Cross-Sectional Area Reference Values of Nerves in the Upper and Lower Extremities using Ultrasonography in the Indian Population

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Abstract

Background and Purpose: Cross-sectional area (CSA) is the most important parameter to study peripheral nerves by high-resolution ultrasonography. The aim was to acquire normative data of CSA of the main upper and lower limb nerves in the Indian population. Methods: CSA of nerves was determined in 100 healthy volunteers at 11 predetermined sites: median and ulnar at the wrist, mid-forearm, elbow; radial (spiral groove); tibial (popliteal fossa, medial malleolus); common peroneal (CPN, fibular head) and sural (lateral malleolus). Results: The mean age of participants was 40.7 ± 13.0 years (range: 18-79). Fifty were < 40 years of age. The mean height, weight and BMI were 161.5 ± 8.3 centimeters (range: 145—179), 58.6 ± 10.1 kilograms (range: 32–90) and 22.4 ± 3.2 kilogram/square meter (range: 14.03-30.44), respectively. The median and ulnar nerve measurements were non-uniform throughout its course, and the CSA was largest at the elbow and ulnar groove, respectively. With advancing age, there was a significant difference for median and ulnar nerves at the wrist (median P = 0.002, ulnar P = 0.009) and tibial nerve (popliteal fossa, P = 0.045, medial malleolus, P = 0.005), CPN (P = 0.047). Men had greater CSA of upper limb nerves and tibial nerves at popliteal fossa (P < 0.05) as compared to women. A positive correlation was noted with weight. Conclusion: It is apt for every defined population to have its own set of normative data of CSA as it varies with ethnicity, age, and the built of individuals. We provide a valuable set of CSA data for nerves in the Indian population, which can be used for comparison while investigating peripheral nerve disorders.

Keywords: Cross-sectional area, India, normative data, peripheral nerve, ultrasound

Introduction

High-resolution ultrasonography (HRU) is a rapidly evolving technique for assessing the peripheral nerves and brachial plexus in several disease conditions like nerve entrapment, hereditary, inflammatory, demyelinating, infectious (leprosy), and diabetic neuropathies.1,2 Prior to the advent of HRU, evaluation of peripheral nerve disease primarily consisted of history, clinical examination, and electrodagnostic studies. However, electrodiagnostic studies evaluate only the functional aspects of the nerve. HRU addresses this limitation by permitting direct assessment of nerve anatomy and its surrounding structures.3 It is non-invasive and easy to perform. Ultrasound machines are radiation-free, compatible with metal implants, and portable, allowing fieldwork. They provide dynamic real-time high-resolution imaging of the peripheral nerves.3 When compared with magnetic resonance imaging (MRI), HRU has a higher sensitivity and equivalent specificity in clinically accessible regions and in detecting multifocal nerve lesions.4

The most widely used parameter to assess the peripheral nerve is the cross-sectional area (CSA). Normative data of nerves in a population is crucial in differentiating from pathological conditions. Studies have shown significant differences in the normative data of the CSA, depending on gender, physical and geographic differences.5-7 A study from India reported that CSA of the median and ulnar nerve was largest at the wrist and was proportional to aging.5,9 In contrast, constant median nerve CSA was reported throughout its course in another study.10 Hence, there is a need to explore the implications of the differences that have been inferred from the studies.

There are a limited number of studies on the CSA of various nerves in the Indian population.5,8,9 The aim of this study was to acquire normative data of CSA of upper and lower limbs nerves at predetermined sites in healthy Indian adult subjects and to correlate with age, gender, height, and body

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mass index (BMI). These normative data are important for the assessment of abnormal nerves in patients with entrapment neuropathies, mononeuritis multiplex, and polyneuropathies.

**Methods**

This prospective, cross-sectional study was carried at a quaternary care center for neurological disorders in India between January 2019 and August 2020. Around 100 to 150 cases with neurological disorders are evaluated daily at the outpatient services, and 3-4% of the cases are likely to have acquired or inherited peripheral nerve disorders. This study was approved by the institutional ethics committee [NO.NIMH/DO/IEC (BS & NS DIV)/2018-19]. Informed written consent was obtained from all the participants.

Healthy adult volunteers (18-80 years) who are residents of India, including relatives and caregivers of the in-patients, admitted to our hospital, institute employees, and medical students were recruited. Pregnant women, alcoholics (>14 units/week for men and >7 units/week for women), subjects with co-morbidities (diabetes, hypothyroidism, obesity (BMI > 30)), preceding neurological illness or history of paresthesias, fasciculations, thinning, weakness, trauma, sensory loss, hereditary neurological illness in the family, abnormal neurological examination or electrophysiological studies were excluded from the study.

Demographic and anthropometric data were collected regarding age, gender, handedness, height, weight, BMI, along with symptoms of systemic and neurological illness. A systemic and neurologic examination was performed. Participants underwent random blood sugar testing (RBS) to look for undetected diabetes (glucometry) and motor conduction of the right ulnar nerve and common peroneal nerve (CPN) using the belly tendon method. The compound muscle action potential (CMAP) latency, amplitude, and velocity were noted.

Power and color doppler modes were used. To avoid anisotropy, the transducer was placed perpendicular to the nerve, and pressure applied was minimized to prevent deformation of the structures underneath. The inner border of the thin hyperechoic epineural rim was traced at every site using the trace function. The intra-observer variability was assessed by repeat ultrasonography on 10 participants after a minimum time gap of 1 month. Inter-observer variability was assessed on 10 participants by another ultrasonographer (JS) who was blinded to the values obtained by the first examiner.

Statistics were performed using IBM SPSS version 22 for windows. Descriptive statistics were used to present basic demographic data of the study population. The mean and standard deviation for age, height, weight, BMI, and CSA of nerves were calculated. The reference range was calculated as mean ± 2 standard deviations. Normality was tested using the Shapiro-Wilk test, and as some of the values did not

**Figure 1:** USG cross section images of median and Ulnar nerves: Median nerve at wrist (a), at mid forearm between the flexor digitorum superficialis and flexor digitorum profundus (b) and at the elbow medial to the brachial artery (c), Ulnar nerve at the wrist beside the ulnar artery (d), at the mid forearm beside the ulnar artery (e) and at the elbow between the olecranon and medial epicondyle (f).
follow a normal distribution, non-parametric tests were used. Spearman’s rank correlation coefficient and multivariate linear regression analysis were used to evaluate the relation between CSA and age, gender, weight, and height. Mann-Whitney U test was used to compare the variation in CSA of nerve segments with respect to the gender of the participants. Chi-square and Friedman tests with Dunn’s correction were used to compare the CSA at various levels of median and ulnar nerves. Inter-rater variability was evaluated using intraclass correlation coefficient, and intra-rater variability was evaluated using Wilcoxon signed-rank test.

**Results**

A total of 105 participants were recruited for the study. Five participants were excluded: abnormal conductions (n = 2), newly detected diabetes mellitus (n = 2), and bifid median nerve (n = 1). Hundred healthy participants (M:F = 1:1) underwent ultrasonography of nerves of the right upper and lower limb.

The mean age of the healthy participants was 40.7 ± 13.0 years (range, 18-79). Among the 100 participants, 50 (50%) were less than 40 years of age. The mean height, weight and BMI was 161.5 ± 8.3 centimeters (range: 145‑179), 58.6 ± 10.1 kilograms (range: 32‑90) and 22.4 ± 3.2 kilogram/square meter (range: 14.03‑30.44), respectively.

The mean, standard deviation, and range of CSA measurements of all 11 nerve segments for men (n = 50) and women (n = 50) are presented in Table 1, Figures 1 and 2. The CSA of the median nerve was not uniform. It was greatest at the elbow and least at the forearm. The CSA of the ulnar nerve was greatest at the elbow, with uniform CSA between the wrist and mid-forearm level.

Mann-Whitney U test was used to compare the variation in CSA of nerve segments with respect to the gender of the participants. Men had significantly higher CSA values compared to women at all sites except the median nerve at the wrist and posterior tibial nerve at the medial malleolus [Table 1].

A statistically significant and positive weak to fair correlation was found between age and the CSA of median and ulnar nerve at the wrist, the tibial nerve at popliteal fossa, and medial malleolus and CPN at the fibular head. A statistically significant and weak positive correlation was seen between the height and CSA at all measured sites except the median nerve at the wrist. A moderate positive correlation was seen between the CSA of the tibial nerve at popliteal fossa and weight. All the other nerves except the radial nerve showed a weak positive correlation with weight [Table 2].

Multivariate regression analysis showed a significant association between the age and CSA of nerves at entrapment sites in the upper limb like median and ulnar at the wrist, ulnar at the elbow, tibial at popliteal fossa and medial malleolus, and CPN at the fibular head. Regression analysis also showed that men, in general, had larger CSA for upper limb nerves and also for the tibial nerve at the popliteal fossa. The weight of the subjects showed consistent relation with nerve CSA at most sites. However, the relation between height and CSA was inconsistent in the regression analysis [Table 3].

Intra-rater variability was evaluated using Wilcoxon signed-rank test, and there was no significant difference between the values obtained by a single observer at two-time frames [Table 4]. Inter-rater variability was evaluated using the intraclass correlation coefficient (ICC). The coefficient values were between 0.86 and 1, which indicated a good reliability [Table 5].

**Discussion**

This study aimed at providing reference values of the common upper and lower limb nerve CSAs for the Indian population. We recruited 100 healthy participants to generate reference values for CSA of nerves at 11 predetermined

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**Figure 2:** USG cross section images of radial and lower limb nerves: Radial nerve at the spiral groove (a), Tibial nerve at the popliteal fossa, just above the popliteal vein (b) and posterior to the medial malleolus in relation to the posterior artery and vein (c), Common peroneal nerve lateral to the fibular head (d) and Sural nerve at the lateral aspect of the distal leg, lateral to the lesser saphenous vein (e)
sides: median and ulnar at the wrist, mid-forearm and elbow, radial (spiral groove), tibial (popliteal fossa, medial malleolus), CPN (fibular head), and sural (lateral malleolus). The group represented an equal number of men and women with ages ranging from 18 to 79 years. The demographics of our cohort more or less represent the average demographic values of the population.\(^{[12]}\) Our study evaluated CSA only on the right side as previous studies have shown no significant side-to-side variation in CSA of nerves.\(^{[13-16]}\) Inter-observer variability of nerve ultrasound in peripheral neuropathy is generally limited, especially for nerves in the arm. Different devices and a multicenter setting have shown no effect on the inter-observer variability. Therefore, nerve ultrasound is a reproducible investigational method for diagnostics in routine exam.
We performed the intra-rater variability using Wilcoxon signed rank test. The intra-rater variability was high for the ulnar nerve at the ulnar groove, followed by the radial and ulnar nerves. This emphasizes that the CSA of nerves can be measured reliably with HRU. However, reference values of CSA of lower limb nerves vary considerably among different studies. The borders of the nerves of the lower limbs are not clearly visible due to the echogenic properties of the surrounding tissues. The CPN at the fibular head has an oblique course, and hence minimal tilting of the probe can lead to discrepancies in the values of the CSA. These reasons account for the wide variability in the CSA values in different studies of the lower limb nerves.

The CSA values in the present study correlated well with previous studies from India and China \[^{8,9,20}\] while other studies have reported marginally greater values. This variation is probably due to the difference in body habitus and ethnicity. The weight of the participants in these studies (74-77 kg) was higher compared to the mean weight of our cohort (58.6 kg). The CSA values of the nerves in previous studies and the present study are summarized in Table 6.

The CSA of median and ulnar nerves were not uniform throughout their course in the current study. The CSA of the median nerve was largest at the elbow, followed by CSA at the wrist and mid-forearm. This may be due to the measurement of the nerve prior to branching and the increased CSA at the wrist due to branching of the nerve fibres within the nerve distally.\[^{16}\] In another Indian study, the CSA of the median nerve was largest at the wrist, but in their study, the CSA at the elbow was not evaluated.\[^{9}\] The largest CSA of the ulnar nerve was at the ulnar groove, which is consistent with findings from other studies.\[^{8,18,20}\] The ulnar nerve at the ulnar groove is a common site of entrapment which explains the larger CSA compared to the other sites. However, in few previous reports, the median and ulnar nerve did not vary widely in CSA throughout their course.\[^{10,22}\]

In the current study, median and ulnar nerves at the wrist and all lower limb nerves were larger with advancing age except the sural nerve, which is similar to findings in earlier studies.\[^{8,9,14-16,20}\] However, few studies found no correlation with age.\[^{1,19,21}\] A study from Germany reported that median nerve in the axilla and radial nerve in spiral groove had decreased CSA with advancing age, and tibial nerve at the ankle showed higher CSA with advancing age.\[^{7}\] The possible explanations given for lower CSA were loss of nerve fibres and degeneration as the age advances and increase in the non-neural elements like connective tissue within the nerve, presence of macrophages, onion bulbs etc., for increased CSA.\[^{7}\] The age group in the above study was a decade higher than most of the studies, including the present study. However, another study with a similar age group did not find any correlation with age.\[^{1}\] In our study, the CSA of radial nerve did not correlate with age as shown in the previous studies.\[^{14,15,21,23}\] Nevertheless, another study reported a statistically significant weak positive correlation between age and radial nerve at spiral groove.\[^{6}\]

The men in our study had a greater CSA when compared to women in the median and ulnar measurements, except the median nerve at the wrist, which is consistent with the previous reports.\[^{8,10,15,18,20}\] However, a German study reported no correlation of gender with CSA at most sites in the upper limb.
**Table 6: Comparison table showing CSA of upper and lower limb nerves with other published studies**

| Parameters | Present Study | Bathala et al[8][9] | Boehm et al[10] | Cartwright et al[11] | Bedewi et al[12][13][14] | Kerasnoudis et al[15] | Seok et al[16][17] | Qrimli et al[18] | Tagliflorio et al[19] | Won et al[20][21] | Sugi moto et al[22] | Niu et al[23][24] |
|------------|---------------|---------------------|----------------|---------------------|-------------------------|-----------------------|------------------|----------------|-------------------|-----------------|------------------|------------------|
| Year       | 2021 | 2014/2012 | 2014 | 2008 | 2018 | 2013 | 2014 | 2016 | 2013 | 2013 | 2013 | 2020 |
| Country    | India | India | Hungary | USA | Egypt | Germany | South Korea | Canada | Italy | South Korea | Japan | China |
| Number     | 100 | 100 | 56 | 60 | 69 | 75 | 100 | 60 | 97 | 60 | 111 |
| Age (years) | 40.7±3.0 | 39.1±1.4 | 51.8±16.4 | 45.9 | 38.3±12.13 | 53.46±14.8 | 41.4±18.4 | 44.1±18.4 | 44.1±18.4 | 35.4±9.7 | 41.69±15.80 |
| Height (cm) | 161.51±8.28 | 160±10 | 171±9 | 168 | 161.48±9.8 | 175±9 | 165.2±9.0 | 165.2±9.0 | 164±10 | 167.07±8.31 |
| Weight (kg) | 58.6±10.06 | 59.3±11.3 | 75.4±13 | 74.5 | 77.14±18.4 | 77.9±10.68 | 62.8±12.2 | 63.1±12.2 | 60.0±12.1 | 65.34±11.06 |
| BMI (kg/m²) | 22.4±3.15 | 22.9±3.5 | 26.5 | 29.31±6.64 | 22.9±3.1 | 25.3±5.3 | 30.70 | 29.31 | 47.50 | 37.0 |
| M/F | 50:50 | 50:50 | 26:30 | 22.38 | 45:30 | 44.50 | 50:50 | 50:50 | 47:50 | 29:31 | 29:31 |
| Wrist level Median (mm²) | 7.42±1.39 | 7.2±1 | 8.5±1.8 | 9.8±2.4 | 9.77±2.88 | 8.43±2.07 | 10.0±2.4 | 8.2±2.3 | 8.33±1.52 | 8.5±1.7 | 6.0±0.9 |
| Forearm Median (mm²) | 5.1±0.91 | 4.8±0.9 | 5.7±1.3 | 5.7±1.3 | 6.4±2.05 | 6.6±1.6 | 7.3±1.7 | 5.5±2.2 | 6.5±1.05 | 5.6±1.1 | 5.4±0.8 |
| Elbow Median (mm²) | 7.7±1.6 | 8.6±2.3 | 11.12±3.94 | 9.7±1.9 | 9.4±3.1 | 9.4±3.1 | 8.1±2.4 | 9.4±3.1 | 8.2±1.7 | 7.8±1.1 | 7.1±1.2 |
| Axilla Median (mm²) | 6.1±1 | 8.9±1.8 | 5.9±1.1 | 4.07±1.56 | 5.16±1.03 | 5.0±1.7 | 3.1±1.0 | 4.28±0.78 | 4.1±1.0 | 2.9±0.5 |
| Axilla Median (mm²) | 5.9±0.9 | 5.9±1.1 | 4.07±1.56 | 5.16±1.03 | 5.0±1.7 | 3.1±1.0 | 4.28±0.78 | 4.1±1.0 | 2.9±0.5 |
| Wrist Ulnar (mm²) | 4.43±0.79 | 3.6±0.5 | 5.46±1.26 | 6.2±1.5 | 6.30±1.0 | 4.6±0.8 | 4.2±0.8 |
| Forearm Ulnar (mm²) | 4.52±0.83 | 4.1±0.6 | 5.2±1.3 | 6.3±1.0 | 5.52±1.90 | 5.46±1.26 | 6.2±1.5 | 6.30±1.0 | 4.6±0.8 | 4.2±0.8 |
| Elbow Ulnar (mm²) | 5.6±1.26 | 7.6±2.1 | 7.49±2.35 | 5.33±1.4 | 6.9±2.3 | 5.9±3.0 | 7.49±1.42 | 6.7±1.9 | 5.2±1.0 | 4.2±0.8 |
| Arm Ulnar (mm²) | 4.7±0.6 | 6.3±1.7 | 7.55±2.60 | 5.33±1.4 | 6.9±2.3 | 5.9±3.0 | 7.49±1.42 | 6.7±1.9 | 5.2±1.0 | 4.2±0.8 |
| Axilla Ulnar (mm²) | 4.28±0.69 | 4.3±0.5 | 6.2±1.1 | 7.9±2.7 | 5.70±1.93 | 6.53±1.82 | 7.1±2.9 | 4.58±0.85 | 2.00±0.53 | 4.2±0.8 |
| Arm Radial (mm²) | 4.28±0.69 | 4.2±1.0 | 7.9±2.7 | 5.70±1.93 | 6.53±1.82 | 7.1±2.9 | 4.58±0.85 | 2.00±0.53 | 4.2±0.8 |
| Forearm Radial (mm²) | 4.28±0.69 | 4.2±1.0 | 7.9±2.7 | 5.70±1.93 | 6.53±1.82 | 7.1±2.9 | 4.58±0.85 | 2.00±0.53 | 4.2±0.8 |
| Popliteal fossa Tibial (mm²) | 20.70±4.41 | 35.3±10.3 | 19.07±6.88 | 8.43±2.68 | 24.4±4.4 |
| Posterior Tibial (mm²) | 10.10±2.23 | 13.7±4.3 | 12.66±4.45 | 6.36±1.45 | 12.1±3.1 | 12.7±3.4 | 9.6±4 |
| Popliteal fossa CNP (mm²) | 11.7±4.6 | 9.71±4.07 | 8.6±1.77 | 10.4±2.7 | 11.8±3.8 |
| Fibula head CNP (mm²) | 9.39±2.12 | 11.2±3.3 | 8.89±3.23 | 7.1±2.3 | 9.2±2.9 | 11.1±3.5 | 13.2±14 |
| Sural (mm²) | 1.85±0.45 | 5.3±1.8 | 3.52±1.40 | 1.82±0.64 | 2.6±0.6 | 2.1±0.8 | 3.6±1.1 |

(Proximal calf) (Distal calf) (between the heads of gastrocnemius) (above lateral malleolus)
except for the ulnar nerve at the wrist. In this report, women had higher values of intra-nerve CSA variability compared to men.[19] In our study, the CSA of the radial nerve correlated with gender, similar to a previous study.[20] However, most of the studies reported no correlation with gender and CSA of radial nerve.[6,14,15,21] In our study, all lower limb nerves were larger in men except the posterior tibial nerve at the medial malleolus, which is similar to previous studies.[7,14] This is in contrast to a few other studies.[16,17,19]

In parallel to previous studies, the CSA at most of the sites in the median, ulnar and lower limb nerves showed a statistically significant weak correlation with weight.[10,14,16,18,20] Few studies have reported a positive correlation with both height and weight,[19,20] few only with height,[20] and the remaining did not find any correlation.[18,19,25] The CSA of radial nerve at spiral groove did not correlate with height and weight as reported in a previous study,[15] but a few other studies on radial nerve showed a strong correlation between CSA of the radial nerve and the individual’s weight and height.[14,21,23]

This study has a few limitations. Nerves were evaluated only on one side, and hence side to side variability was not assessed. Earlier studies have reported a strong correlation between wrist circumference and CSA of median and ulnar nerves.[18,26] Unfortunately, in the current study, the wrist circumference was not measured.

In conclusion, focal or diffuse thickening of a particular nerve can be easily appreciated or confirmed only when there is a set of established normative data for the given population. Reference values that have been established in previous reports from different countries show variation in the values and correlation studies due to different ethnicity, age and built of the participants, technique and the equipment used, different sites of measurement, and the skill of the examiner. Hence it is apt for every defined population to have its own set of normative data of ultrasonographic reference values of the nerves and this has been well established in the current study for Indians.

**Abbreviations**

BMI: Body Mass Index, CMAP: Compound Motor Action Potential, CPN: Common Peroneal Nerve, CSA: Cross Sectional Area, kg: kilogram, HRU: High Resolution Ultrasonography, MHz: Megahertz, mm: millimeter, MRI: Magnetic Resonance Imaging, RBS: Random Blood Sugar.

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**Ethical publication statement**

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate consent forms. In the form the participants (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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