Received: 2 April 2023 | Revised: 22 June 2023 | Accepted: 28 June 2023

DOI: 10.1002/hsr2.1412

ORIGINAL RESEARCH

Health Science Reports Open Access WILEY

The normal value and influencing factors of shear wave elastography in healthy tibial nerves: A cross-sectional study

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Funding information
NSFC Pilot Project Funds of GDPH, Grant/Award Number: 8200070654; Guangzhou Municipal Science and Technology Project, Grant/Award Number: 202102020004

Abstract

Background and Aims: Shear wave elastography is a potential method for evaluating peripheral neuropathy, but lacking reference values. The aim of this study was to measure tibial nerve stiffness in healthy individuals using shear wave elastography and to investigate the influencing factors of tibial nerve stiffness.

Methods: Shear wave elastography of bilateral tibial nerves was performed in 50 healthy individuals 4 cm proximal to the medial malleolus. Mean shear modulus data of tibial nerves were obtained and recorded. Intra- and interobserver agreement were assessed using intraclass correlation coefficients. Differences among groups (grouped by laterality, sex, age, and body mass index) were analyzed with independent-samples *t*-tests and paired *t*-tests. Effect size (Cohen's *d*) was also calculated.

Results: The intra-and interobserver agreement were moderate (intraclass correlation coefficient, 0.700–0.747) for all participants, and was poor (intraclass correlation coefficient, 0.265–0.088) in very thin people (body mass index <18.5 kg/m^2). The shear wave elastography measurements of the tibial nerve did not show a significant difference between legs, sexes, or different age groups. Higher values of tibial nerve stiffness were found in thinner participants.

Conclusions: Shear wave elastography is a method to evaluate the stiffness of peripheral nerves. The measurement results were likely influenced by body mass index of the participants.

KEYWORDS

influencing factors, normal value, shear wave elastography, tibial nerve

1 | BACKGROUND

Elastography is a technique that describes the mechanical characteristics of tissues using noninvasive ultrasonic imaging to observe the tissue shear deformation after applying a force. Shear wave elastography (SWE) can quantify this deformation as the shear modulus and shear wave velocity.[1]

Peripheral neuropathy (PN) is usually associated with increased intraneural pressure, nerve edema, and ischemia and eventually leads to demyelination, axonal atrophy, and secondary fibrosis.[2] Multiple

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studies have applied elastography in the evaluation of peripheral nerves, finding that the affected nerves in patients with PN became stiffer than in healthy controls.[3–5] Some researchers suggested that the elasticity of affected nerves was reduced before development of neuropathy and was associated with the severity of neuropathy.[3] Therefore, quantification of stiffness of peripheral nerves is required for the early diagnosis and accurate tracking the progression of PN.

As a quantitative method, SWE can be used to evaluate peripheral nerve elasticity. However, a lack of data on healthy controls currently limits its clinical applications. In this study, we analyzed the feasibility and reliability of using SWE to evaluate tibial nerves in healthy individuals and collected normal values of SWE measurements of tibial nerves. The factors influencing tibial nerve stiffness were also investigated.

2 | METHODS

2.1 | Participants

A total of 50 healthy participants consisting of volunteers and medical staff were included during April to October 2021. Participants were excluded if they had clinical signs or symptoms of polyneuropathy, history of chronic disease, great of alcohol consumption (>20 g/day), diabetes mellitus, skin lesions, or swelling.

Medical history was collected using a questionnaire to obtain detailed neurological information from all participants. General information such as sex, age, height, and weight were also obtained and recorded. Body mass index (BMI) was calculated by using the formula: weight (kg) divided by the square of height (m).

The study protocol was approved by ethics committee of Guangdong Provincial People's Hospital. All methods in the study were carried out in accordance with relevant guidelines and regulations, and written informed consent was obtained from all participants.

2.2 | Peripheral nerve elastography technique

2.2.1 | Equipment

Ultrasound examinations were performed by two examiners using high-resolution ultrasonography equipped with a 4–15 MHz linear array probe (Mindray Resona 8; Mindray Medical International). During the examination, the probe frequency, gain, and mechanical index were kept constant.

2.2.2 | Participant position and measurement sites

All examinations were performed in a room with a comfortable temperature. First, participants were examined in the supine position. The ankles were in slight planar flexion position and were slightly rotated externally while the lower limbs were in a neutral position. SWE measurements were performed on the tibial nerve 4 cm proximal to the medial malleolus.

2.2.3 | SWE measurements

SWE examinations were conducted by two sonographers (sonographer A and sonographer B) with more than 5 years of experience with SWE, and one of the sonographers (sonographer A) repeated the examination about 1 week after the initial measurement. Both sonographers were blinded to the results of the other.

First, the tibial nerve was identified using the B-mode on the transverse imaging plane, and the transducer was rotated 90° to obtain the longitudinal imaging plane (parallel orientation to the nerve). The elastogram was displayed as an overlay in dual mode alongside greyscale images. An electronic box displaying the stiffness in chromatic scale was used for SWE measurements. The chromatic scale from blue to red indicated progression of tissue stiffness from low to high. To obtain the SWE parameters of tibial nerves, 2-mm circular regions of interest (ROIs) were drawn around the measurement sites within the elastography window (Figure 1). During acquisition, the transducer was placed onto the skin surface of participants with light contact and kept stationary. Any movement of limbs during the imaging acquisitions was avoided. The mean shear modulus data of tibial nerves were obtained and recorded. All measurements were performed in triplicate.

2.3 | Statistical analysis

SPSS software (v26.0; IBM Corp.) and Python (v3.8; PSF) were used for statistical analysis. Normality was confirmed using the Kolmogorov–Smirnov test. Normally distributed data are expressed as means ± standard deviations and nonnormally distributed data are expressed by medians and interquartile ranges. Prespecified analyses were conducted as follows: Independent-samples *t*-tests were used to compare stiffness parameters between groups (sex: male and female; age: 20–39 years old and ≥40 years old; BMI: <18.5 and ≥18.5 kg/m^2). A paired *t*-test was used to assess differences in tibial nerve stiffness between bilateral lower limbs. Effect size (Cohen's *d*) was calculated as well. Intra- and interrater intraclass correlation coefficients (ICCs) were calculated for two examiners. A two-sided $p < 0.05$ was regarded as statistically significant for all tests. ICC > 0.75 was considered as excellent agreement.

3 | RESULTS

3.1 | Demographic data

Between April and October 2021, 50 healthy participants were included in this study. Demographic data of study participants are

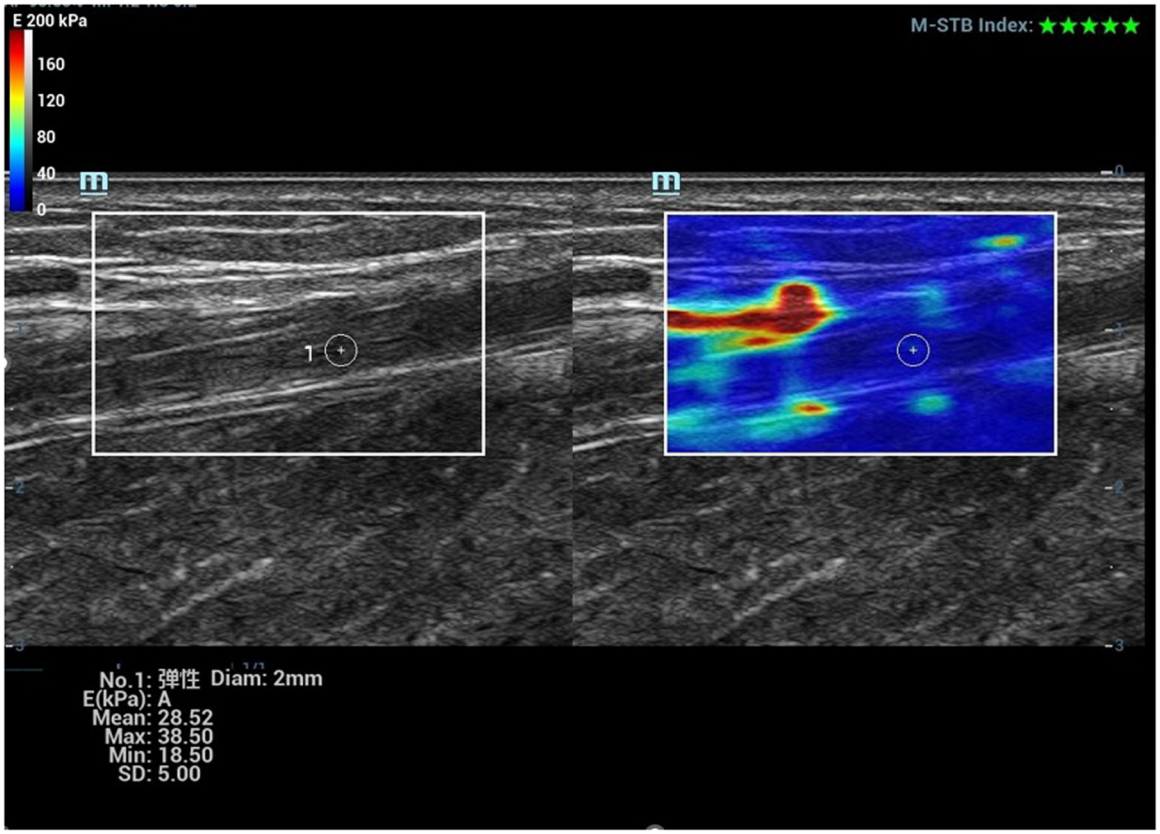

FIGURE 1 Shear wave elastography measurement of tibial nerves. Longitudinal section image of tibial nerve in a 43-year-old male within the elastography window. The color represents the relative stiffness of tissues. A 2-mm circular region of interest was drawn in the tibial nerve area, 4 cm proximal to the medial malleolus, to acquire the shear modulus of the tibial nerve. All measurements were performed in triplicate and averaged.

TABLE 1 Study demographics of participants.

	N	Age (years) (mean ± SD)	Height (m) (mean ± SD)	Weight (kg) (mean ± SD)	BMI (kg/m^2) (mean ± SD)
Female	27	35.85 ± 10.15	1.61 ± 0.05	53.41 ± 5.62	20.44 ± 1.92
Male	23	44.65 ± 10.49	1.75 ± 0.04	70.13 ± 8.75	22.86 ± 2.49
Total	50	39.90 ± 11.12	1.67 ± 0.08	61.10 ± 11.04	21.55 ± 2.49

Abbreviations: BMI, body mass index; SD, standard deviation.

summarized in Table 1. The median age was 38 (interquartile ranged from 33.00 to 47.25) years, and the mean BMI was 21.55 ± 2.49 (range: 17.53–27.76) kg/m^2. The distribution of participants' age was as follows: 20–39 years (n = 30), 40–59 years (n = 17), >60 years (n = 3). The population was predominately women (Female: n = 27, male: n = 23).

3.2 | Inter- and interobserver reliability of SWE measurements

The intra- and interobserver reliability of the SWE measurements in this study are presented in Tables 2 and 3. ICCs analyzed for the stiffness parameters of all participants' tibial nerves ranged from 0.700 to 0.747, which was indicative of moderate intra- and interobserver agreement. ICCs of different BMI groups were also calculated. The intra- and interobserver agreement of SWE measurements were 0.265 and 0.088 in lower-BMI participants (BMI < 18.5 kg/m^2), and were 0.782 and 0.738 in participants with higher BMI (≥18.5 kg/m^2). Figure 2 shows the intra-and interobserver reliability of different groups.

3.3 | The difference in stiffness measurements of tibial nerve among groups

The mean shear modulus of tibial nerve in all participants was 36.86 ± 5.52 kPa. Differences in tibial nerve stiffness among groups

TABLE 2 Intraobserver reliability in stiffness parameters obtained from tibial nerves with using elastography.

	Shear modulus (kPa) (mean ± SD)		95% confidence interval			
	Sonographer A1	Sonographer A2	ICC	Lower bound	Upper bound	*P*
All participants (*N* = 50)	37.46 ± 5.98	36.75 ± 5.17	0.747	0.646	0.823	<0.001
Participants with BMI ≥ 18.5 kg/m^2 (*N* = 41)	35.90 ± 4.85	35.69 ± 4.67	0.782	0.680	0.853	<0.001
Participants with BMI < 18.5 kg/m^2 (*N* = 9)	44.58 ± 5.52	41.60 ± 4.61	0.265	−0.217	0.643	0.14

Note: Sonographer A1: The initial SWE measurement of sonographer A obtained from tibial nerves.
Sonographer A2: The second SWE measurement of sonographer A about one week after the initial measurement obtained from tibial nerves.
Abbreviations: BMI, body mass index; ICC, intraclass correlation coefficient; SD, standard deviation.

TABLE 3 Interobserver reliability of stiffness parameters obtained from tibial nerves using elastography.

	Shear modulus (kPa) (mean ± SD)		95% confidence interval			
	Sonographer A1	Sonographer B	ICC	Lower bound	Upper bound	*P*
All participants (*N* = 50)	37.46 ± 5.98	36.36 ± 5.38	0.700	0.584	0.788	<0.001
Participants with BMI ≥ 18.5 kg/m^2 (*N* = 41)	35.90 ± 4.85	35.16 ± 4.62	0.738	0.621	0.823	<0.001
Participants with BMI < 18.5 kg/m^2 (*N* = 9)	44.58 ± 5.52	41.83 ± 5.30	0.088	−0.383	0.522	0.36

Note: Sonographer A1: The initial SWE measurement of sonographer A obtained from tibial nerves.
Sonographer B: The SWE measurement of sonographer B obtained from tibial nerves.
Abbreviations: BMI, body mass index; ICC, intraclass correlation coefficient; SD, standard deviation.

are shown in Table 4. The SWE measurements of the tibial nerve did not show significant differences between bilateral legs ($p = 0.39$, Cohen's $d = 0.2147$) or sexes ($p = 0.23$, Cohen's $d = 0.4711$). Higher values of tibial nerve stiffness were also found in the lower BMI group (BMI < 18.5 kg/m^2) compared to other participants ($p < 0.001$, Cohen's $d = 1.9104$). We compared the nerve stiffness of people older than 40 years and those in their 20s or 30s, and found that the p value was 0.01 ($p < 0.05$) while the effect size was 0.1307 (Cohen's $d < 0.20$).

4 | DISCUSSION

PN is traditionally evaluated using nerve biopsy, nerve conduction studies (NCSs), and evaluation of symptoms and signs, each with their own limitations. These methods are either invasive or not sensitive enough and are inappropriate for long-term and repetitive follow-up.[6]

Ultrasound provides an alternative method for evaluating PN. The distribution and morphology of peripheral nerves can be clearly visualized using high-frequency ultrasound. Moreover, elastography could be a potential tool for assessing peripheral nerve stiffness. Numerous studies have shown that high-frequency ultrasound is clinically applicable for the diagnosis and monitoring of PN by visualizing the morphology of peripheral nerves.[7] However, relatively few studies have assessed the elasticity of peripheral nerves using elastography. Previous studies using elastography found that the peripheral nerves of patients with PN were stiffer than those in healthy individuals. Some studies suggested that elastography was able to detect changes in peripheral nerve stiffness before the onset of symptoms or morphological alterations in patients with PN.[3–5]

Ultrasonography has opened perspectives for the noninvasive and accurate diagnosis of PN. Nevertheless, there is still no unified diagnostic standard for both high-frequency ultrasound and elastography. Ultrasonography is operator-dependent, and the results can be easily influenced by factors related to the participants, so quantification is essential for PN diagnosis using ultrasound.

Several ultrasonographic scoring systems for the diagnosis of neuropathy have been proposed based on the cross-sectional area of peripheral nerves showing good performance with sensitivity and specificity ranging from 60.9% to 90% and 74% to 97.3%, respectively.[8–12] The existing ultrasonographic scoring systems were built based solely on morphological information; elasticity of peripheral nerves is not evaluated. However, several studies have suggested that elasticity might be a better indicator of neuropathy severity than the cross-sectional area.[3,13,14] As SWE provides parameters that quantitatively reflect the elasticity of peripheral nerves, it is reasonable to include SWE measurements as a supplemental evaluation index for ultrasonographic scoring systems.

SWE has been applied in different diseases such as nodules of the thyroid or breasts, hepatic fibrosis, and musculoskeletal disorders, among others. It enables clinicians to quantitatively evaluate the elasticity of body tissues in situ and has aroused the attention of many researchers who specialized in neurology. Dikici et al. evaluated the elasticity of tibial nerves in patients with diabetes using SWE and found that those with and without diabetic PN had significantly stiffer tibial nerves than healthy controls. The cutoff value of tibial nerve stiffness at 4 cm proximal to the medial malleolus was 51.0 kPa with a sensitivity of 90% and a specificity of 85%.[15] Kantarci et al. demonstrated that SWE is a highly reproducible method for the diagnosis of carpal tunnel syndrome (CTS). The median nerve

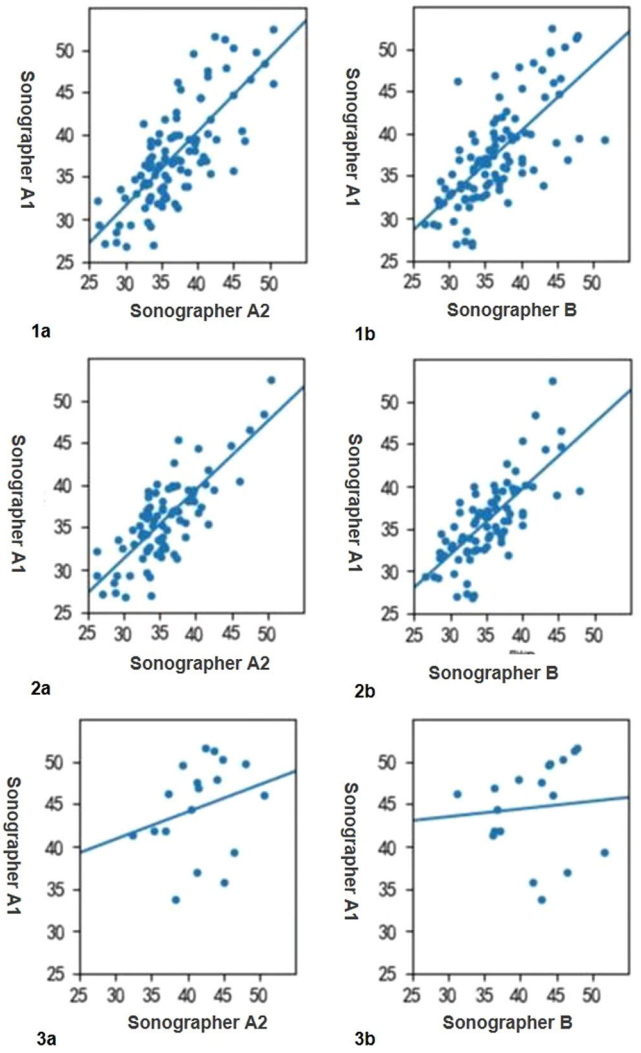

FIGURE 2 Intra- and interobserver reliability in different participant groups; All participants: 1a, 1b; participants with BMI ≥ 18.5 kg/m^2: 2a, 2b; participants with BMI < 18.5 kg/m^2: 3a, 3b.

stiffness was significantly higher in patients with CTS compared with controls. The cutoff value was 40.4 kPa at the level of the proximal carpal row, with a sensitivity and specificity of 93.3% and 88.9% for diagnosing CTS, respectively.[16]

Although SWE achieves good performance in the diagnosis of PN, there are still several issues to be addressed before SWE can be routinely applied in examinations of PN. Noting the statistic difference between nerve stiffness values in patients with PN and in healthy controls, a considerable proportion of patients' SWE measurement results overlapped with those of healthy controls. The cutoff values for SWE measurements differ from study to study. Discrepancies might be due to differences in devices, patient position, and measurement sites, imaging axes, participant-related characteristics, or other confounders.

In the present study, we evaluated stiffness parameters of tibial nerves in healthy individuals using SWE. Aslan et al. examined median and posterior tibial nerve stiffness in 57 adolescents (25 with type 1 diabetes and 32 healthy controls) and found that the interobserver agreement for SWE measurements was lower on the transverse axis (0.210–0.633) than on the longitudinal axis (0.682–0.748).[17] Therefore, we chose the longitudinal axis for nerve stiffness measurements.

Many studies have reported a high consistency of SWE in evaluating peripheral nerve stiffness. He et al. evaluated the median and tibial nerve stiffness of patients with diabetes (with or without neuropathy) and healthy controls using SWE. The inter- and intra-observer agreement rates were 0.958 and 0.960, respectively.[13] SWE was considered a reproducible, relatively objective method for quantitative evaluation of peripheral nerve stiffness. On the whole, the intra- and interobserver consistency for assessing tibial nerve stiffness was moderate (ICC: 0.747 and 0.700) in our study. As we noticed that it was more difficult to acquire stable images in lower-BMI participants during SWE measurement because of insufficient soft tissue for proper transducer placement, we grouped participants according to BMI. A poor consistency was seen in SWE

TABLE 4 Differences in tibial nerve stiffness among groups.

	Groups	*N*	Shear modulus (kPa) (mean ± SD)	*t*	*P*	Cohen's *d*
Bilateral legs	Left	50	36.71 ± 5.68	−0.863	0.39	0.2147
	Right	50	37.01 ± 5.37			
Sex	Female	27	37.21 ± 5.38	1.196	0.23	0.4711
	Male	23	36.44 ± 5.67			
Age (years)	20–39	30	36.22 ± 5.39	−2.472	0.01*	0.1307
	≥40	20	37.81 ± 5.60			
BMI (kg/m^2)	<18.5	9	42.67 ± 5.24	−9.812	<0.001*	1.9104
	≥18.5	41	35.58 ± 4.71			

Abbreviations: BMI, body mass index; SD, standard deviation.

*Significant at $p < 0.05$.

measurements in participants with low BMI (BMI < 18.5 kg/m^2), with intra- and interobserver agreements of 0.265 and 0.088, respectively, which might be explained by "bone-proximity" hardening artifacts caused by insufficient tissue surrounding the nerves these participants.[18] The intra- and interobserver agreement increased to 0.782 and 0.738 after excluding low-BMI participants.

While the diagnostic value of SWE in evaluating PN has been demonstrated by multiple studies, the lack of standardization remains a barrier for clinical applications. Within the present study, normal values of tibial nerve stiffness were collected. The mean shear modulus of tibial nerves in all participants was 36.86 ± 5.52 kPa, which correlated well with data from a previous study.[14] The SWE measurements of the tibial nerve did not show significant differences between legs or sexes, consistent with Zhu's study.[19] An inverse correlation between nerve stiffness and BMI was suggested according to our results. Higher values of tibial nerve stiffness were found in low-BMI participants (BMI < 18.5 kg/m^2), which was somewhat in accordance with a study of Bortolotto et al. They found that the stiffness of the median nerve in healthy people increased progressively as the nerve becomes superficial.[18] Further work using larger samples is needed to verify this, because there was low reproducibility in evaluating tibial nerves using SWE among low-BMI participants in our study.

Concerning age, Ishibashi et al. reported an inverse correlation between the elasticity of tibial nerves and age in both patients with diabetic PN and healthy controls.[3] Conversely, a trend toward a positive correlation was found between tibial nerve elasticity and age according to a study by Greening et al.[20] In the present study, we compared the nerve stiffness of the people older than 40 years and those in their 20s or 30s. Even though the p value showed a significant difference between different age groups, the small effect size indicated that further study is still required. This might be a consequence of our relatively young participant sample. To further verify the potential age dependency in the elasticity of peripheral nerves, more representative samples should be included in future studies.

The present study has some limitations. The sample size could be larger, and the demographic characteristics could have been more balanced. Further research is needed to strengthen the reliability of the present results. Here, the participant age skewed young. As the correlation between age and nerve stiffness is to be further studied, older healthy participants should be included to collect normative data on peripheral nerve stiffness.

5 | CONCLUSIONS

SWE is a reproducible, quantitative, and simple method for the evaluation of PN. The present study laid the groundwork by collecting values of tibial nerve stiffness from healthy participants using SWE and investigating the factors influencing nerve stiffness. We plan to build a scoring system for the ultrasonic evaluation of neuropathy based on both morphologic and elastic characteristics and to evaluate its diagnostic value in patients with PN. It can be expected that an ultrasonographic scoring system will promote the standardization and clinical utilization of ultrasound for the diagnosis of neuropathy, so as to assist physicians to identify PN timely and accurately.

AUTHOR CONTRIBUTIONS

Shiyao Shang: Conceptualization; funding acquisition; writing—original draft. **Wenxiao Yan**: Investigation; validation. **Yuping Guo**: Project administration; resources. **Hantao Guo**: Data curation; project administration. **Rumin Chen**: Investigation; methodology. **Shuzhen Cong**: Supervision; writing—review and editing. **Chunwang Huang**: Formal analysis; methodology; writing—review and editing.

ACKNOWLEDGMENTS

We would like to express our gratitude to Jiansong Ma. Jiansong Ma is a statistician from Sun Yat-sen University and kindly provided statistical advice for this manuscript. This work is supported by the Guangzhou Municipal Science and Technology Project (202102020004), the NSFC Pilot Project Funds of GDPH (8200070654). The funding sources had no involvement in study design, collection, analysis, interpretation of data, writing of the report, and the decision to submit the report for publication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study protocol was approved by ethics committee of Guangdong Provincial People's Hospital All methods in the study were carried out in accordance with relevant guidelines and regulations, and written informed consent was obtained from all participants.

TRANSPARENCY STATEMENT

The lead author Shuzhen Cong, Chunwang Huang affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Shang S, Yan W, Guo Y, et al. The normal value and influencing factors of shear wave elastography in healthy tibial nerves: a cross-sectional study. *Health Sci Rep*. 2023;6:e1412. doi:10.1002/hsr2.1412