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REVIEW

Peripheral Nerve Ultrasound Findings in Leprosy: A Scoping Review of Echogenicity, Cross-Sectional Area, and Vascularization Across 15 Studies

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Background: Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, primarily affecting the skin and peripheral nerves. Neuropathy in leprosy can result in significant disability, making early detection crucial. Ultrasound offers a non-invasive method to detect neuropathy by assessing echogenicity, cross-sectional area (CSA), and peripheral nerve vascularity.

Objective: This review aimed to map and synthesize diagnostic role of peripheral nerve ultrasound, focusing on echogenicity, cross-sectional area, and vascularization, in detecting leprosy-related neuropathy.

Methods: This scoping review was conducted in accordance with the PRISMA-ScR guidelines and included 15 studies assessing echogenicity, CSA, and vascularity in leprosy patients (sample sizes ranging from 20–308 participants).

Results: Ultrasound consistently identified nerve abnormalities across 15 studies, including hypoechogenicity and fascicular pattern loss (up to 72% of nerves), CSA enlargement, and Doppler vascularity (11–45%) correlating with active inflammation. Reported CSA cut-offs (10–50 mm^2) yielded sensitivities of 63–90% and specificities of 67–100% across studies. Ultrasound demonstrated superior sensitivity over clinical palpation and nerve conduction studies for subclinical neuropathy detection.

Conclusion: This scoping review demonstrates ultrasound's utility for early leprosy-related neuropathy detection. Ultrasound shows superior sensitivity over clinical palpation for subclinical involvement, particularly valuable for household contacts and pure neural leprosy. However, methodological heterogeneity precludes definitive diagnostic thresholds. Future research should standardize protocols and validate ultrasound parameters to optimize clinical application and disability prevention in endemic regions.

Keywords: early detection, leprosy, peripheral nerve, ultrasound

Introduction

Leprosy is a chronic granulomatous disease caused by the obligate intracellular bacteria *Mycobacterium leprae* (*M. leprae*) and *M. lepromatosis*, which primarily affect the skin and peripheral nerves.[1] According to the World Health Organization (WHO) 2023 data, a total of 182,815 new leprosy cases were detected worldwide, with the majority reported from India, Brazil, and Indonesia.[2,3] Indonesia ranked third globally with 14,376 new cases in 2023, underscoring its endemic status in the country.[2,4]

The disease's progression involves thickening of peripheral nerves, leading to functional impairments in sensory, motor, and autonomic nerve functions. Approximately 10% of cases develop neuropathy, contributing to nerve dysfunction and can lead to disability.[5,6] These disabilities may arise directly from the disease itself or as a result of leprosy reactions.[7]

Early neuropathy detection is crucial to prevent irreversible damage. While nerve conduction studies (NCS) assess function and biopsy provides histology, imaging modalities like magnetic resonance neurography (MRN) and high-

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resolution ultrasound (HRUS) evaluate structural changes noninvasively. MRN excels in visualizing deep nerve edema, fascicular disruption, and proximal involvement (eg, plexus/ganglionitis in pure neural leprosy) but is limited by high cost, limited availability in endemic low-resource settings, and longer acquisition times.[8–11]

In contrast, high-resolution ultrasound has emerged as a valuable tool in this context, offering a noninvasive, real-time bedside assessment of peripheral nerve structure. HRUS can measure echogenicity, cross-sectional area (CSA), and vascularization of the nerves, with increased vascularization detected by color Doppler ultrasound potentially indicating inflammation.[8] A study conducted in Brazil by Akita et al in 2021 demonstrated that color Doppler ultrasound might be more effective than nerve conduction studies (NCS) in identifying inflammatory changes in patients with leprosy reactions.[9] Furthermore, findings such as decreased echogenicity and an increased anteroposterior diameter of the nerve's CSA suggest nerve thickening and may help in the diagnosis of neuropathy.[10,11]

The widespread availability of ultrasound enhances accessibility to early leprosy detection, particularly in endemic regions, such as India, Brazil, and Indonesia.[10,12] This broad access means that patients in rural or underserved areas can benefit from earlier diagnoses, which may reduce neuropathy-related disabilities. Despite its potential, there remains a lack of comprehensive literature exploring ultrasound as a diagnostic modality for early leprosy detection. Therefore, this scoping review seeks to address this gap by mapping and analyzing the role of peripheral nerve ultrasound findings, specifically all three parameters (echogenicity, CSA, and vascularity) in the early diagnosis of leprosy.

Materials and Methods

Protocols, Search Strategy, and Studies Selection

This scoping review was conducted in following the PRISMA Extension for Scoping Review (PRIMSA-ScR) guidelines. We followed the framework outlined by Arksey and O'Malley.[13] The review involves stages of (1) identifying the research question, (2) identifying relevant studies, (3) selecting study, (4) charting the data, (5) collating, summarizing, and reporting, (6) and consultation (optional). The PRISMA-ScR checklist is provided (shown in Supplementary) to demonstrate alignment with the recommended framework.[14]

Our broad research question was pre-defined as *What is the diagnostic role of peripheral nerve ultrasound (echogenicity, cross-sectional area, and vascularization) in detecting leprosy-related neuropathy?*

A comprehensive literature search was then performed using Google Scholar and PubMed. In Google Scholar, the search terms included: ("Neural Ultrasonography" OR "Ultrasonography" OR "ultrasound") AND ("Leprosy" OR "Morbus Hansen"). For PubMed, a combination of MeSH terms was used: (Ultrasonography[MeSH] OR Diagnostic Imaging[MeSH] OR ultrasound[Text Word]) AND (Leprosy[MeSH] OR Mycobacterium leprae[MeSH] OR Leprosy, Multibacillary[MeSH] OR Leprosy, Paucibacillary[MeSH]) AND (Peripheral Nervous System Diseases[MeSH] OR Peripheral Neuropathy[MeSH]).

The search, completed by September 10th, 2024, identified a range of relevant studies. Two independent reviewers screened the titles and abstracts, followed by full-text reviews of the selected articles. The reference lists of the included studies were also examined for additional relevant sources. Duplicate records were removed, and any discrepancies between reviewers were resolved through discussion (Figure 1).

Eligibility Criteria

Inclusion criteria included (1) original articles published until the date of last search, that was, September 10th, 2024; (2) studies involving the usage of ultrasound in leprosy cases, as defined in the joint consensus statement by the World Health Organization; (3) reporting at least 1 potential diagnostic value for leprosy; and (4) free full-text available to access. Exclusion criteria included (1) nonoriginal articles; (2) studies written in a language other than English (3) duplicate studies; and (4) studies with irrelevant content about the main topic.

Data Charting

Information regarding the year of publication, study design, sample size, study population, and the operational definitions used in each study were collected and presented in the results. The authors focused on ultrasound findings within the

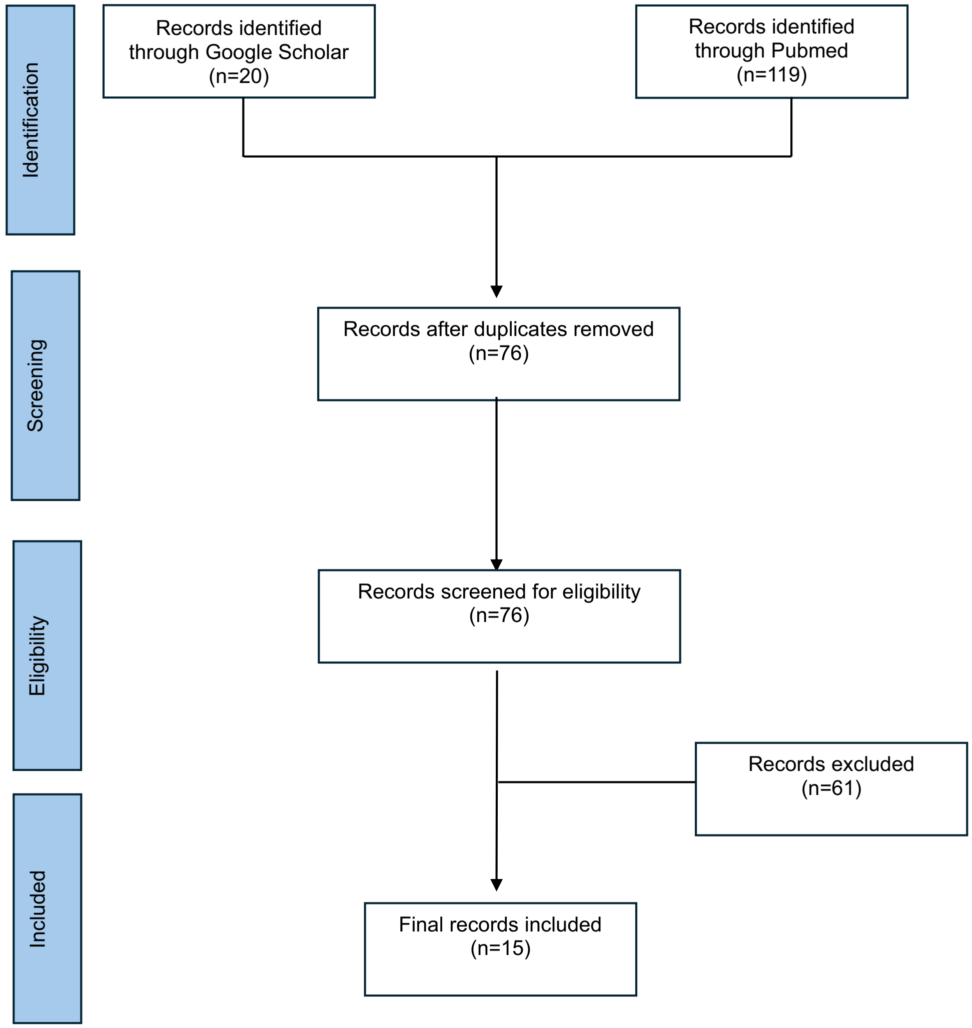

Figure 1 Flow diagram of study selection following PRISMA guidelines. From 139 initially identified studies, 15 were included in the final review after applying inclusion and exclusion criteria.

domains of echogenicity, CSA, and vascularity in the population of patients with leprosy across the selected relevant studies. Details about the type of ultrasound machine and the sonography frequency used in each study will also be elaborated in the review results.

Result

Of the 139 articles initially found, across 79 different medical journals over the last fifteen years, a thorough selection led to the exclusion of those that did not meet the set inclusion or exclusion criteria (shown in Figure 1). Consequently, only 15 studies were considered relevant and included in this review. Findings are presented descriptively due to methodological heterogeneity across studies, including differences in ultrasound equipment, measurement protocols, and outcome definitions. These selected studies have been systematically organized as shown in Tables 1 and 2.

Characteristics of the Included Studies

This review included 15 studies, all employing observational or cross-sectional designs to assess ultrasound findings in leprosy patients. Sample sizes varied between 20 and 308 participants, primarily consisting of multibacillary and paucibacillary leprosy patients, as well as individuals experiencing type 1 or type 2 leprosy reactions. Several studies also included healthy controls for comparison.

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Table 1 Characteristic of the Studies

No.	Authors (Year)	Study Design	Subject & Population	Nerve	Ultrasound Machine	Frequency		Operational Standard
						Broadband	Color-Doppler	
1.	Jain et al (2009)[16]	Comparative Observational	50 Subjects • 10 Tuberculoid • 7 Lepromatous • 3 Borderline Lepromatous • 30 Healthy Controls	• Ulnar • Median • Lateral Popliteal (LP) • Posterior Tibial (PT)	Voluson −730 Expert	10–14 MHz	6–3 MHz	**Echogenicity** • Mild: Some Hypo-reflectivity • Moderate: Obvious Hypo-reflectivity • Severe: Absence of Fascicular Pattern **Cross-Sectional Area** • Transverse area surrounded within hyperechoic rim **Vascularity** • Hypervascularity: Presence of Blood Flow in Perineural Plexus/Intrafascial Plexus
2.	Lugao et al (2015)[17]	Observational	96 Subjects • 11 Paucibacillary • 85 Multibacillary	• Ulnar • Median • Median • Common Fibular	Phillips HDI-11	12 MHz	NA	**Cross-Sectional Area** • Inner borders of the hyperechoic rims of the nerves measured at the level of maximum nerve thickening • DeltaCSA reflects nerve asymmetry with the contralateral nerves
3.	Lugao et al (2016)[24]	Longitudinal Observational	73 Subjects • 9 Paucibacillary • 64 Multibacillary	• Ulnar (Cubital Tunnel & Proximal Tunnel) • Median • Common Fibular	Phillips HDI-11	12 MHz	PRF 0.7–1.0 kHz	**Echogenicity**: • Abnormal: Hypoechoic or Hyperechoic area with loss of the normal fascicular pattern **Cross-Sectional Area**: Inner borders of the hyperechoic rims of the nerves measured at the level of maximum nerve thickening **Vascularity**: • Hypervascularity: Detection of doppler signal in the intraneural or epineural segment **Ultrasound Outcomes**: • Good (Significant): A significant increase of CSA between pre- and post-treatment measurement as above 30% (Ulnar, Median) or 40% (Common Fibular) difference from the baseline • Poor: Post-treatment CSA measured above the normal limits (mean + 2 standard deviations of the control group measurement) AND with less than a 30% (Ulnar, Median) or 40% (Common Fibular) reduction from the baseline

4.	Singh et al (2017)[26]	Case-Control	40 Subjects • 20 leprosy patients • 20 healthy patients	• Ulnar • Median • Lateral • Posterior Tibial	Phillips Epiq 7G	5–18 MHz	-	**Echogenicity**: • Reduced Echogenicity: Increased intraneural edema • Inflammatory Pathology: Loss of fasicular pattern **Cross-Sectional Area**: • Inner margin of the hyperechoic rum **Vascularity**: • Hypervascularity: Color flow in the nerves
5.	Chen et al (2018)[25]	Observational	100 Subjects • 71 leprosy patients • 29 healthy patients	• Median • Ulnar • Common Fibular	Sonosite M-Turbo & S-Series	13–6 MHz	NA	NA
6.	Nagappa et al (2021)[18]	Prospective Cross-Sectional	78 Subjects • 26 Leprosy patients • 26 CTS patients • 26 Healthy Controls	• Median	Phillips CX50	15–7 MHz	NA	**Echogenicity**: • Hypoechogenicity with loss of fascicular architecture **Cross-Sectional Area**: • A significant enlargement was considered when the CSA exceeded normal reference values, particularly at M1, where the CSA in leprosy patients averaged 16.07 ± 5.20 mm^2. **Vascularity**: • Hypervascularity: Detection of abnormal blood flow in the epineurium and endoneurium.
7.	Venugopal et al (2021)[19]	Cross-Sectional	40 Subjects • 24 Borderline Tuberculoid • 7 Borderline Lepromatous • 6 Lepromatous Leprosy • 1 Indeterminate	• Ulnar • Median • Common Peroneal • Posterior Tibial	GE Logic S8	4.5–15 MHz	NA	**Echogenicity**: • Hypoechogenicity with loss of fascicular architecture. **Cross-Sectional Area**: • Increased cross-sectional area (>8.5 mm^2 ulnar, >6.2 mm^2 median) **Vascularity**: • Hypervascularity: Increased blood flow signals in epineurium and endoneurium.

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Table 1 (Continued).

No.	Authors (Year)	Study Design	Subject & Population	Nerve	Ultrasound Machine	Frequency		Operational Standard
						Broadband	Color-Doppler	
8.	Sreejith et al (2021)[20]	Comparative Cross-Sectional	60 Subjects • 30 Leprosy patients • 30 Healthy controls	• Ulnar • Median • Radial • Lateral Popliteal • Posterior Tibial	High-Resolution ultrasound (HRultrasound)	8–18 MHz	NA	**Echogenicity**: • Mild-to-severe hypoechogenicity is observed based on the loss of the honeycomb pattern • Mild: Some hypo-reflectivity • Moderate: Obvious hypo-reflectivity • Severe: Absence of fascicular pattern **Cross-Sectional Area**: • Nerve Thickening: Cross-sectional area (CSA) >8.17 mm^2 for the ulnar nerve, >7.1 mm^2 for the radial nerve, >10.17 mm^2 for the median nerve, >9.5 mm^2 for the lateral popliteal nerve, and >11.21 mm^2 for the posterior tibial nerve. **Vascularity**: • Hypervascularity: Increased blood flow in the perineural plexus or intrafascial plexus
9.	Akita et al (2021)[9]	Observational	35 Subjects • 5 Type-1 Reactions patients • 30 Type-2 Reactions patients	• Ulnar • Median • Tibial • Common Peroneal	Samsung Medison LA3-16AD	3–16 MHz	1 kHz	**Echogenicity**: • Changes in echotexture were graded according to the loss of the fascicular pattern. **Cross-Sectional Area**: • Thickening was defined based on nerve enlargement and inflammatory reactions visible on ultrasound **Vascularity**: • Doppler imaging detected blood flow in nerves with inflammatory activity (IA)

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10.	Dugad et al (2022)[21]	Cross-Sectional	37 Subjects • 32 Leprosy patients with no reactions • 1 Leprosy patient with Type-1 Reaction • 4 Leprosy patients with Type-2 Reaction	• Ulnar • Median • Radial • Lateral Popliteal • Posterior Tibial	Siemens Acuson S2000/ S3000	4.5–15 MHz	NA	**Echogenicity**: • 0 (Normal): Normo-echogenic (normal honeycomb pattern) • 1 (Mild): Some hypoechogenicity • 2 (Moderate): Obvious hypoechogenicity • 3 (Severe): Complete loss of fascicular pattern **Cross-Sectional Area**: • Ulnar nerve: CSA >8.17 mm^2 (mean CSA = 12.47 mm^2 for thickened nerves) • Radial nerve: CSA >7.1 mm^2 (mean CSA = 8.8 mm^2 for thickened nerves) • Median nerve: CSA >10.17 mm^2 (mean CSA = 17.06 mm^2 for thickened nerves) • Lateral Popliteal nerve: CSA >9.5 mm^2 (mean CSA = 15.70 mm^2 for thickened nerves) • Posterior Tibial nerve: CSA >11.21 mm^2 (mean CSA = 17.12 mm^2 for thickened nerves) **Vascularity**: • NA
11.	Spitz et al (2022)[22]	Prospective Cross-Sectional	22 Subjects • 15 Multibacillary Leprosy • 7 Paucibacillary Leprosy	• Ulnar • Median • Posterior Tibial	Toshiba Aplio XG	12–15 MHz	750 Hz	**Echogenicity**: • Loss of fascicular pattern and presence of hyperechoic regions in the epineurium. **Cross-Sectional Area**: • Nerve Thickening: Defined by increased cross-sectional area (CSA) values measured by ultrasound o Ulnar nerve: CSA > 9.8 mm^2 o Median nerve: CSA > 8.1 mm^2 o Posterior Tibial nerve: CSA > 9.5 mm^2

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Table 1 (Continued).

No.	Authors (Year)	Study Design	Subject & Population	Nerve	Ultrasound Machine	Frequency		Operational Standard
						Broadband	Color-Doppler	
12.	Voltan et al (2023)[27]	Observational	308 Subjects • 176 Leprosy patients • 83 Household Contacts patients • 49 Healthy controls	• Ulnar • Median • Common Fibular	High-Resolution ultrasound (HRultrasound)	4–17 MHz	NA	**Echogenicity**: • Hypoechoic changes and loss of the honey-comb pattern **Cross-Sectional Area**: • Nerve Thickening: Defined by CSA values exceeding the reference mean + 2 SD at specific nerve points (ulnar, median, common fibular, tibial). o ΔCSA measures asymmetry between right and left nerves considered significant if >2 SD of the reference. o ΔTpT assesses localized thickening within the same nerve. **Vascularity**: • Not Assessed
13.	Khan et al (2023)[28]	Cross-Sectional	20 Subjects • 11 Multibacillary Leprosy • 9 Paucibacillary Leprosy	• Ulnar, • Median, • Common Peroneal	High-Resolution ultrasound (HRultrasound)	5–18 MHz	NA	**Echogenicity**: • Graded from 0 (normal) to 3 (severe): o 0: Normal honeycomb pattern. o 1: Some hypoechogenicity. o 2: Moderate hypoechogenicity. o 3: Complete loss of the fascicular pattern. **Cross-Sectional Area**: • Neural thickening is determined by comparing the CSA of each peripheral nerve to reference values. A CSA greater than mean + 2 standard deviations (SD) from healthy control values is considered abnormal. • For asymmetry detection, the difference in CSA between the right and left sides of the same nerve (ΔCSA) is calculated. A significant asymmetry is defined when ΔCSA >mean + 2 SD. **Vascularity**: • Hypervascularity: Detection of Doppler signals in the nerves with inflammation

14.	Luppi et al (2023)[13]	Cross-Sectional	162 Subjects of Leprosy • 79 Seropositive Household Contacts • 30 Seronegative Household Contacts • 53 Healthy Controls	• Ulnar, • Median, • Common Fibular, • Tibial	Esaote MyLab™ 50 XVision	6–18 MHz	NA	**Echogenicity**: • Loss of honeycomb pattern was prevalent in thickened nerves, signifying more advanced nerve damage in household contacts and leprosy patients. **Cross-Sectional Area**: • Nerve Thickening: Defined by CSA values exceeding the reference mean + 2 SD at specific nerve points (ulnar, median, common fibular, tibial). **Vascularity**: • Abnormal Blood Flow: No detection of Doppler signals in the nerves of household contacts or healthy volunteers.
15	Aggarwal et al (2024)[23]	Cross-Sectional	34 Subjects of Histopathologically proven Leprosy	• Ulnar • Median • Common Peroneal	GE LOGIQ P6	7–10 MHz	NA	**Echogenicity**: • Echogenicity assessed for hypoechoic/hyperechoic patterns. **Cross-Sectional Area**: • Neural thickening is determined by comparing the CSA of each peripheral nerve to reference values. A CSA greater than mean + 2 standard deviations (SD) from healthy control values is considered abnormal. • For asymmetry detection, the difference in CSA between the right and left sides of the same nerve (ΔCSA) is calculated. A significant asymmetry is defined when ΔCSA >mean + 2 SD. **Vascularity**: • Doppler used to detect vascularity in inflamed nerves

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Table 2 Summary of Findings Within Each Study

No.	Authors	Findings on Leprosy Patients			Ref
		Echogenicity	**Nerve Thickening**	**Vascularity**	
1.	Jain et al (2009)[16]	• 72% of nerves showed abnormal echogenicity with mild, moderate, or severe hypo-reflectivity. • Nerves displayed hypo-reflectivity, indicating nerve inflammation or damage.	• Leprosy patients showed significantly greater CSA compared to controls ($p < 0.0001$). • Ulnar nerves reached up to 50 mm^2 in patients with type 1 reactions.	• 26% of nerves showed increased blood flow on Doppler imaging • Increased vascularity correlated strongly with clinical signs of neuritis, sensory loss, and muscle weakness	[13]
2.	Lugao et al (2015)[17]	• NA	• MB patients had significantly thicker nerves compared to PB patients, particularly in the ulnar (Ut and Upt) and median nerves ($p < 0.05$). • MB patients with reactions had greater asymmetry than those without reactions ($p < 0.05$). • Patients with reactions (type 1, type 2, or neuritis) had significantly greater nerve thickening at all nerve points examined, as well as greater asymmetry indices, compared to those without reactions.	NA	[14]
3.	Lugao et al (2016)[24]	• Post-treatment, 54.8% of patients exhibited abnormal echogenicity, which had increased from 42.5% pre-treatment ($p < 0.05$).	• 77.8% of MB patients had poor CSA outcomes (ie, CSA remaining above normal limits and not reducing by at least 30–40% post-treatment), compared to 40.6% in PB patients. • In PB patients, the common fibular nerve (CF) showed the most significant worsening after treatment. • In MB patients, the ulnar and median nerves showed the poorest outcomes after treatment.	• Doppler imaging revealed reduced vascularity after treatment in most patients (from 19.2% pre-treatment to 8.3% post-treatment). • Patients with ongoing neuritis continued to exhibit intraneural Doppler signals	[15]
4.	Singh et al (2017)[26]	• 55% of leprosy patients exhibited reduced echogenicity, indicating intraneural edema and inflammation. • 30% had moderately reduced echogenicity, and 5% had severely reduced echogenicity, where the fascicular pattern was completely lost.	• Significant nerve thickening was found in leprosy patients compared to healthy controls across all examined nerves. • The ulnar nerve had the highest average CSA of 19.66 mm^2 in leprosy patients, compared to 7.94 mm^2 in healthy controls. • 90% of leprosy patients had thickened nerves on ultrasound, compared to only 30% detected via clinical palpation	• 45% of leprosy patients showed increased vascularity on color Doppler, with the presence of epineural, perineural, or endoneural blood flow indicating active inflammation • Among the patients with diagnosed leprosy reactions (type 1 or type 2), 75% showed increased neural vascularity, whereas no vascularity was detected in patients without reactions	[16]

5.	Chen et al (2018)[25]	• NA	• Significant enlargement of median and ulnar nerves in the upper limbs of leprosy patients compared to controls. • CSA of median nerve in the forearm (1/3) showed significant differences: • Leprosy patients: $p = 0.0045$ (left), $p = 0.0394$ (right). • Paucibacillary (PB) group had greater nerve enlargement compared to Multibacillary (MB) group. • For ulnar nerves, significant enlargement at the cubital tunnel (Ut) and proximal to the tunnel (Upt) was observed.	NA	[17]
6.	Nagappa et al (2021)[18]	• 14.4% of nerves (46 nerves) showed hypoechogenicity, indicating a loss of fascicular architecture. • Most prominent in ulnar and median nerves, suggesting inflammatory changes.	• CSA of the median nerve was significantly greater in leprosy patients, particularly at the M1 point (2 cm proximal to the wrist). • M1 CSA in leprosy: 16.07 ± 5.20 mm^2, compared to 8.42 ± 1.44 mm^2 in CTS and 6.03 ± 1.06 mm^2 in healthy controls ($p < 0.05$).	• 10.9% of nerves (35 nerves) showed increased vascularity. • 50% of right ulnar nerves and 26.7% of left ulnar nerves with abnormal CSA exhibited increased blood flow, especially in patients with type 1 and type 2 reactions.	[18]
7.	Venugopal et al (2021)[19]	• Hypoechogenicity with loss of fascicular architecture was observed in 14.4% of nerves (46 nerves). • Most common in ulnar and median nerves, indicating inflammatory changes.	• 22.18% of nerves were clinically abnormal, while 19.7% were sonologically abnormal. • Ulnar nerves were the most affected (45% right ulnar, 37.5% left ulnar). • Increased cross-sectional area was the most consistent sonological finding (present in all 63 sonologically abnormal nerves).	• 10.9% of nerves (35 nerves) showed increased vascularity, more frequent in severe cases. • 50% of sonologically abnormal right ulnar nerves and 26.7% of left ulnar nerves exhibited increased blood flow. • Vascularity was frequently associated with type 1 and type 2 leprosy reactions.	[19]
8.	Sreejith et al (2021)[20]	• 72% of the examined nerves exhibited abnormal echogenicity (hypoechogenicity) in leprosy patients.	• Ultrasound detected thickening in 141 of 300 nerves (47%), significantly more than the 60 nerves (20%) detected by clinical palpation ($p < 0.001$). • Thickening was more prevalent in nerves with functional impairment, detected in 50 of 70 nerves (71.4%) with impairment, compared to 91 of 230 nerves (39.6%) without impairment.	• Hypervascularity was observed in 77% of the thickened nerves, correlating with nerve damage and clinical symptoms like sensory loss and muscle weakness. • 26% of nerves showed increased blood flow on Doppler imaging, with hypervascularity strongly associated with clinical signs of neuritis ($p < 0.0001$).	[20]

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Table 2 (Continued).

No.	Authors	Findings on Leprosy Patients			Ref
		Echogenicity	**Nerve Thickening**	**Vascularity**	
9.	Akita et al (2021)[9]	• Loss of fascicular architecture was noted in 54.8% of nerves post-treatment, an increase from 42.5% pre-treatment (p < 0.05),	• Ultrasound diagnosed inflammatory activity (IA) in 74% of patients, slightly greater than the 68% detected by nerve conduction studies (NCS).	• 26% of nerves exhibited hypervascularity on Doppler imaging • In patients with minor or early-stage nerve inflammation, 34% of nerves with axonal involvement also showed blood flow on Doppler imaging through ultrasound.	[9]
10.	Dugad et al (2022)[21]	• Changes in echogenicity were observed in 91.17% of cases, with a 100% positive predictive value (PPV) for detecting nerve damage.	• Nerve thickening was detected in 18.4% (68 of 370 nerves) across 37 leprosy patients. • The most affected nerve was the ulnar nerve, with 38 out of 68 nerves (55.88%) showing significant thickening (mean CSA = 12.47 mm^2, above the normal threshold of 8.17 mm^2).	• Sensitivity for detecting hypervascularity was 10.52% for the ulnar nerve and 11.11% for the median nerve, suggesting that ultrasound is more effective in early inflammatory stages rather than in advanced cases with long-standing damage.	[21]
11.	Spitz et al (2022)[22]	• 52% of nerves exhibited changes in fascicular architecture, which is a key indicator of neuritis and nerve damage.	• 76.2% of ulnar nerves with nerve function impairment (NFI) and 41% without NFI showed thickening by ultrasound.	• 26% of nerves had power Doppler flow, strongly linked to neuritis and sensory loss	[22]
12.	Voltan et al (2023)[27]	• Abnormal echogenicity was detected in 54.8% of patient's post-treatment, up from 42.5% pre-treatment, indicating ongoing nerve damage in some patients despite therapy.	• 40% of patients diagnosed with Hansen's disease (HD) showed significant nerve thickening, as indicated by ultrasound. • Asymmetry in nerves (ΙCSA) was detected in >20% of household contacts (HHCs), suggesting subclinical nerve involvement.	• 19.2% of patients had detectable vascularity before treatment, dropping to 8.3% post-treatment, suggesting a reduction in inflammation with therapy.	[23]
13.	Khan et al (2023)[28]	• 91.17% sensitivity for detecting abnormal echogenicity, with hypoechogenicity associated with nerve thickening.	• 71% of patients showed nerve thickening, detected earlier on ultrasound than by clinical palpation. • Ulnar nerve: CSA >0.085 cm^2 in 38 cases; Median nerve: CSA >0.062 cm^2 in 9 cases; Common Peroneal: CSA >0.059 cm^2 in 5 cases	• Doppler ultrasound detected hypervascularity in 7.35% of nerves, correlating with active inflammation in early-stage patients	[24]
14.	Luppi et al (2023)[13]	• NA	• 26.5% of seropositive household contacts (SPHCs) showed detectable nerve thickening (p = 0.0038), indicating early or subclinical nerve involvement. • On average, 1.8 nerves per contact were affected. • The ulnar and median nerves were the most affected nerves in the study.	• No Doppler signals were detected in any nerve in SPHCs or healthy controls, suggesting a lack of active inflammation.	[12]

15	Aggarwal et al (2024)[23]	• Reduced echogenicity was observed in thickened nerves, indicating nerve damage or inflammation, common in affected ulnar and common peroneal nerves.	• 5.8% of ulnar nerves and 11.7% of common peroneal nerves showed thickening on ultrasound. These nerves had no electrophysiological impairments (no motor/ sensory dysfunction). • The most common nerve to show thickening was the ulnar nerve, particularly at the medial epicondyle (elbow), which is a frequent site for nerve hypertrophy in leprosy patients.	• Increased vascularity in thickened nerves, seen in both ulnar and common peroneal nerves, suggests nerve inflammation or repair.	[23]

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The most frequently examined nerves were the ulnar, median, and common fibular nerves, with some studies extending their analysis to the posterior tibial and radial nerves.[1] Ultrasound machines used in these studies included the Voluson 730 Expert, Phillips HDI-11, and Siemens ACUSON, with transducer frequencies ranging from 3 MHz to 18 MHz depending on the nerve and study protocols (Table 1).

The key ultrasound parameters investigated were echogenicity, cross-sectional area (CSA), and vascularity. Echogenicity findings varied from mild hypoechogenicity to severe loss of fascicular patterns, reflecting varying degrees of nerve damage and inflammation. All studies reported significant increases in CSA among leprosy patients, particularly in the ulnar and median nerves, indicating nerve thickening. Doppler imaging, used in several studies, revealed increased blood flow in affected nerves, which was strongly correlated with active inflammation and leprosy reactions (Tables 1 and 2).

Echogenicity and Nerve Damage

Changes in echogenicity are critical indicators of nerve damage in leprosy, with hypoechogenicity being a hallmark of nerve inflammation and degeneration. Jain et al observed abnormal echogenicity in 72% of nerves, with changes ranging from mild to severe hypo-reflectivity, indicating different stages of nerve damage.[18] Lugao et al showed that echogenicity abnormalities increased post-treatment, rising from 42.5% to 54.8% ($p < 0.05$), suggesting that while treatment mitigated some inflammatory processes, it did not fully resolve nerve damage.[19]

In parallel findings, Nagappa et al reported that 14.4% of nerves exhibited hypoechogenicity, with the ulnar and median nerves being most affected, indicating significant structural damage.[20] Similarly, Venugopal et al noted that 14.4% of nerves showed hypoechogenicity with the loss of the fascicular pattern, further confirming the presence of inflammatory nerve damage in leprosy patients.[21]

Complementing these findings, Sreejith et al documented hypoechogenrevicity in 72% of examined nerves, often accompanied by honeycomb pattern loss and clinical dysfunction.[22] Dugad et al further emphasized the diagnostic value of echogenicity alterations, reporting structural disruption in over 91% of cases.[25] Spitzid et al observed fascicular architectural loss in more than half of examined nerves,[15] while Aggarwal et al confirmed hypoechogenicity in thickened nerves, even in the absence of measurable functional loss.[17] These results reinforce the role of echogenicity assessment as an early and sensitive indicator of nerve damage in leprosy.

Nerve Thickening and Cross-Sectional Area

One of the most consistent findings across studies is the increased CSA in nerves affected by leprosy. Jain et al demonstrated that CSA measurements in leprosy patients were significantly greater compared to controls ($p < 0.0001$), with ulnar nerves showing some of the highest increases, especially in patients experiencing type 1 leprosy reactions.[18] Similarly, Lugao et al found that multibacillary leprosy patients exhibited thicker ulnar and median nerves compared to paucibacillary patients ($p < 0.05$),[15] further supporting the role of ultrasound in differentiating leprosy subtypes.[16,23]

In a more detailed study, Nagappa et al highlighted the prominence of nerve thickening in the median nerve, particularly at the M1 point (2 cm proximal to the wrist), with a CSA of 16.07 ± 5.20 mm^2 in leprosy patients, significantly greater than in carpal tunnel syndrome patients (8.42 ± 1.44 mm^2) and healthy controls (6.03 ± 1.06 mm^2, $p < 0.05$).[19] Moreover, Singh et al reported that 90% of leprosy patients showed nerve thickening detectable by ultrasound while only 30% were detectable via clinical palpation, underscoring the superior sensitivity of ultrasound in detecting subclinical neural involvement.[24]

Further supporting these observations, Chen et al reported significant nerve thickening in both median and ulnar nerves, with greater enlargement in paucibacillary patients and prominent involvement at the cubital tunnel.[23] Spitzid et al found sonographic thickening in 76.2% of nerves with function loss, and even 41% of those without symptoms, demonstrating ultrasound's sensitivity.[15] Voltan et al detected significant asymmetry in CSA among >20% of household contacts,[26] while Luppi et al reported similar thickening in 26.5% of seropositive contacts.[12] Khan et al24 observed CSA abnormalities in 71% of leprosy patients,[27] and Aggarwal et al confirmed focal thickening in the ulnar and common peroneal nerves,[17] highlighting that nerve hypertrophy can be present even without concurrent electrophysiological changes.

Vascularity and Inflammation

Vascularity, assessed using Doppler ultrasound, provides insight into the inflammatory activity within leprosy-affected nerves.[9,15,18] Jain et al reported that 26% of nerves exhibited increased vascularity, with a strong correlation between blood flow and neuritis, sensory loss, and muscle weakness ($p < 0.0001$).[18] This finding was further supported by Singh et al, who observed increased vascularity in 45% of leprosy patients, especially those with type 1 and type 2 reactions, of whom 75% displayed Doppler-detectable blood flow within affected nerves.[24]

In addition, Nagappa et al demonstrated that 10.9% of nerves exhibited increased vascularity, with 50% of right ulnar nerves and 26.7% of left ulnar nerves showing Doppler signals, particularly in patients experiencing type 1 or type 2 leprosy reactions.[20] This increase in vascularity reflects the heightened inflammatory activity within these nerves. However, Lugao et al showed that after leprosy treatment, the frequency of Doppler signal detection decreased from 19.2% to 8.3%, reflecting a reduction in inflammatory activity post-therapy.[16]

Additional studies validate the diagnostic value of vascularity assessment. Akita et al found that Doppler imaging detected inflammatory flow in 26% of nerves, including early-stage patients with only subtle axonal signs.[9] Sreejith et al observed hypervascularity in 77% of thickened nerves, tightly linked to clinical symptoms like muscle weakness.[22] Similarly, Spitz et al noted Doppler flow in 26% of nerves with suspected neuritis.[15] Aggarwal et al confirmed increased vascularity in structurally thickened nerves, suggesting that Doppler evaluation may be useful not only for detecting active inflammation but also for monitoring potential repair.[17]

Sensitivity of Ultrasound in Detecting Subclinical Neuropathy

Ultrasound has proven to be more sensitive than clinical palpation in detecting subclinical neuropathy in leprosy patients.[18,26,27] Sreejith et al found that ultrasound detected thickening in 47% of nerves, compared to only 20% detected through clinical examination, highlighting the utility of ultrasound in identifying nerve damage early in the disease process.[22] Khan et al further corroborated these findings, demonstrating that ultrasound identified nerve thickening in 71% of patients, even in cases where no clinical symptoms were present.[27] These findings underscore the importance of ultrasound as a diagnostic tool in identifying early-stage neuropathy, particularly in asymptomatic patients or those with subtle clinical signs, making it invaluable for early intervention and management of leprosy.

Further insights strengthen this argument. Luppi et al demonstrated that subclinical nerve involvement could be visualized in seropositive contacts with no Doppler signal, suggesting that structural changes may precede inflammation.[12] Akita et al found that ultrasound detected inflammation in 74% of cases, slightly outperforming nerve conduction studies (68%).[9] These results validate the role of ultrasound in preclinical screening, particularly for individuals in endemic settings or with close household contact to leprosy cases.

Discussion

Leprosy presents a broad spectrum of clinical manifestations dependent on the host's immunity to M. leprae.[26] Experimental models suggest that the bacillus gains access to the endoneurium via blood supply, either through direct infection of endothelial cells or transmigration of infected monocytes.[28,29] Toll-like receptor (TLR)-mediated interactions play a significant role in nerve damage, as evidenced by in vitro studies showing Schwann cell destruction via TLR2 activation by M. leprae.[28,30] The most commonly affected nerves include the ulnar, radial, median, tibial, and common peroneal nerves, leading to symptoms such as sensory loss, paresthesia, and motor impairments.[5,7] In endemic regions like India and Indonesia, delayed diagnosis frequently results in patients presenting at grade I disability, underscoring the critical need for accessible and accurate diagnostic modalities.[31,32]

A fundamental challenge in synthesizing evidence from the 15 included studies is the substantial methodological heterogeneity. Studies differed considerably in ultrasound equipment (Voluson 730 Expert, Philips HDI-11, Siemens Acuson), transducer frequencies (3–18 MHz), Doppler settings including pulse repetition frequency (PRF) and gain, anatomical measurement points, and operational definitions of abnormality. This variability limits direct inter-study comparability and precludes quantitative pooling of results. Accordingly, all figures in this review, including ranges of Doppler positivity (11–45%), proportions of hypoechogenicity (14–72%), and reported sensitivities (63–90%) with specificities (67–100%), represent ranges across individual studies, not pooled estimates, and must be interpreted as qualitative diagnostic patterns reflecting the current state of evidence rather than precise quantitative benchmarks.

Echogenicity and Nerve Architecture

Echogenicity assessment via ultrasound offers valuable structural insight into nerve pathology in leprosy. Hypoechogenicity, commonly reflecting edema, inflammation, or fascicular disorganization, has been consistently reported across studies, albeit with variable prevalence likely attributable to differences in patient populations disease severity, equipment, and grading criteria. Jain et al first highlighted its diagnostic relevance, identifying echogenicity abnormalities in 72% of nerves affected by leprosy. In contrast, both Nagappa et al and Venugopal et al each reported hypoechogenicity in 14.4% of nerves, while Sreejith et al found abnormalities, as in honeycomb patterns loss, in 72% of examined nerves[22] and Dugad et al reported structural disruption in 91.17% using a 4-point grading scale.[25]

Lugao et al further observed that such changes can persist or worsen post-treatment, rising from 42.5% to 54.8% ($p < 0.05$), suggesting ongoing or irreversible damage despite therapy.[16] Khan et al linked increasing echogenicity severity with inflammatory activity and CSA enlargement, supporting its use in disease monitoring.[27] Importantly, Luppi et al documented fascicular disruption in asymptomatic household contacts,[12] and Aggarwal et al observed hypoechogenicity in structurally damaged nerves undetectable by electrophysiological testing,[17] both suggesting that echogenicity changes may precede clinical manifestations and represent the earliest detectable stage of neuropathic involvement.

These findings emphasize echogenicity as a sensitive, non-invasive marker of both overt and subclinical neural involvement, complementing CSA and vascularity in comprehensive ultrasound evaluation.

Cross-Sectional Area: Sensitive but Nonspecific

Nerve enlargement measured by CSA is the most consistently reported ultrasound finding across all 15 studies. Jain et al demonstrated a mean ulnar nerve CSA of 19.66 mm^2 in leprosy patients compared to 7.94 mm^2 in healthy controls ($p < 0.0001$),[14] with particularly marked enlargement in type 1 reaction patients. Lugao et al found that severe multibacillary leprosy cases showed ulnar nerve CSA exceeding 50 mm^2.[19] Nagappa et al highlighted prominent median nerve thickening at the M1 point (2 cm proximal to the wrist), with a CSA of 16.07 ± 5.20 mm^2 in leprosy patients versus 8.42 ± 1.44 mm^2 in carpal tunnel syndrome patients and 6.03 ± 1.06 mm^2 in healthy controls ($p < 0.05$). Singh et al reported that 90% of leprosy patients showed detectable nerve thickening by ultrasound, compared to only 30% by clinical palpation, reinforcing ultrasound's superior sensitivity for subclinical involvement.

Although several studies employed CSA cut-offs in the range of 8–12 mm^2 for ulnar and median nerves in endemic settings, no universal diagnostic threshold can be derived from the available evidence. Studies differed in reference standards, from clinical criteria alone to combined clinical, microbiological, and electrophysiological assessments, and several used relative measures such as delta-CSA (ΔCSA) rather than absolute values, with thresholds frequently determined post-hoc. Critically, CSA enlargement is not specific to leprosy: comparable patterns are documented in diabetic peripheral neuropathy,[33] chronic inflammatory demyelinating polyneuropathy (CIDP),[34] and entrapment neuropathies such as carpal tunnel syndrome.[35] CSA should therefore be regarded as a sensitive but nonspecific screening marker whose interpretation requires integration with clinical, epidemiological, and Doppler findings to avoid diagnostic error, particularly in non-endemic settings where alternative neuropathies are more prevalent.

Doppler Vascularity: Active Neuritis and Technical Considerations

Ultrasound, especially high-resolution ultrasound, has emerged as a valuable tool in detecting and managing leprosy-related neuropathy.[11] Ultrasound provides precise imaging, revealing key anatomical changes, such as nerve thickening and architectural alterations. For example, transverse ultrasound images often display a "honeycomb-like" pattern due to hypoechoic nerve fascicles separated by hyperechoic perineurium, while longitudinal views show a "bundle of straws" appearance.[27]

Doppler ultrasound further enhances ultrasound's diagnostic capabilities by assessing vascularity, a key indicator of inflammation.[15,25] This feature is particularly useful for distinguishing between active inflammatory processes and chronic nerve damage, as active inflammation is typically associated with increased vascularity in affected nerves.[11]

Jain et al reported increased vascularity in 26% of nerves with strong correlations to neuritis, sensory loss, and muscle weakness ($p < 0.0001$).[18] Singh et al observed Doppler-detectable flow in 45% of leprosy patients, particularly prominent in 75% of those experiencing type 1 or type 2 reactions.[23] Nagappa et al found vascularity in 10.9% of nerves overall, rising to 50% of right and 26.7% of left ulnar nerves during active reactions.[20] Akita et al detected inflammatory flow in 26% of nerves including early-stage patients with only subtle axonal signs,[9] and Sreejith et al reported hypervascularity in 77% of thickened nerves closely linked to clinical symptoms.[22] Post-treatment reductions, from 19.2% to 8.3% (Lugao et al),[16] underscore its potential for monitoring treatment response.[19,20,32]

The wide variability in Doppler positivity across studies (11–45%) likely reflects technical differences rather than true biological variation alone. PRF settings, gain adjustments, transducer frequency, and insonation angle substantially affect sensitivity to low-velocity intraneural flow, making cross-study comparison of Doppler rates unreliable without standardized acquisition protocols. It is equally important to recognize that Doppler is primarily a tool for identifying active neuritis and monitoring inflammatory disease activity,[15,25] rather than for detecting chronic structural nerve damage. Nerves with persistent CSA enlargement and hypoechogenicity from long-standing damage may show absent Doppler signals once the inflammatory phase has subsided.[9] A negative Doppler result therefore does not exclude leprosy neuropathy when structural abnormalities are present, and this distinction carries direct clinical relevance for patient management.[17,36]

Limitations and Negative Findings Across Included Studies

Several studies revealed important limitations of ultrasound application. Lugao et al demonstrated echogenicity abnormalities can persist or even worsen post-treatment (42.5%→54.8%, $p < 0.05$), indicating incomplete structural recovery despite clinical improvement.[15] Doppler vascularity normalized after therapy (19.2%→8.3%) but correlated poorly with functional NCS recovery.[9,16] Aggarwal et al found ultrasound detected abnormalities in only 63% of clinically palpable nerves,[17] while NCS identified axonal loss in chronic cases where ultrasound appeared normal.[17,36] These findings highlight ultrasound's reduced sensitivity for longstanding damage and underscore the need for multimodal evaluation.

Household Contacts and Subclinical Neuropathy: The Earliest Diagnostic Window

Among the most clinically significant findings of this review is the detection of subclinical structural nerve abnormalities in seropositive household contacts without overt clinical symptoms. Voltan et al identified significant CSA asymmetry in more than 20% of household contacts of Hansen's disease patients,[26] while Luppi et al demonstrated structural nerve changes, including fascicular disruption and CSA enlargement, in 26.5% of seropositive contacts, notably in individuals without any Doppler signal.[12] This latter finding suggests that structural nerve involvement may precede inflammatory activity, positioning HRUS as uniquely capable of identifying the earliest phase of neuropathic disease before clinical, electrophysiological, or Doppler changes emerge [[9,12,26–22]]. These observations are further corroborated by Sreejith et al, who found ultrasound-detectable thickening in 47% of nerves compared to only 20% by clinical examination,[27] and Khan et al, who identified CSA abnormalities in 71% of leprosy patients including asymptomatic cases.[27]

Pure Neural Leprosy: Bridging the Diagnostic Gap

Pure neural leprosy (PNL), characterized by peripheral nerve involvement in the absence of cutaneous lesions, represents a diagnostically challenging subtype that is systematically underdiagnosed by conventional approaches.[1] Clinical examination and NCS may both be insufficient in early PNL, leaving a critical diagnostic gap. HRUS directly addresses this challenge: Roy et al recently demonstrated that HRUS consistently reveals asymmetric nerve enlargement in PNL, most frequently of the ulnar nerve, and when combined with ultrasound-guided fine needle aspiration cytology (FNAC), achieved a diagnostic yield exceeding 90%.[37]

This approach enables histological confirmation without the invasiveness of open nerve biopsy, substantially reducing procedural risk. The clinical relevance of this application is particularly high in endemic regions where PNL may account for a significant proportion of undiagnosed or misattributed neuropathies, and further prospective studies are needed to validate ultrasound-guided procedures as a standard diagnostic pathway in this subgroup.

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Ultrasound in Context: Comparison with Other Diagnostic Modalities

Ultrasound offers distinct practical advantages over alternative diagnostic modalities for leprosy neuropathy. NCS assesses functional nerve integrity but may remain normal despite detectable structural damage on HRUS:[15,36] Aggarwal et al confirmed CSA enlargement and hypoechogenicity in nerves with normal electrophysiology,[17] while Akita et al found HRUS with color Doppler detected inflammatory changes in 74% of reaction cases compared to 68% by NCS,[9] demonstrating superior sensitivity in the acute inflammatory setting [[25]—[17]]. Conversely, NCS may reveal functional deficits before structural HRUS changes appear, supporting a complementary rather than substitutive relationship between modalities.[9,27]

Magnetic resonance neurography (MRN) provides detailed visualization of deep nerve segments and plexopathies but is substantially limited by high cost, equipment scarcity in low-resource endemic settings, and longer acquisition times. In contrast, HRUS is portable, repeatable, bedside-capable, and cost-effective, attributes that make it particularly well-suited to high-volume endemic settings and community-level screening. The present review is the first to comprehensively synthesize all three key HRUS parameters (echogenicity, CSA, and vascularity) within a single analysis, providing an integrated evidence base for their combined diagnostic utility.

Conclusion

This scoping review confirms ultrasound's utility for early leprosy neuropathy detection, revealing consistent patterns of hypoechogenicity (14–72% of nerves), CSA enlargement (particularly ulnar/median in multibacillary cases), and Doppler vascularity (11–45%, correlating with active neuritis). These findings highlight its superior sensitivity over clinical palpation for subclinical involvement, especially among household contacts and PNL suspects.

For clinicians in endemic areas: integrate routine ultrasound screening of ulnar/median nerves in high-risk contacts, use Doppler for reaction monitoring, and combine with NCS for comprehensive evaluation, facilitating timely intervention and disability prevention.

However, key limitations preclude definitive diagnostic thresholds, such as substantial methodological heterogeneity, predominance of single-center cross-sectional designs with small samples, and inconsistent reference standards across studies. Future research should focus on methodological standardization, longitudinal designs, and development of consensus definitions for ultrasound parameters in leprosy neuropathy.

Abbreviations

CSA, Cross-sectional area; FNAC, Fine needle aspiration cytology; HRUS, High-resolution ultrasound; MB, Multibacillary; *M. leprae, Mycobacterium leprae*; MRN, Magnetic resonance neurography; NCS, Nerve conduction studies; NLP, Pure neural leprosy; PB, Paucibacillary; PRF, Pulse repetition frequency; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-ScR, PRISMA extension for Scoping Reviews; TLR, Toll-like receptor; WHO, World Health Organization.

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