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Role of high resolution ultrasonography in leprosy

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ABSTRACT

Background: Ultrasonography is a safe and cost-effective modality to assess gross morphological changes in nerves non-invasively. Early diagnosis will allow the early institution of therapy and arrest the progression of the disease thus, helping in decreasing disability grading. **Aims and Objectives:** The aim of the study was to assessing the role of high-resolution ultrasonography (HRUS) in leprosy. The objectives of the study were to detect sonographic changes in nerves in leprosy patients, and to detect neural complications by sonography in leprosy patients. **Materials and Methods:** The study was conducted over 18 months from the year 2020–2021 at 'Teerthanker Mahaveer Medical College and Research Centre, Moradabad. A total of 37 patients were included in our study. HRUS was performed on the bilateral ulnar nerve (UN), median nerve (MN), radial nerve (RN), lateral popliteal (LPN) nerve, and posterior tibial nerve (PTN) to see the following parameters: Nerve thickening, echogenicity, color flow, and abscess. **Results:** The UN was most frequently involved followed by the PTN, MN, LPN, and RN. Diagnostic performance of HRUS for echogenicity was good with sensitivity, positive predictive value, and accuracy and was observed as 91.17%, 100%, and 91.17%, respectively. **Conclusion:** HRUS has several benefits in leprosy scanning; it is a reliable and non-invasive method of assessing alternations in the nerve at sites that may be difficult to be biopsied for histology.

Key words: High-resolution ultrasonography; Leprosy; Non-invasive

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INTRODUCTION

Even known in the old times, leprosy is considered a major human epidemic disease.[1] Leprosy aka Hansen's disease is a rare infectious disease, but still, there are more than 2 lakh new cases worldwide, and is speculated that globally, greater than 4 million people with leprosy remain undiagnosed.[2,3] Mycobacterium leprae and mycobacterium lepromatosis develop a chronic and slowly progressing inflammatory illness. It principally affects the skin, and causing peripheral nerve damage, landing in paralysis and anesthesia and leading to the deformities and trophic changes, which are characteristic of leprosy, and in high bacilli state, internal organs also get affected.[4-6]

Relapses are uncommon, but any destruction caused by neuropathy is permanent and may need lifetime care.[7-9]

High-resolution ultrasonography (HRUS) in diagnosing leprosy

HRUS is non-invasive and can be used to evaluate structural alterations in nerves which are difficult for biopsy for histopathology. It is also less expensive than magnetic resource imaging (MRI). The usefulness of HRUS is becoming more recurrent in the differentials of peripheral neuropathy. HRUS is a method for examining soft tissues in static and dynamic states, like blood flow, in real-time.[10] This technique can essentially portray all nerves in the extremities in superb detail due to its enhanced contrast and spatial resolution, which is notably useful in the case of leprosy.[11] HRUS can become a standard technique to augment the clinical diagnosis of leprosy as technological advances lead to greater picture quality, handy ultrasonographic equipment, and economical costs.[12,13]

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Since nerve enlargement and inflammation are central tenets of leprosy, this study was designed to assess peripheral nerve damage in leprosy patients by HRUS and also to establish HRUS as an initial and helpful aid for the diagnosis of leprosy.

HRUS is a sensitive, cost-effective, non-invasive, and rapid imaging tool to obtain a clear morphological overview of nerves. It is readily available, well accepted by patients, and provides a dynamic evaluation in real-time. MRI is a time-consuming, costly investigation with limited expertise and is not widely available. HRUS in expert hands provides high accuracy and specificity. Our study aims to assess the role of HRUS in leprosy.

Aims and objectives

Aim

The aim of the study was to assessing role of HRUS in leprosy.

Objectives

The objectives of the study were to detect sonographic changes in nerves in leprosy patients, and to detect neural complications by sonography in leprosy patients.

MATERIALS AND METHODS

A cross-sectional observational study was conducted over 18 months from the year 2020–2021 at Teerthanker Mahaveer Medical College and Research Centre, Moradabad. The study was done on patients referred to the Radiology Department by other departments after clinical diagnosis of leprosy.

A total of 37 patients were included in our study. The sample size achieved was 37* patients. (*As per the govt. orders no.1090/5-5-2020 dated May 4, 2020- TMMC and RC has been a dedicated COVID-19 Hospital).

Inclusion criteria

Patients of all ages andboth sexes with the clinical diagnosis of leprosy were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

- Non-cooperative patients
- Previous nerve biopsy or surgery, systemic lupus erythematous, alcoholism, and any other cause of peripheral neuropathy
- Pregnant women
- Patients having diabetes mellitus, hypothyroidism, HIV, and trauma-related peripheral nerve diseases.

A total of 37 clinically diagnosed patients with leprosy meeting the inclusion criteria were taken for study. The patients were informed about the procedure and duration along with the associated risk (if any) with the procedure. Written consent was taken from all patients who met the inclusion criteria and data were collected on printed Pro forma, an ethical clearance was obtained from the Teerthanker Mahaveer Medical College and Research Centre, Moradabad.

High resolution ultrasonography was performed on bilateral ulnar nerve (UN), median nerve (MN), radial nerve (RN), lateral popliteal (LPN) nerve, posterior tibial nerve (PTN) to see for nerve thickening, echogenicity, color flow, and abscess.

Included nerves were examined at the same specific locations in study patients. UN examined at elbow level at medial epicondyle and 4 cm above with arm abducted and elbow flexed slightly. MN assessed at wrist and 4 cm above with patient arm in supine position. RN is assessed in radial groove posterolaterally with probe placed perpendicular and midway along shaft of humerous. LPN nerve assessed in popliteal fossa over fibular head with patient in prone position and knees extended. PTN assessed above and behind medial malleolous with probe placed perpendicular with the lower limb rotated externally.

- Measurement of maximum nerve thickness (C.S.A.) was recorded in each patient.
- As per Sreejith et al.,[14] studies cutoff values for the nerve to be thickened were > 8.17 mm^2 for the UN. >7.1 mm^2 for RN, 10•17 mm^2 for MN, >9.5 mm^2 for LPN, and >11.21 mm^2 for PTN were taken as references for this study.
- Nerves with C.S.A. values above the reference cutoff are considered to be enlarged.
- All nerves were studied for echogenicity. Ultrasound normal nerve gives characteristic honey comb appearance visualized as hypoechoic nerve fascicles surrounded by hyperechoic epineurium. Change in echotexture of nerves was graded as follows:
    - 0: Normal: Normo-echogenic,
    - 1: Mild: Some hypo-echogenicity,
    - 2: Moderate: Obvious hypo-echogenicity, and
    - 3: Severe: Loss of fascicular pattern.
- All nerves were assessed for color flow as evidence of hypervascularity.
- Abscess formation in nerves was noted as a neural involvement complication.
- All findings were recorded and appropriate statistical tests were applied.

RESULTS

After the acquisition of images, they were interpreted and the findings were recorded on a predefined pro forma. The

collected data were systemized in a Microsoft Excel sheet and then appropriately analyzed statistically. The statistical software SPSS version 20 and Medcalc 19.5 were used for the analysis. Results were compared across the modality and from the previous studies.

The facility required for my study was a highly equipped ultrasound machine which was available in our radiology department using SIEMENS ACUSON S 2000 and S 3000. Thus, the facilities available here were the most optimum to carry out my study.

The patients' age ranged from 17 to 70 years with mean age of 42.56±14.8 years. The most commonly affected age group was 56-60 years with 6 (16.2%) patients, closely followed by18–25 and 46–50 years age group with 5 (13.5%) and 5 (13.5%) patients, respectively. Maximum number of affected males was in the age group of 41–45, 51–55, and 56-60 years with total of14 (10.8%) in each. None of the male patient was affected below 18 year age group. Females were affected more in the age group of 31–35 years with a total of 3 (8.1%) women in this age group, followed by 18–25, 26–30, 36–40, 41–45, 56–60, and >60 years group with 2 (5.4%) patients in each group.

Number of patients were highest in duration of disease 0–0.5 years (29.7%) and 1–1.5 years (29.7%) followed by 0.5–1 years (16.2%) and were lowest in 2.5–3 years and >3 years duration group with 5.4% each.

Among spectrum, BT was common in patients with total of 11 (29.7%) followed by borderline lepromatous, tuberculoid, lepromatous, and indeterminate with total of 10 (27%), 9 (24.3%), 6 (16.2%), and 1 (2.7%), respectively.

No reaction was observed in 32 (86.5%) patient in majority. Type 1 and Type 2 reactions were observed with 1 (2.7%) and 4 (10.8%), respectively.

On examination, out of total 370 nerves studied in 37 patients. 68 nerves (18.4%) were thickened nerves. It was observed that 38 were UN followed by the PTN, MN, LPN nerve, and RN with 14, 9, 5, and 2 numbers, respectively.

Table 1 depicts the mean cross-sectional area of peripheral nerves measured through HRUS. Out of 370 nerves examined in leprosy patients and grouped based on their respective cutoff values and tabulated. 38 UNs followed by 14 post-tibial, 9 MN, 5 LPN nerve, and 2 RN with mean cut-off cross sectional area (CSA) of 12.47 mm^2 (mean cut off - >8.17) 17.12 mm^2 (mean cutoff - > 11.21), 17.06 mm^2 (mean cutoff - >10.17), 15.70 mm^2 (mean cutoff - >9.5), and 8.8 mm^2 (mean cutoff - >7.1).

To explore the diagnostic performance of HRUS, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated considering only positive findings. Since in this study we considered only positive findings, specificity and NPV were not obtained.

Table 2 depicts Diagnostic performance of HRUS for echogenicity. For UN echogenicity, sensitivity, PPV, and accuracy were observed at 94.74%, 100%, and 94.74%, respectively. Similarly for other nerves sensitivity, PPV and accuracy were observed more than 80%, for RN (100%, 100%, and 100%), MN (88.88%, 100%, and 88.88%), LPN (80.00%, 100%, and 80.00%), and PTN (85.71%, 100%, and 85.71%), respectively.

Table 3 depicts that Diagnostic test of HRUS for color flow showed poor performance and sensitivity, PPV and accuracy were observed at 10.52%, 100%, and 10.52% and 11.11%, 100%, and 11.11% for UN and MN, respectively. No findings were observed for RN, LPN, and PTN.

Table 4 depicts that For nerve abscess, HRUS showed very poor performance, sensitivity, PPV, and accuracy were observed at 7.89%, 100%, and 7.89%, respectively, for UN while no findings were observed for MN, RN, LPN, and PTN.

Table 5 depicts the overall diagnostic performance of HRUS for echogenicity, sensitivity, PPV, and accuracy were observed at 91.17%, 100%, and 91.17%, respectively. Similarly for other parameters sensitivity, PPV and accuracy were observed for color flow (7.35%, 100%, and 7.35%) and nerve abscess (4.41%, 100%, and 4.41%) (Figures 1-3).

DISCUSSION

In leprosy, the involvement of peripheral nerves results in disability, ulcer formation, and deformities that can be stigmatizing. Thus the importance of early diagnosis

Table 1: Distribution of nerves based on cut-off cross sectional area

Nerve	Cut-off	N	Min.	Max.	Mean	SD
UN	<8.17	36	4	6.9	5.35	0.81
	>8.17	38	9.2	35	12.47	5.13
RN	<7.1	72	1.3	5.3	2.74	0.84
	>7.1	2	8.7	8.9	8.8	0.14
MN	<10.17	65	3.4	7	4.64	0.72
	>10.17	9	10.5	33	17.06	9.01
LPN	<9.5	69	4.3	8	6.30	0.88
	>9.5	5	10.5	18	15.70	3.07
PTN	<11.21	60	5	9.2	7.53	0.99
	>11.21	14	12	33	17.12	6.60

UN: Ulnar nerve, MN: Median nerve, RN: Radial nerve, LPN: Lateral popliteal nerve, PTN: Posterior tibial nerve

of nerve involvement in leprosy has been emphasized in various studies.[15-17]

In this study, it was observed that the patients' age ranged from 17–70 years with a mean age of

Table 2: Diagnostic performance of HRUS for echogenicity in leprosy patients

Echogenicity		Thickened nerve		Diagnostic performance	
Nerve		Absent	Present		
UN	Absent	0	2	Sensitivity (%)	94.74
	Present	0	36	Specificity (%)	0.00
		0	38	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	94.74
RN	Absent	0	0	Sensitivity (%)	100
	Present	0	2	Specificity (%)	0.00
		0	2	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	100
MN	Absent	0	1	Sensitivity (%)	88.88
	Present	0	8	Specificity (%)	0.00
		0	9	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	88.88
LPN	Absent	0	1	Sensitivity (%)	80.00
	Present	0	4	Specificity (%)	0.00
		0	5	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	80.00
PTN	Absent	0	2	Sensitivity (%)	85.71
	Present	0	12	Specificity (%)	0.00
		0	14	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	85.71

HRUS: High-resolution ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value, UN: Ulnar nerve, MN: Median nerve, RN: Radial nerve, LPN: Lateral popliteal nerve, PTN: Posterior tibial nerve

Table 3: Diagnostic performance of HRUS for color flow in leprosy patients

Color flow		Thickened nerve		Diagnostic performance	
Nerve		Absent	Present		
UN	Absent	0	34	Sensitivity (%)	10.52
	Present	0	4	Specificity (%)	0.00
		0	38	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	10.52
RN	Absent	0	2	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	2	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00
MN	Absent	0	8	Sensitivity (%)	11.11
	Present	0	1	Specificity (%)	0.00
		0	9	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	11.11
LPN	Absent	0	5	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	5	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00
PTN	Absent	0	14	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	14	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00

HRUS: High-resolution ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value, UN: Ulnar nerve, MN: Median nerve, RN: Radial nerve, LPN: Lateral popliteal nerve, PTN: Posterior tibial nerve

Table 4: Diagnostic performance of HRUS for nerve abscess in leprosy patients

Nerve abscess		Thickened nerve		Diagnostic performance	
Nerve		Absent	Present		
UN	Absent	0	35	Sensitivity (%)	7.89
	Present	0	3	Specificity (%)	0.00
		0	38	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	7.89
RN	Absent	0	2	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	2	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00
MN	Absent	0	9	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	9	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00
LPN	Absent	0	5	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	5	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00
PTN	Absent	0	14	Sensitivity (%)	0.00
	Present	0	0	Specificity (%)	0.00
		0	14	PPV (%)	0.00
				NPV (%)	0.00
				Accuracy (%)	0.00

HRUS: High-resolution ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value, UN: Ulnar nerve, MN: Median nerve, RN: Radial nerve, LPN: Lateral popliteal nerve, PTN: Posterior tibial nerve

Table 5: Overall diagnostic performance of HRUS in leprosy patients

Overall		Thickened nerves		Diagnostic performance	
		Absent	Present		
Echogenicity	Absent	0	6	Sensitivity (%)	91.17
	Present	0	62	Specificity (%)	0.00
			68	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	91.17
Color flow	Absent	0	63	Sensitivity (%)	7.35
	Present	0	5	Specificity (%)	0.00
			68	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	7.35
Nerve abscess	Absent	0	65	Sensitivity (%)	4.41
	Present	0	3	Specificity (%)	0.00
			68	PPV (%)	100
				NPV (%)	0.00
				Accuracy (%)	4.41

HRUS: High-resolution ultrasonography, PPV: Positive predictive value, NPV: Negative predictive value

42.56±14.8 years and the most commonly affected age group is 56–60 years which has partial similarity with the Ashwini et al., study.[18] In that study, patients majorly belonged to the age group 30–60 years. Sreejith et al.,[14] reported in their study age ranging from 16 to 78 years with a mean of 44.4±17.3 years which is almost similar to our findings. Similarly in Elias et al.,[19] studies, patients' age ranged from 10 to 71 years with a mean age of 47.7±17.2 years. The predominant gender is male patients, affected in 54.1% while females in 45.9%, and these findings were found concordant with the study reported by Cavalcanti et al.,[20] (Male 51.1% and females 49.9%).

In our study, disease duration was found to range from 0 to >3 years with the majority in 0-0.5 and 0.5–1.5 years groups with 29.7% each. Our study findings correlate with Jain et al.,[15] studies that studied the role of HRUS in leprosy.

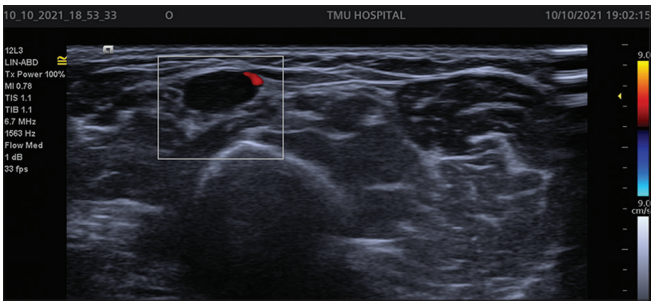

Figure 1: Transverse view showing thickened posterior tibial nerve with complete loss of fascicular pattern with color flow

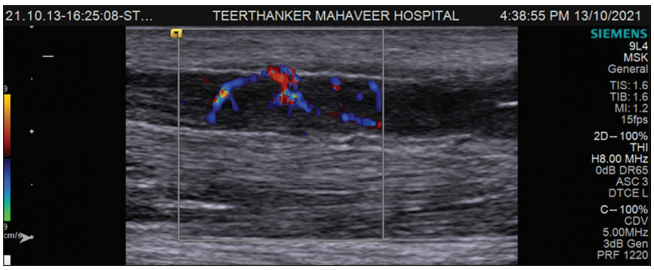

Figure 2: Longitudinal view of thickened ulnar nerve showing color flow

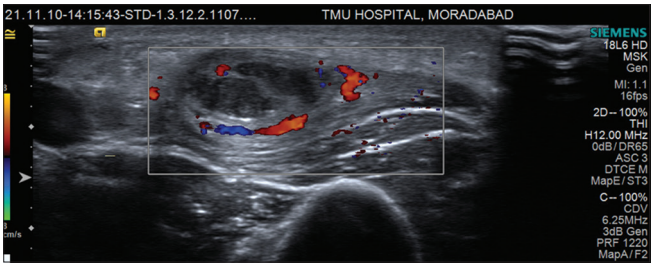

Figure 3: Transverse view showing ulnar nerve (UN) abscess heterogeneously hypoechoic collection with internal echoes within the ulnar nerve. On color Doppler, there is peripheral vascularity around the abscess. Adjacent nerve and perineural tissue also show increased vascularity suggestive of inflammation

Amongst the spectrum of leprosy in patients, the most common spectrum is borderline, in which borderline tuberculoid spectrum accounted for 29.7%, which is in similarity to the study by Ashwini et al.,[18] there also borderline tuberculoid was a major spectrum. Also in the study conducted by Jain et al., 15 patients mostly belonged to the borderline tuberculoid spectrum, which is also in line with our study. Similar findings are also reported by previous studies.[20,21] However, in Elias et al.,[19] studies, patients had polar tuberculoid forms of leprosy in the majority.

In coming to reaction, 32 (86.5%) of the patients had no reaction and Type 1 and Type 2 reactions were observed with 1 (2.7%) and 4 (10.8%) respectively. Whereas in Martinoli et al.,[22] studies, 14 of 58 nerves in the study showed reaction while in Jain et al.,[15] 16 patients showed reactions.

In the study of Jain et al.,[15] CSA mean observed for ulnar, median, LPN, and PTN were 22.7, 14.7, 12.8, and 12 mm^2, respectively. These findings were higher in some instances when compared to our study. This may be attributed due to sample size differences and clinical spectrum variation. Another study by Sreejith et al.,[14] also observed increased CSA for ulnar, radial, median, LPN, and PTN as 10.15±5.118, 6.38±2.19, 11.45±4.25, 13.45±7.67, and 14.82±6.35 mm^2 with statistically significant differences ($P<0.001$).

So these significant rises observed statistically in the mean CSA of ulnar, median, LPN, and PTNs in our cases with leprosy are also in line with other previous reports by Elias et al.,[19] Afsal et al.,[23] and Gupta et al.[24]

In our study, color flow patterns were observed in a total of 5 nerves with 4 in UNs and 1 in MNs whereas, in Jain et al.,[15] studies, 39 nerves presented flow which included 23 ulnar, 10 median, 4 LPN, and 2 PTNs. Increased blood flow is associated with nerve inflammation. The increased flow was noted in patients who were under reaction. Similarly, the increased flow was also seen in patients at risk of reactions or impending reactions. This aids in preventing nerve damage by starting early treatment.

In our study, nerve abscess showed in 3 UNs while no abscess was observed in other nerves. No such study was found in the literature that compared nerve abscesses and matched them with our study setting. Most of the previous study was found to be case report based. Moreover, nerve abscesses are observed in our country in approximately 1.3% of leprosy patients[25,26] and this finding can be considered as partially matching our findings.

To best our knowledge in literature, only a single study done by Elias et al.,[19] reported the diagnostic performance of sonography. Their study looked into the role of UN's sonography in neuropathy due to leprosy and for CSA of 9.8 mm^2 as the cutoff value, their study's sensitivity and specificity were 0.91 and 0.90, respectively. This discordant finding may be attributed due to the sample size and setting condition of the study.

Limitations of the study

- This is a single-center-based study. More extensive studies are hence recommended to remove the pitfalls of this study.
- Time limit and a limited sample size due to the COVID-19 situation. Even though our study had limitations, we employed all of the available resources to achieve the intended results.

CONCLUSION

The following conclusions can be drawn from our study:

- The most commonly affected age group in leprosy is 50–60 years.
- The predominant gender is male patients, affected in 54.1% while females in 45.9%.
- Disease duration was found to range from 0 to >3 years with the majority of the patients falling in the duration period of 0–0.5 and 0.5–1.5 years group. The occurrence was 29.7% in each group.
- The UN was most frequently involved followed by the PTN, MN, LPN, and RN.
- Of all nerves examined UN showed more echo textural abnormality. A significant correlation was found between echogenicity and nerve thickening.
- Increased flow is seen in patients who were in reaction.
- Nerve abscess was found in 3 UNs, while no abscess was observed in other nerves.
- Overall diagnostic performance of HRUS for echogenicity was good with sensitivity, PPV, and accuracy were observed at 91.17%, 100%, and 91.17%, respectively.
- Diagnostic performance for color flow and abscess showed poor performance.
- Thus, HRUS has several benefits in leprosy scanning; it is a reliable and non-invasive method of assessing alternations in the nerve at sites that may be difficult to be biopsied for histology.

When compared to clinical evaluation, HRUS is a non-invasive and cost-efficient method that plays the role of an effective and reliable predictor of nerve thickening in leprosy, indicating increased vascularity, thickness, hypoechoicity, and loss of nerve fascicles. It is a critical modality in the identification of illnesses such as pure neurological Hansen's disease with smear-negative, which requires rapid treatment. Based on the assumed cutoff value for the relevant nerve, it demonstrated appropriate sensitivity, specificity, and accuracy.

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KD- Concept and design of the study, reviewed the literature, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript; **SP**- Concept and design of the study, coordination, interpreted the results, reviewed the literature; **RR**- Concept and design of the study, coordination, statistical analysis, interpreted the results.

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