

# Sural Radial Amplitude Ratio: A Study in Healthy Indian Subjects

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## Abstract

**Context:** The amplitude ratio of sural radial sensory nerve action potential is used as a sensitive measure for the diagnosis of an early distal axonal peripheral neuropathy. There is no age-stratified reference data available. **Aim:** To establish age-stratified sural radial amplitude ratio (SRAR) reference data in healthy Indian subjects. **Study Setting and Design:** The study was conducted in the electrodiagnostic laboratory of a tertiary city hospital and is an analytical, prospective, and field trial study. **Materials and Methods:** A prospective study was conducted on 146 healthy volunteers between 18 and 86 years, stratified into 6 groups, a = 18–30 years, b = 31–40 years, c = 41–50 years, d = 51–60 years, e = 61–70 years, and f = >70 years. Sural: Radial amplitude ratio was calculated. **Statistical Methods:** Stata 12.1 statistical program was used. Lower limit of SRAR was obtained (mean-2SD of transformed data). ANOVA defined the intergroup variability, and linear regression and Pearson's correlation assessed the statistical significance. **Results:** The lower limit of normal SRAR, for each age group is as follows: a: 0.30, b: 0.23, c: 0.20, d: 0.17, e: 0.17, and f: 0.08. SRAR of groups a, b, c was significantly different from groups e and f. Similarly, SRAR was significantly different between groups d and f but not between groups d and e or a, b, c, d. **Conclusion:** This study provides age-stratified reference data for SRAR. There is evidence to suggest that SRAR varies with age; hence, a single value of SRAR should not be used when diagnosing a peripheral neuropathy based on this criterion.

**Keywords:** Age-stratified, Indian population, reference data, SRAR

## INTRODUCTION

The sural sensory nerve action potential (SNAP) is the most frequently used and reliable nerve conduction study for the diagnosis of a length-dependent distal sensory or sensory-motor axonal peripheral neuropathy.<sup>[1-6]</sup> However, when the peripheral neuropathy is mild or early, the Sural SNAP amplitude may remain “within normal limits” for age, even when the patient is symptomatic as it has a wide variation even in the healthy subjects.<sup>[7,8]</sup> Medial plantar and dorsal sural SNAP study, F wave minimal latency from the tibial nerve, and denervation in lower leg and muscles of feet are the other tests to be included in the recommended criteria for diagnosing a distal peripheral neuropathy.<sup>[9-12]</sup> Recording the orthodromic medial plantar SNAP becomes a technical challenge in populations where footwear is not routinely used and the sole is very coarse. Dorsal sural SNAP can be absent due to local foot injuries, ill-fitting footwear, and callus formation due to sitting cross-legged on the floor.<sup>[13]</sup> Tibial minimal F wave latency should also be age and height matched to be useful as a sensitive parameter for detecting peripheral neuropathy and is not useful if the neuropathy is sensory. Denervation in the small muscles of the feet will be absent if the neuropathy is sensory. All of the above make it difficult to fulfill the recommended electrodiagnostic criteria in the diagnosis of a length-dependent distal axonal peripheral neuropathy. Some studies have utilized the ratio of the amplitude of the sural SNAP to that of the radial SNAP—called the sural radial amplitude ratio (SRAR) for detecting early or “sub-clinical,” axonal,

length-dependent peripheral neuropathy—when the absolute age-related sural SNAP amplitude is within normal limits.<sup>[14-23]</sup> The sural and radial SNAPs show significant correlation, and a length-dependent axonal peripheral neuropathy would cause a decrease in the sural SNAP amplitude before the superficial radial SNAP amplitude, hence lowering the SRAR early in the course of the neuropathy. Literature review of studies on SRAR, however, revealed a paucity of reference data for lower limit of normal<sup>[14-17,23]</sup> and only two studies have been done age-stratified<sup>[16,23]</sup> and none are on Indian subjects. Most studies showed that SRAR values are not affected by the age of the subject.<sup>[14-16]</sup> Early studies defined a single value for the lower limit of SRAR, some as 0.21<sup>[15,16]</sup> and others as 0.4.<sup>[14]</sup> Since these early studies, a single value of the SRAR has been used in other studies to determine the presence or

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absence of a peripheral neuropathy, irrespective of the age of the patient.<sup>[16-22,24,25]</sup> The diagnosis of a peripheral neuropathy is primarily confirmed by electrodiagnostic tests.<sup>[9]</sup> There are studies to show that electrodiagnosis is operator dependent and its utility in the diagnosis of peripheral neuropathy has been questioned;<sup>[26]</sup> hence, tests that increase the sensitivity of the procedure, without much increase in the time taken to perform the test, could increase the yield and aid diagnosis. Hence, this study was prospectively undertaken to define age-stratified SRAR reference values and determine whether SRAR varies significantly with age, height, gender, BMI, and stimulation site.

## SUBJECTS AND METHODS

This was a prospective, analytical, field trial study and part of it was conducted when we evaluated the sural SNAP reference data.<sup>[8]</sup> It was cleared by the Institutional ethics committee of our hospital. The subjects included in this study were:

1. Healthy volunteers
2. Healthy relatives who accompanied our patients
3. Patients referred to the department with unrelated conditions, which did not affect the lower motor neuron or peripheral nerves

Subjects with history suggestive of recent or past symptoms suggestive of a peripheral neuropathy, family history of an inherited neuropathy, frequent alcohol consumption (more than 2 drinks per day for more than 4 weeks), diabetes mellitus, treatment for tuberculosis, local trauma in the ankle or wrist region, and surgery on the back, neck, arm, or leg were not included in this study. Subjects were examined and only those with normal ankle jerks in the younger age group and preserved ankle jerks with preserved position sense in the older age group were included in this study. Patients who were referred for the electrodiagnostic test, but found to have normal tests were not included in this study.<sup>[27]</sup>

One hundred and fifty patients were included between 18 and 90 years and 4 patients were later eliminated due to local causes at recording site—old missed injury and edema. The study was spread over 5 years as it was difficult to get healthy subjects over the age of 70 years.

Anthropometric parameters of all subjects included age, weight, height, and BMI.

### Sensory nerve conduction study technique

Standard protocols<sup>[28]</sup> were followed for studying bilateral sural and radial SNAPs antidromically. The tests were done on Synergy ultra-pro electromyograph (Natus Medical Inc). Recording and acquisition parameters were: Filter settings: 3 Hz to 2 kHz, sweep speed: 20 millisecond (ms), amplitude gain setting: 10 microvolts per division ( $\mu\text{V}/\text{div}$ ), stimulus duration: 0.1 ms to 0.2 ms (in obese patients) with supramaximal intensity, and 8–10 responses were averaged after obtaining the best amplitude SNAP. The test was explained to the subject; the stimulating and recording sites were cleaned with spirit, and

temperature was maintained at 30°C at the lateral malleolus and 32°C at the wrist and was measured before, during, and after the test using a “Testo” digital skin thermometer. The limbs were warmed using a hairdryer. Onset latency and peak to peak amplitudes were measured of the SNAPs. All tests were done by neurophysiologists (physicians) trained in the same department and following identical protocols.

### Sural sensory nerve conduction<sup>[8]</sup>

Recorded with the subject in the opposite lateral position. Active recording (E1) electrode was placed just behind the upper border of the lateral malleolus and the reference electrode (E2) was placed 4 cm distal to it. The ground electrode (E0) was placed between the recording and stimulating electrodes after marking the stimulus sites along the lower leg at 10, 12, and 14 cm distances proximal to the active recording electrode.

### Superficial radial nerve sensory conduction

The test was done in the supine position, forearm was in prone position, with the E1 in the anatomical snuffbox and the E2, 4 cm distal to it. E0 was placed between the stimulating and recording electrodes after marking the stimulation sites 10, 12, and 14 cm proximal to the active electrode along the lateral border of the forearm. The sural: radial amplitude ratio was calculated for each stimulation site.

### Statistical analysis

The data was analyzed using the Stata Corp 12.2 (StataCorp LP, College Station, Texas) statistical software program. Summary statistics of the variables were obtained. The mean side-to-side amplitude difference was calculated as a ratio that was 0.99 at 14 cm, 0.97 at 12 cm, and 0.98 at 10 cm with standard deviation (SD) of 0.19. This was found to be statistically insignificant using the Student’s paired “t”-test ( $P > .05$ ). Also, the maximum difference in the side-to-side amplitude ratio at 14 cm, 12 cm, and 10 cm were 1.5, 1.5, and 1.6, respectively. Hence, the data from the right side only was included in this study. Two-sample t-test with unequal variances showed no statistically significant difference in the SRAR between males and females [ $t(133.749) = 1.2935, P = 0.198$ ]; hence, the data was pooled.

The SRAR values were not in the Gaussian distribution [Skewness/Kurtosis tests for Normality: Pr (Skewness) 0.0144, Pr (Kurtosis) 0.8608, adj Chi<sup>2</sup> (2) 5.83, Prob > Chi<sup>2</sup> 0.0543]. Hence, the data was optimally transformed using square root of the values [Pr (Skewness) 0.8948 Pr (Kurtosis) 0.1173 adj Chi<sup>2</sup> (2) 2.51 Prob > Chi<sup>2</sup> 0.2849] and then retransformed for calculating the lower limit of normal Scatter plot of age against the SRAR was plotted, which showed a linear correlation. The subjects were stratified by age into 6 groups: a = 18–30 years, b = 31–40 years, c = 41–50 years, d = 51–60 years, e = 61–70 years, and f >70 years. Statistical analysis for obtaining the lower limit of age-stratified value of SRAR was done using mean minus 2SD of the transformed data, which was then retransformed into the original units, as suggested by Robinson *et al.*<sup>[29,30]</sup> Percentiles were also calculated and

the 5<sup>th</sup> percentile used as the lower limit of normal. Pearson's product-moment correlation was run to assess the relationship between SRAR and age. One-way ANOVA with Bonferroni correction and also a Tukey post-hoc test were run to look for the significance of the age groups on SRAR. Linear regression analysis was done to determine the statistical significance and effect of age, height, and BMI on SRAR. All prerequisite assumptions for the above statistical tests were satisfied, prior to applying the tests.

## RESULTS

One hundred and forty-six healthy subjects (82 males and 64 females) between the ages of 18 years and 86 years were included in this study. The anthropometric details are in Table 1. The lower limit of SRAR value to be used as reference data was calculated for stimulation site— 12 cm above the recording electrodes for both sural and superficial radial sensory nerve, as that is used as a standard distance for both nerves in our laboratory. The sural age-stratified reference data has been published in an earlier paper.<sup>[8]</sup>

The lower limit for age-stratified SRAR values is shown in Table 2 and Figure 1. They were calculated by both methods, parametric and nonparametric. SRAR values were transformed to a normal distribution by using the square root function as it best reduced the skew in the distribution.<sup>[27,30]</sup> Mean minus 2 standard deviations (SD) and reversion of the values gave the normal lower limits for each group. The 5<sup>th</sup> percentile of the actual data has been also listed as the lower limit of normal. Scatter plot of age against the SRAR [Figure 2] shows a negative linear correlation. A Pearson's product-moment correlation test shows a moderate negative correlation between age of the subject and the SRAR,  $r(144) = -0.485$   $P < .0005$ , with age explaining 24.5% ( $r^2$ ) of the variation in the SRAR. Nonparametric Spearman's correlation was also run to assess the relationship between age and the not-transformed SRAR data. There was a strong negative correlation between age and SRAR, which was statistically significant  $r^s = -0.4685$ ,

$P < .001$ . A one-way ANOVA was conducted to determine the SRAR variability with age. There was statistically significant difference between groups  $[F(5,140)] = 9.39$ ,  $P < .05$ . Tukey and Bonferroni correction (post-hoc test) further revealed the SRAR intergroup variation with statistical significance. There was significant intergroup variation of SRAR between the age groups below 50 years and those above 60 (i.e. subjects of groups a, b, c had significantly higher SRAR than those in group e and f), but within the groups a, b and c, there was no statistically significant difference in the SRAR values. The group between 51 years and 60 years (group d) showed statistically higher SRAR value as compared to the group above 70 years (group f) but not with the age group between 61 and 70 years (group e). Groups e and f did not show any statistical difference. Detailed in Table 3. Kruskal–Wallis equality-of-populations rank test (nonparametric) was also run and it showed that there was significant difference in SRAR between the groups  $X^2(5) = 34.99$ ,  $P = 0.0001$ . A pair-wise

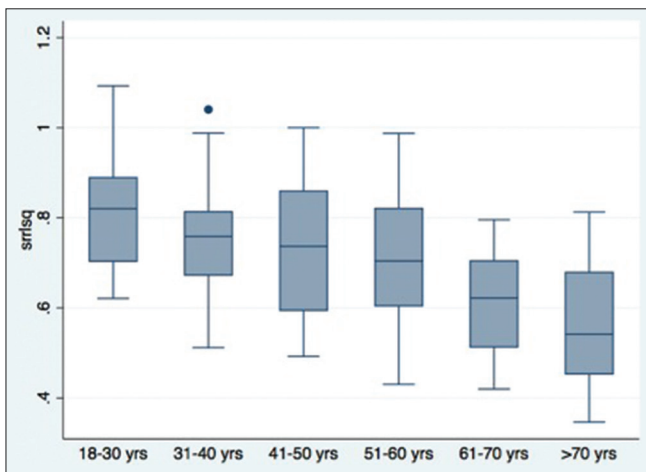
**Table 1: Anthropometric details of subjects in the study**

Variable	Obs	Mean	Std. Dev.	Min	Max
Age (years)	146	49.69178	17.46743	18	86
Height (cm)	144	159.5729	8.874606	139	182.5
Weight (kg)	143	60.79021	11.47186	38	101
BMI	141	23.82955	3.801203	15.3	35.8

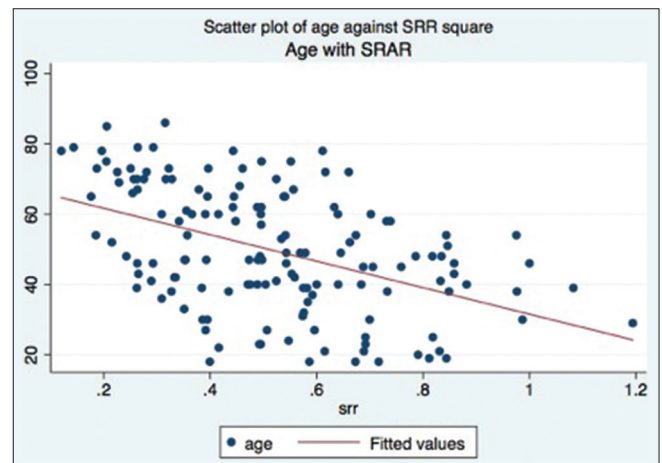
**Table 2: SRAR: Age-stratified SRAR (lower limit of normal)**

Age group	LLN*	5 <sup>th</sup> percentile
18-30 (n=25)	0.30	0.39
31-40 (n=24)	0.23	0.31
41-50 (n=33)	0.20	0.26
51-60 (n=21)	0.17	0.22
61-70 (n=22)	0.17	0.23
>70 (n=21)	0.08	0.14

\*LLN=Lower limit of normal: computed as mean 2SD of optimally transformed and then reconverted



**Figure 1:** Box plot of the SRAR in each age group. X-axis: Age groups. Y-axis: SRAR



**Figure 2:** Scatter plot of SRAR against age with linear regression

correlation post-hoc test showed significant difference in SRAR between groups which varied minimally with the findings in one-way ANOVA test [Table 4]. Linear regression analysis established that age could statistically predict SRAR,  $F(1,144) = 44.40, P < .001$ , adjusted  $R^2 = 0.23$ , i.e. age accounted for 23.6% of the explained variability in SRAR. Though an  $R^2 = 0.23$  may not be a high statistical value, 23% of variability in SRAR explained by age is clinically significant.

The regression equation was: Predicted SRAR =  $[-.0042 + 0.913 \times \text{age}]^2$ . Linear regression models of BMI and height with SRAR showed statistical significance  $F(1,139) = 4.95, P = 0.02$  in both cases but the effect measured by R-squared was only 3% and 3.5%, respectively. Similarly, the Pearson's coefficient showed a negative small correlation of BMI with SRAR:  $r(141) = -0.1855, P = 0.027$  with BMI explaining only 3.4% of the variation in SRAR ( $r^2$ ). Height showed a positive small correlation with SRAR  $r(144) = 0.1855, P = 0.0237$  explaining only 3.4% of the variation in SRAR. Linear regression model built with all three parameters: Age, BMI, and height did not increase the effect by any significant value  $F(3,137) = 16.71, R\text{-squared} = 0.228, P < .001$ , while the model with age alone had an R-squared value of 0.23. SRAR was also computed when stimulating the sural and radial nerves at distances of 10 and 14 cm. The SRAR obtained from all 3 sites were compared in the same subject to determine if distance had any effect on the values. Paired student's "t" test was

computed and it did not show any statistical significance when comparing the SRAR values from different stimulus sites. SRAR at 10 cm (mean 0.49, SD 0.19) compared with 12 cm (mean 0.49, SD 0.21),  $t = -0.229, P = .81$ ; SRAR at 10 cm compared with 14 cm (mean 0.48, SD 0.21),  $t = 0.453$ ,

**Table 4: Kruskal–Wallis equality-of-populations rank test for SRAR with different age groups**

Age groups	Obs	Rank Sum
18-30 yrs	25	2487.00
31-40 yrs	24	2059.00
41-50 yrs	33	2712.00
51-60 yrs	21	1603.00
61-70 yrs	22	1044.00
>70 yrs	21	826.00

chi-squared = 34.998 with 5 d.f.  
probability = 0.0001

chi-squared with ties = 34.998 with 5 d.f.  
probability = 0.0001

Pairwise comparisons

Age groups	Contrast	Std. Err.	t	P> t
a vs b	13.68834	10.71277	1.278	0.2034
a vs c	17.29819	9.939544	1.74	0.0840
a vs d	23.14667	11.09631	2.086	0.0388
a vs e	52.02546	10.9584	4.748	0.0000
a vs f	60.14667	11.09631	5.42	0.0000
b vs c	3.609848	10.05667	.359	0.7202
b vs d	9.458328	11.20135	.8444	0.3999
b vs e	38.33712	11.06474	3.465	0.0007
b vs f	46.45833	11.20135	4.148	0.0001
c vs d	5.84848	10.46429	.5589	0.5771
c vs e	34.72727	10.31793	3.366	0.0010
c vs f	42.84848	10.46429	4.095	0.0001
d vs e	28.87879	11.43649	2.525	0.0127
d vs f	37	11.56871	3.198	0.0017
e vs f	8.121212	11.43649	.7101	0.4788

**Table 3: One-way ANOVA Age groups with SRAR**

Source	Analysis of Variance			F	Prob > F
	SS	df	MS		
Between groups	.839852756	5	.167970551	9.39	0.0000*
Within groups	2.50557929	140	.017896995		
Total	3.34543204	145	.023071945		

Bartlett's test for equal variances:  $\chi^2(5) = 3.4443, \text{Prob} > \chi^2 = 0.632$

\*p value is significant for variation between age groups

Pairwise comparisons of means with equal variances over age groups

SRAR	Contrast	Std. Err.	Tukey t	P> t	Tukey [95% Conf. Interval]
b vs a	-.0470072	.0382307	-1.23	0.822	[-.1574782, .0634638]
c vs a	-.0629628	.0354713	-1.78	0.485	[-.1654603, .0395346]
d vs a	-.0831074	.0395995	-2.10	0.294	[-.1975335, .0313188]
e vs a	-.1803491	.0391073	-4.61	0.000*	[-.2933531, -.0673452]
f vs a	-.2263155	.0395995	-5.72	0.000*	[-.3407417, -.1118894]
c vs b	-.0159556	.0358893	-0.44	0.998	[-.1196609, .0877496]
d vs b	-.0361002	.0399743	-0.90	0.945	[-.1516095, .0794092]
e vs b	-.1333419	.0394868	-3.38	0.012*	[-.2474425, -.0192413]
f vs b	-.1793083	.0399743	-4.49	0.000*	[-.2948176, -.063799]
d vs c	-.0201445	.037344	-0.54	0.994	[-.1280532, .0877641]
e vs c	-.1173863	.0368216	-3.19	0.021*	[-.2237856, -.0109869]
f vs c	-.1633527	.037344	-4.37	0.000*	[-.2712613, -.055444]
e vs d	-.0972418	.0408134	-2.38	0.170	[-.2151758, .0206923]
f vs d	-.1432082	.0412853	-3.47	0.009*	[-.2625057, -.0239107]
f vs e	-.0459664	.0408134	-1.13	0.870	[-.1639005, .0719676]

\*Significant variation is seen as noted by p < .05



$P = .65$ ; and SRAR at 12 cm compared with 14 cm  $t = 0.69$ ,  $P = .49$ . Hence, BMI, height, and distance from recording site were not significant contributors to the variability of SRAR, while age of the subject showed moderate effect on the SRAR, more so after the age of 60 years.

## DISCUSSION

This study has helped in obtaining age-stratified reference values for SRAR in healthy Indian subjects, even above the age of 70 years. Further, it has statistically demonstrated that age has a negative and significant correlation on the SRAR values, especially in subjects above the age of 60 years. It has shown that ratio is not significantly affected by gender, site of stimulation (both nerves being stimulated at the same distance), height, or BMI. Thus, if age-stratified values are considered, SRAR could be a promising indicator for the electrodiagnosis of early peripheral neuropathy. These new lower limits of normal need to be validated in patients with early axonal, length-dependent peripheral neuropathy. Comparing to some earlier studies done for SRAR reference values, Rutkove *et al.*<sup>[14]</sup> were the first to define SRAR based on the principle that sural SNAP amplitude would reduce before the superficial radial SNAP amplitude in a length-dependent axonal neuropathy and hence, the ratio would reduce and that could be used as a sensitive indicator to diagnose a subclinical peripheral neuropathy. However, they obtained the value of 0.40 as the lower limit of normal for SRAR. Further, their study using Spearman's rank correlation showed that SRAR had no definite correlation with age ( $\rho = -0.151$ ,  $P = 0.426$ ). However, they had only 30 healthy subjects in this study as controls for their patients with polyneuropathy. Subsequently Overbeek *et al.*<sup>[15]</sup> showed that the value of 0.40 as a lower limit of normal was too high and that would qualify 57% of their healthy subjects as abnormal. Overbeek *et al.*<sup>[15]</sup> found a small inverse correlation of SRAR with age ( $r = -0.2$ ,  $P = 0.04$ ) but did not find any difference in SRAR between subjects below 60 and over. Since, in our study, we have tried to include similar number of subjects in each age group, the number of older subjects (>60 years) maybe higher in our study though the mean age is similar in both studies. They have also not used linear regression models to compute the effect of age on SRAR. They too did not find any statistical difference in SRAR between men and women, or a significant difference between the 2 sides or significant correlation of SRAR with length or BMI as in our study. Pastore *et al.*<sup>[17]</sup> used SRAR to demonstrate sensitivity in diagnosing diabetic peripheral neuropathy; however, their reference data was calculated in 31 normal subjects only. Esper *et al.*<sup>[16]</sup> calculated the SRAR stimulating the radial nerve at a distance of 10 cm and the sural at 12 cm. Hence, the amplitude of the radial SNAP would be much higher than that in our study leading to a lower ratio level even in healthy subjects. Further, they did not calculate age-stratified SRAR though linear regression graph showed a significant inverse correlation  $P < .003$  and  $R^2 = 0.095$ . We have followed both methods, optimally transforming the data

and using mean 2SD, plus using 5<sup>th</sup> percentiles to get the lower limit of normal for each age group. In our study, regression analysis and Pearson's coefficient showed significant effect and correlation of age with SRAR. Rajabally *et al.*<sup>[19]</sup> also used a single value of SRAR lower limit as 0.21 in their study. Shin *et al.*<sup>[25]</sup> used an SRAR lower limit of 0.5, which has already been demonstrated to be too high. Vrancken *et al.*<sup>[23]</sup> found the SRAR to be not sensitive in the diagnosis of an early peripheral neuropathy though they used age-stratified data in their reference population; they recorded the radial SNAP over the 2<sup>nd</sup> metacarpal and, hence, their reference data cannot be compared to this study as the amplitude of the radial SNAP is likely to be lower—giving larger ratios. Though their study had 393 referents, the SRAR was calculated in 179 subjects. The lower limit of normal SRAR calculated as 5<sup>th</sup> percentile was 0.45 in age group 18–39 years ( $n = 40$ ), 0.32 in age group 40–59 years ( $n = 74$ ), and 0.17 ( $n = 65$ ) in subjects above 60 years. They too showed a significant effect of age on SRAR. Sullivan *et al.*<sup>[20]</sup> found the yield of SRAR poor in the absence of clinical signs of large fiber involvement, but they too used a value of 0.21 as the lower limit of normal for SRAR across all ages. Zis *et al.*<sup>[18]</sup> in their study used the SRAR at a cut-off point of 0.21, suggesting its utility as an early indicator, but not useful for predicting severity. Guo *et al.*<sup>[22]</sup> used the SRAR cut-off of 0.21 and came to the conclusion that SRAR is not a sensitive indicator in the diagnosis of axonal peripheral neuropathy. Eren *et al.*<sup>[21]</sup> used an SRAR cut-off of 0.4 to diagnose patients of neuropathy in Sjogren's syndrome. Hence, most studies in patients with distal axonal peripheral neuropathy due to any cause have been done using a single value as a cut-off value, either 0.21, 0.4, or 0.5 across all ages, which possibly has led to the varying conclusions of SRAR being sensitive or not for the early recognition of a peripheral neuropathy.

## Limitations of our study

Our study could have been made stronger by including more subjects in each group, and by studying patients with confirmed peripheral neuropathy applying the age-stratified values, this can be done as a second study.

## CONCLUSION

This is the first study to provide age-stratified reference values for the lower limit of normal for SRAR in Indian subjects. This study shows that age has a significant effect on the SRAR, contrary to earlier studies, while height, BMI, gender, and site of stimulation do not. Using a single value for the lower limit of normal for all ages may not be advisable. SRAR is not useful for multifocal peripheral neuropathy, mononeuritis multiplex, or demyelinating peripheral neuropathies. Further studies on patients with clinically suspected early/mild distal, axon loss, length-dependent peripheral neuropathy may validate this claim.

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## Conflicts of interest

There are no conflicts of interest.

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