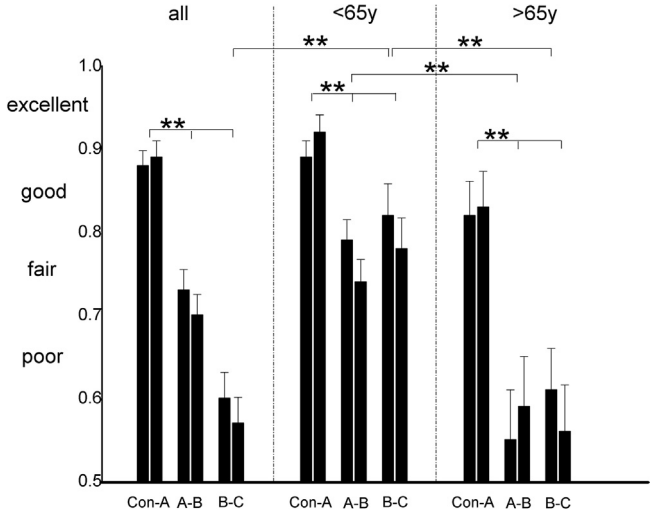

Fig. 5. Summary column graph presenting the capability of HRUS measures in CTS grading in the three age groups studied (all, <65 y and ≥65 y) (Control = Con, mild = A, moderate = B, severe = C). First part of each double column: CSA. Second part of each double column: WFR. In every group, the ability of CSA and WFR to discriminate patients with mild CTS from controls is better than discriminating A from B and B from C (double asterisk, $p < 0.0001$). Furthermore the ability of CSA and WFR to discriminate B from C is better in the younger age group than in the other two groups (double asterisk, $p < 0.0001$). Finally, the ability of CSA, WFR to discriminate between A and B is better in the younger than in the older age group (double asterisk, $p < 0.0001$).

correlated with increasing age, thus confirming and extending the finding of the previous study (Miwa and Miwa, 2011). This finding has several implications. For one, it limits the utility of CSA and WFR as screening tests in the older population, since HRUS accuracy for CTS diagnosis in this age group is satisfactory but not excellent (c-statistic for CSA 0.85, for WFR0.86). Second, it highlights that CSA and WFR have limited value in grading CTS severity in older patients.

Current practice guidelines (Cartwright et al., 2012) of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) underscore CSA as an accurate diagnostic test for CTS diagnosis and advocate that it should be used to screen for structural abnormalities in patients with CTS. The sensitivity and specificity of the optimal cut-off value of CSA in our study (0.09 cm^2) falls in the middle of those reported (0.07–0.11 cm^2) in previous class I studies (Cartwright et al., 2012), supporting the concept of CSA as an accurate screening test for CTS diagnosis. In addition, the sensitivity and specificity of the optimal cut-off value of WFR (1.6) also parallels the results of previous studies (Miyamoto et al., 2016). The present study provides original information introducing the notion that both CSA and WFR are less accurate as screening tests in patients older than 65 years.

The following hypotheses may account for the reduced CSA and WFR values in older patients (>65 y). It is well known that the principal underlying mechanism of median nerve swelling in CTS is oedema formation (Faithfull et al., 1986; Fuchs et al., 1991). Furthermore, in cases of long-standing severe compressive

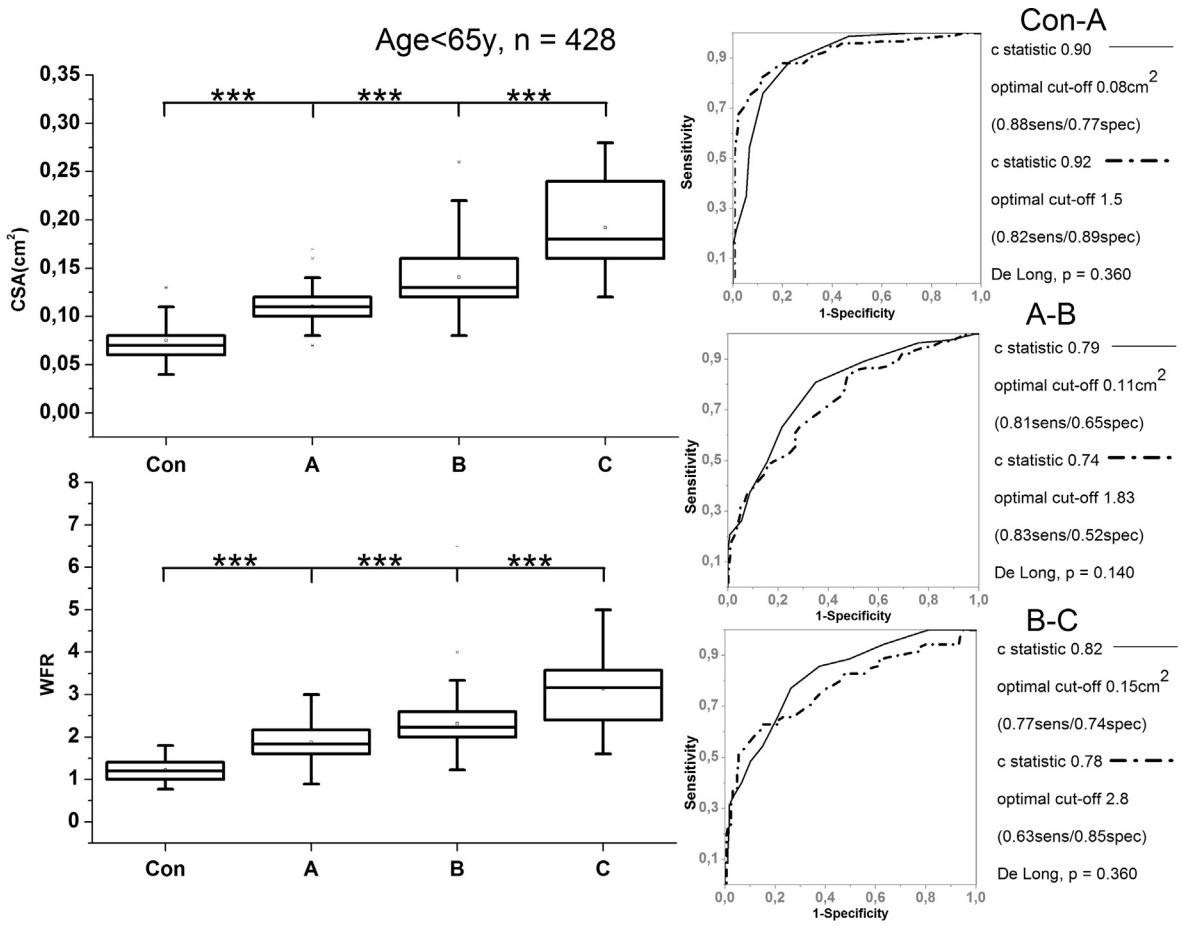

Fig. 6. CSA, WFR and CTS severity in the <65 y patient group. Left: box charts of CSA and WFR values for different grades of CTS severity (Control = Con, mild = A, moderate = B, severe = C). Both CSA and WFR measurements are different between patients with different grades of CTS severity (*** $p < 0.00001$). Right: ROC analysis for CSA (solid line) and WFR (dash dot) shows that CSA is an excellent screening test for discriminating mild CTS from control and a good screening test for discriminating mild from moderate CTS and moderate from severe CTS. Values of c-statistics as well as optimal cut-offs of CSA and WFR for discrimination between severity groups are presented on the right of the figure. Differences of the c-statistics between CSA and WFR were not significant (p for De Long statistics across all three comparisons >0.1).

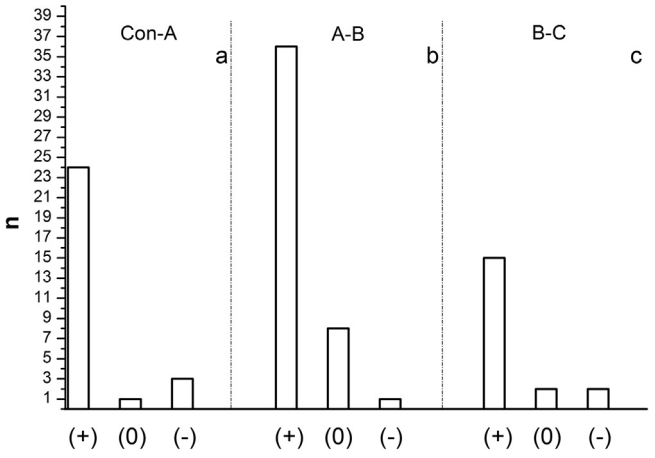

Fig. 7. Histogram showing the agreement of HRUS findings with EDx studies in younger patients (<65 y) who were examined bilaterally and were found to have EDx grading of CTS differing by one grade between sides (Control = Con, mild = A, moderate = B, severe = C). (a) 28 patients with no CTS in one hand and mild CTS in the other were included. HRUS detected CTS on the correct side in 24 patients (+), found no difference in one patient (0) whereas detected CTS on the wrong side in three patients (−). (b) 45 patients with mild CTS on one side and moderate CTS on the other side were included. HRUS detected the side with more severe CTS in 36 patients (+), found no difference between sides in 8 of them (0) whereas showed wrong results in one patient (−). (c) 19 patients with moderate CTS on one side and severe CTS on the other were included. HRUS detected the side with more severe CTS in 15 patients (+), found no difference between sides in 2 of them (0) whereas showed wrong results in 2 patients (−).

neuropathies, atrophy of the nerve and degeneration of axons has been described. In addition, the ability for oedema formation may be limited in elderly individuals (Verdú et al., 2000). Consequently, it may be assumed that the degree of swelling of median nerve at carpal tunnel inlet may be reduced in elderly patients with chronic moderate to severe CTS.

We also documented that WFR and CSA have similar diagnostic yield for CTS diagnosis and grading of severity. Our findings are partially at variance with the small pilot study of Hobson-Webb (Hobson-Webb et al., 2008) that proposed WFR measurement as a more sensitive diagnostic test for CTS. Nevertheless, a follow-up study by the same group conducted in a larger patient sample showed less robust performance of WFR (Mhoon et al., 2012). Our results are more in line with a Dutch study which, after evaluating a large sample of patients, concluded that these two ultrasound parameters have similar diagnostic accuracy for the screening of CTS (Visser et al., 2008).

The potential correlation between CSA and WFR with EDx grading of CTS is a matter of current debate. Most of the previous studies agree that the mean values of CSA and WFR increase when CTS severity also increases (El Miedany et al., 2004; Karadağ et al., 2010; Kim et al., 2014; Kutlar et al., 2017; Lee et al., 2005; Padua et al., 2008; Yurdakul et al., 2016). However, other investigators either failed to reproduce this correlation or questioned the clinical utility of HRUS in grading of CTS severity (Kaymak et al., 2008; Mhoon et al., 2012; Mondelli et al., 2008). Our finding that strong positive associations of CSA and WFR with CTS severity are present

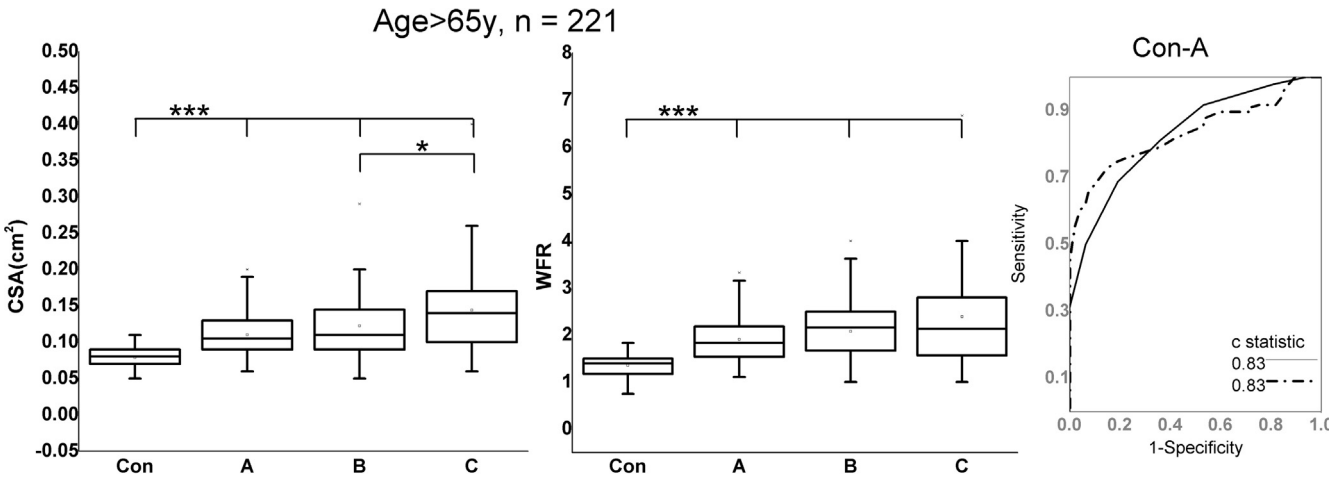

Fig. 8. CSA, WFR and CTS severity in the ≥65 y patient group. Left & middle: Box charts of CSA and WFR values for different grades of CTS severity (Control = Con, mild = A, moderate = B, severe = C). Both CSA and WFR measurements are highly significantly different between patients with different grades of CTS severity and controls (*** $p < 0.00001$). However, differences are no or weakly significant between (A) and (B) or (B) and (C) (* $p < 0.05$). Right: ROC analysis for CSA (solid line) and WFR (dash dot) for discriminating mild CTS from control.

only in subjects aged <65 y may in part account for the controversy.

Very few researchers have provided quantitative measures of CSA and WFR diagnostic accuracy in CTS grading (El Miedany et al., 2004; El Habashy et al., 2017). In one of these (El Habashy et al., 2017), WFR was used for grading CTS severity. The investigators reported WFR as an excellent diagnostic test to discriminate controls from patients with mild CTS, a fair diagnostic test to discriminate moderate from mild CTS and a poor diagnostic test to discriminate severe from moderate CTS. They claimed that their findings may be partly attributed to the small sample size of their study. Interestingly, our results indicate that age represents a critical factor, which highlights the limitations of small sized samples. More specifically, the decrease of median CSA and WFR values in moderate and severe CTS that is observed in older patients appears to attenuate the differences between the different grades of CTS in this age group. The net result is that CSA is a good diagnostic test in discriminating different grades of CTS in younger patients only.

Certain limitations of the present report need to be acknowledged. First, our results do not apply to CTS patients who were excluded because of comorbidities such as diabetes, polyneuropathy or radiculopathy. Further studies specifically addressing these patient groups are needed to clarify whether or not our conclusions can be extended to them. Another limitation was that symptom duration was not documented and could not be evaluated as a potential confounder. Furthermore, the intra- and inter-rater reliability of the two sonographers in CSA and WFR measurements should have ideally been evaluated in a pilot study. Finally, we chose not to include nerve echogenicity measurements as part of the present project and therefore we were unable to investigate if evaluation of this parameter may increase the diagnostic yield of HRUS in CTS diagnosis and grading.

In conclusion, this is to our knowledge the largest case-control study evaluating the diagnostic utility of HRUS in CTS diagnosis and grading. Our findings highlight the impact of aging on the most commonly used ultrasonographic measurements (CSA, WFR) in assessing compressive median nerve pathology. We show that both CSA and WFR are excellent diagnostic tests for CTS (with sensitivity and specificity reaching 90%) in patients younger than 65 y. Moreover, these measurements have satisfactory accuracy (sensitivity and specificity ranging between 70% and 80%) in evaluating CTS severity in this specific age group. On the other hand, in patients older than 65 y, HRUS can be used only as a good screening tool for CTS diagnosis, but cannot reliably assess CTS severity. Further research, probably assessing sonographic parameters beyond CSA and WFR, especially in elderly patients, is required to overcome the confounding role of age on the diagnostic accuracy of HRUS in CTS.

Author statements

Christos Moschovos: literature search, figures, study design, data collection, statistical analysis, data interpretation, writing.

Georgios Tsivgoulis: literature search, figures, study design, data collection, statistical analysis, data interpretation, writing.

Andreas Kyrozis: study design, statistical analysis, data interpretation, writing.

Apostolia Ghika: data interpretation, writing.

Persefoni Karachalia: data interpretation, writing.

Konstantinos Voumvourakis: data interpretation, writing.

Elisabeth Chroni: data analysis, data interpretation, writing.

Conflict of interest

Dr. Moschovos, Dr. Tsivgoulis, Dr. Kyrozis, Dr. Ghika, Ms. Karachalia, Dr. Voumvourakis and Dr. Chroni report no disclosures.

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