REVIEW ARTICLE

Progress in the nerve ultrasound of inflammatory peripheral neuropathies

Article history:
Received: 03-03-2023
Revised: 25-06-2023
Accepted: 15-07-2023

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ABSTRACT

Objective: In recent years, high-resolution nerve ultrasound has been increasingly used as a complementary tool to nerve conduction studies in the diagnosis of peripheral neuropathies. Inflammatory peripheral neuropathies include a heterogeneous group of neuropathies mainly including chronic inflammatory demyelinating polyneuropathies (CIDP), multifocal motor neuropathy (MMN), systemic vasculitic neuropathy (SVN), and Guillain-Barre syndrome (GBS). We describe the ultrasonic characteristics of different inflammatory neuropathies.

Data sources and study selection: The MEDLINE database was searched to find studies on nerve sonography in inflammatory peripheral neuropathies. Reported studies up to December 2022 were included in this review.

Results: In neuropathies, the changes in ultrasound include enlarged nerve size, nerve echo-intensity, fascicle diameter and vascularity. Most CIDP patients have moderately enlarged CSA, some have dramatically enlarged CSA, and few have CSA within the normal range. Since the enlargement patterns are different, ultrasound is useful to help differentiate CIDP from CMT1. In follow-ups after immune treatment, nerve CSAs in CIDP could decrease, increase, or remain unchanged. Regional enlargement next to normal segments predominated in MMN. Nerve enlargement and hyper vascularization were found in vasculitic neuropathy. In GBS patients, there were enlarged peripheral nerve and nerve roots, which became normal at follow-up.

Conclusions: High-resolution nerve ultrasound is complementary to the diagnosis of inflammatory peripheral neuropathies. CSA enlargement and its distribution are the most useful and quantifiable parameters in the evaluation of peripheral nerves. For patients suspected to have inflammatory neuropathies, we advise measuring the CSA of several pre-determined sites in the median, ulnar nerve, C5-8 cervical roots, and brachial plexus.

Keywords: nerve ultrasound; inflammatory peripheral neuropathies; chronic inflammatory demyelinating polyneuropathies; multifocal motor neuropathy; systemic vasculitic neuropathy; Guillain-Barre syndrome.

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INTRODUCTION

Inflammatory peripheral neuropathies include a heterogeneous group of dysimmune neuropathies. Chronic inflammatory neuropathies include chronic inflammatory demyelinating polyneuropathies (CIDP), multifocal motor neuropathy (MMN), systemic vasculitic neuropathy

(SVN) and other rare entities. Acute inflammatory neuropathies are mainly Guillain-Barre syndrome (GBS) and other rare entities, including diabetic radiculoplexus neuropathy, neuralgic amyotrophy, etc.[1] Nerve conduction studies (NCS) are routinely used in the diagnosis and differential diagnosis of peripheral neuropathies. Although NCS could show the electrophysiologic information of the nerve, it couldn't provide morphology information. High-resolution nerve ultrasound could provide morphology information and is increasingly used in peripheral neuropathies Addition of nerve ultrasound to nerve conduction studies significantly improves the detection of chronic inflammatory neuropathies.[2] There are some reviews about nerve ultrasound in chronic dysimmune neuropathies.[3,4] In this article, we review the updated characteristic of nerve ultrasound in different inflammatory neuropathies.

SEARCH METHODS

The MEDLINE database was searched to find studies on nerve sonography in inflammatory peripheral neuropathies. The terms 'nerve ultrasound', 'nerve sonography', and 'reference value', 'healthy control', 'inflammatory neuropathy', 'CIDP', 'MMN', 'vasculitic neuropathy', 'Guillain-Barre syndrome' and also listed references in the articles found were used. For this review, studies mentioning the sonographic features of nerves in inflammatory neuropathy were focused on, confining the search to reports originally published in English. Reported studies up to December 2022 are included in this review.

RESULTS

1. The ultrasound of normal peripheral nerve

The ultrasound of peripheral nerves reflects the macroscopic anatomy. Axially, the peripheral nerves demonstrate a "honeycomb" appearance, with hypoechoic fascicles separated by hyperechoic perineurium. Longitudinally, the nerves demonstrate a "track" appearance, with hypoechoic fascicles separated by hyperechoic perineurial connective tissue (Fig. 1). In neuropathies, the changes in ultrasound include enlarged nerve size, nerve echo intensity, fascicle diameter and vascularity. Nerve cross-sectional area (CSA) is the most quantifiable parameter with good reproducibility. It should be noted that the reference values of peripheral nerve CSA varied significantly among different countries and continents. The nerve CSA of Americans and Europeans is larger than that of Asians.[5-14] The CSAs were also affected by gender and age. The nerve CSAs in men were greater than those of women.[13-16] Nerves grew until early to middle adulthood and remained stable thereafter.[17,18] Abnormal nerve enlargement might reflect different pathologic changes, including nerve edema and acute inflammation,[19] proliferation of Schwann cells caused by repeated demyelination and remyelination, and fibrosis in the interstitial tissue. However, comparisons between ultrasound and histopathologic findings have not been published.[20,21] Enlargement with different echogenicity might reflect different pathology.[22,23] In normal nerves there is no detectable blood flow. Increased blood flow may be detected in inflammatory neuropathy and neurolymphomatosis.

The median nerve, ulnar nerve, and brachial plexus should be measured. Two to ten predetermined sites could be measured on the median and ulnar nerves,[5-8,24-26] according to the clinical or research requirements. The sites most often measured on the median nerve are wrist, mid-forearm, elbow, and mid-arm, and on the ulnar nerve are the wrist, mid-forearm, ulnar groove, and mid-arm. The cervical 5th to 8th roots could be measured at their exits from the intervertebral foramina, and the upper/middle/lower trunks of brachial plexus measured around Erb's point between the anterior and middle scalene muscles.[17]

Since ultrasound imaging is "live" in nature, knowledge of regional anatomy is critical for reliably capturing images and measuring parameters. As a result, it is optimal for clinicians to perform the studies.[27]

2. Nerve ultrasound in inflammatory peripheral neuropathy

2.1. CIDP

2.1.1. CSA

Most CIDP patients (86-98%) have enlarged CSA of peripheral nerve and cervical nerve roots detected by ultrasound.[20,22,24,28] Heterogeneous morphologies of nerves exist in patients with CIDP, widely ranging from normal to moderate to giant nerve enlargement.[29-31] Most patients have moderately enlarged

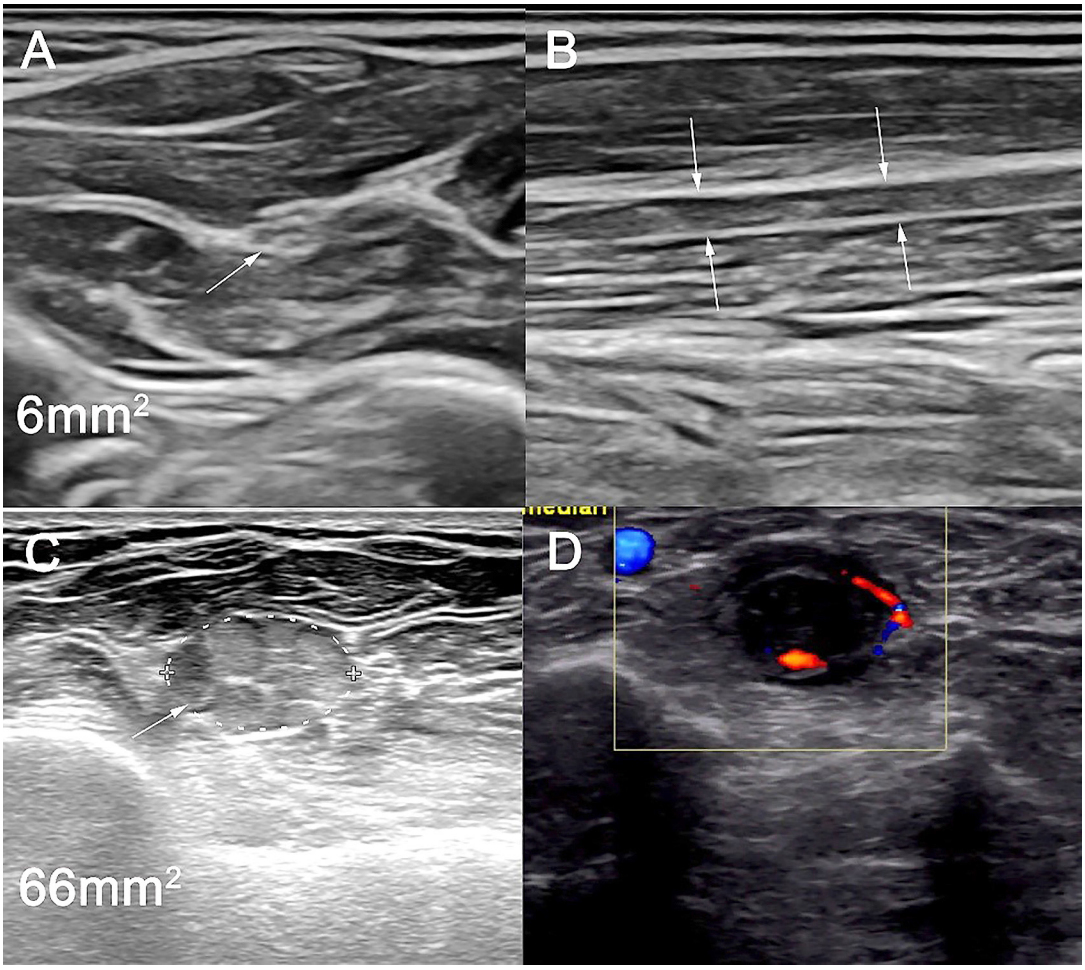

Figure 1. The illustration of ultrasonographic parameters. A. Axial view of forearm median nerve in healthy control. B. Longitudinal view of forearm median nerve in healthy control. C. Enlarged CSA of forearm median nerve in a CIDP patient. D. Increased vascularity inside and around the forearm median nerve in a patient with neurolymphomatosis.

CSA, some patients have dramatically enlarged CSA, and few patients have CSA within the normal range (Fig. 2). Among the 89 treatment-naïve CIDP patients in one cohort, 20 (22.5%) patients had markedly enlarged CSA, 58 (65.2%) patients had moderately enlarged CSA, and 11 (12.4%) patients had CSA within the normal range.[32] In some cases, giant nerve enlargements, which are 10 times the upper cutoff value, have been described.[23,24] Generally, CSA enlargement and disease duration are positively correlated[33,34.] However, the relationship between disease duration and CSA enlargement could not be well established, especially among different patients.

Nerve ultrasound of CIDP is different from that of CMT1A, GBS, MMN, POEMS, etc. In CIDP, markedly enlarged nerves show multifocal or segmental enlargement. In CMT1A, nerve enlargement is homogeneous without segmental enlargement.[29,35,36] Compared with GBS patients, CIDP revealed significant nerve enlargement on nerves of limbs, while both showed increased CSA on the roots and vagus nerve. Pure sensory nerves were enlarged in CIDP but not in GBS. Based on these characteristics, Kerasnoudis *et al.* used a low Bochum ultrasound score (<2) to distinguish AIDP from CIDP.[37] After 6 months, in CIDP, the nerve enlargement persisted, whereas, in GBS, all segments almost normalized.[38] MMN showed greater side-to-side intranerve variability compared with CIDP.[39] Compared with CIDP, nerve CSA enlargement was more homogeneous along the same nerve in individual POEMS patients, as well as among different POEMS patients.[40]

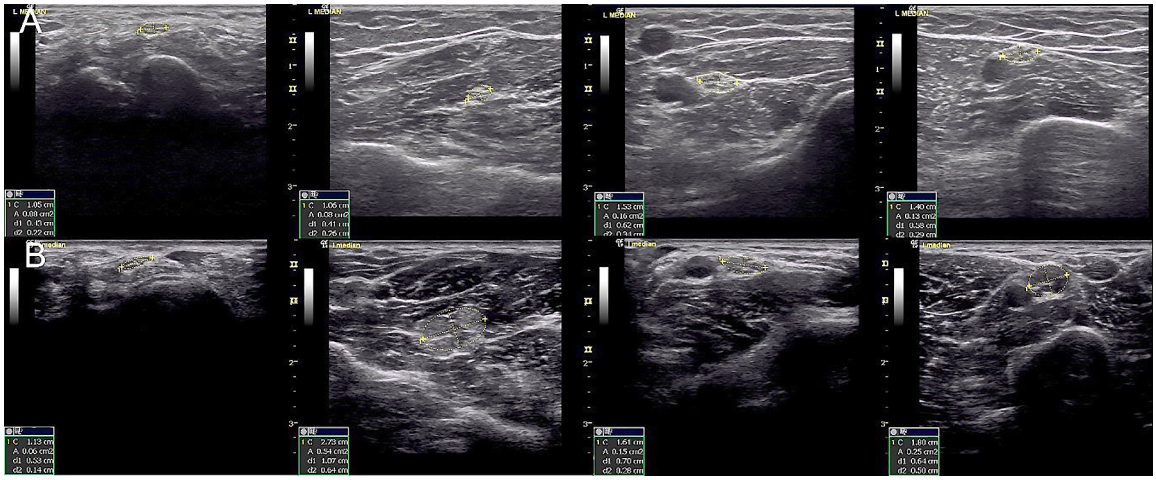

Figure 2. The four sites of the left median nerve (wrist, forearm, elbow, arm) in two chronic inflammatory demyelinating polyneuropathies (CIDP) patients. A. CIDP patient with moderately enlarged cross-sectional area (CSA). B. CIDP patient with segmental prominent enlargement.

No consistent relationship exists between CSA and motor conduction velocity (MCV) in different individuals. In the follow-ups of an individual, CSA and MCV showed relatively consistent relationships.[24] Conduction block is correlated with CSA enlargement. Most nerve segments with conduction block or temporal dispersion showed enlarged CSA.[20, 24, 41]

In follow-ups after immune treatment, nerve CSAs in CIDP could decrease, increase, or remain unchanged. In a 3-year follow-up study of 23 CIDP patients by Fionda *et al.*, CSA increased in 51% of nerve segments, especially in the demyelinating nerve segments.[33] Zaidman *et al.* found that most enlarged nerves decreased during follow-up: nerve size normalized in 6, decreased in 5, remained unchanged in 5, and enlarged in 1.[42] After a 1-year follow-up study of 80 CIDP patients, Hartig *et al.* found different CSA changing patterns, including nerve enlargement despite clinical improvement/stabilization. In those cases, therapy was either delayed or applied with an inconsistent therapeutic regime.[22] A large prospective study led by Tellman *et al.* showed that the development of sonographic nerve size over time is heterogeneous in CIDP. In their study, there was a poor correlation between nerve size and clinical outcome measures.[43] During the follow-up of 45 patients in our hospital, we found that the CSAs increased in 23 patients, decreased in 15, and remained unchanged in 7.[32] Most of those with decreased CSAs had good IVIG and steroid responses (83%) and no need for immune suppressant treatment (82%).[32]

2.1.2. Echogenicity

Three ultrasound patterns were identified in CIDP based on CSA and echogenicity: (1) large nerves with hypoechoic nerves/fascicles; (2) large nerves with heterogeneous hypo-and hyperechoic fascicles; (3) normal size nerve.[22, 23] The different echogenicity patterns might reflect different pathologic changes, as revealed by Hartig *et al.*: hypoechoic enlargement reflects active inflammation and onion bulbs, enlargement with hyperechogenic fascicles might reflect axonal degeneration, and almost no enlargement reflects "burned-out" or "cured" disease without active inflammation.[22] Clinical improvement after 12 months was the best in patients with pattern 1.[22] Goedee *et al.* however, found a higher nerve echogenicity in CIDP than in axonal neuropathies in some sites.[44] Fisse *et al.* studied the alteration of echogenicity in 20 CIDP patients, finding that patients with hyperechogenic arm nerves more frequently show clinical worsening, whereas patients with hypoechogenic arm nerves remain stable or even improved over time. Echogenicity mostly didn't change during follow-up. Echogenicity might be used as a prognostic marker, but not as a follow-up tool for evaluating clinical changes.[45] Further investigations about echogenicity are needed.

2.1.3. Vascularity

Increased nerve vascularity on Doppler US may be detected in a few patients with CIDP. Goedee *et al.*

	CSA	Follow-up of CSA after treatment	Echogenicity	Vascularity
CIDP	Most have enlarged CSA, ranging from normal to moderate to giant nerve enlargement.	CSA might decrease, remain unchanged, or enlarge.	Three ultrasound patterns : (1) hypoechoic enlargement; (2) heterogeneous hypo-and hyperechoic enlargement; (3) normal size nerve	Increased vascularity was very rare.
MMN	Most have enlarged nerves. Regional enlargement next to normal segments.	—	—	Increased vascularity was very rare.
SVN	Peripheral nerve enlargements with sparing of the brachial plexus.	CSA normalized quickly following steroid treatment.	—	Increased vascularity in some patients.
GBS	Enlargement of peripheral nerve and nerve roots.	CSA normalized at follow-up.	—	

CSA, cross-sectional area; CIDP, chronic inflammatory demyelinating polyneuropathies; MMN, multifocal motor neuropathy; SVN, systemic vasculitic neuropathy; GBS, Guillain-Barre syndrome

Table 1. The main ultrasound findings in inflammatory peripheral neuropathies.

detected hypervascularization of nerves in only one out of 44 CIDP patients.[44] We have a similar experience that hypervascularization was seldom seen in CIDP.

2.2. MMN

Multifocal motor neuropathy (MMN) is an asymmetrical pure motor multiple mononeuropathy which prominently involves the upper limbs. The differential diagnosis of MMN and amyotrophic lateral sclerosis (ALS) with leading lower motor neuron disease could be difficult, as conduction block in nerve conduction studies could be missing in up to 40% MMN patients.[46] The value of ultrasound in the diagnosis of MMN has been explored.

2.2.1. CSA

Most MMN patients had enlarged nerves, as 25 out of 31 had ultrasonographic enlarged nerves revealed by van Rosmalen *et al.*[47] Regional enlargement next to normal segments predominates.[29] Beekman *et al.* found multiple sites with nerve enlargement along the course of the brachial plexus, median, ulnar, and radial nerves in the majority (90%) of 21 patients with MMN. Oudeman *et al.* found an AUC of 0.762 for CSA for distinguishing between MMN and SMA.[48] Moreover, some nerve sites showed enlargement without clinical or electrophysiologic abnormalities.[2,49] Forty-two percent of the nerves with a normal CMAP amplitude showed enlargement anywhere along the course.[50] Kerasnoudis *et al.* studied 12 MMN patients, finding inhomogeneous CSA enlargement (high intranerve CSA variability) in various peripheral nerves, with a weak correlation to electrophysiological findings. Neither nerve sonography nor electrophysiology correlated with functional disability.[51] Rattay *et al.* followed up 17 MMN patients, finding that all showed at least localized but often multifocal peripheral nerve enlargement. An enlarged overall CSA as well as enlarged single fascicles were found in clinically and electrophysiologically affected (>90%) and unaffected (>70%) nerves. However, the Ultrasound Pattern Sum Score (UPSS) did not correlate with clinical disability.[52] Pitarokoili *et al.* found multifocal nerve enlargements in MMN without conduction block.[53] We also compared nerve enlargement and CB in 12 MMN patients, finding CB and enlargement were not always correlated.[54] These results indicate that nerve ultrasound could be a complementary tool for diagnosing MMN without typical electrodiagnostic features.

The follow-up study of 17 MMN by Rattay *et al.* shows that the change in clinical disability (evaluated as difference in Medical Research Council Sum Score, MRCSS) and the change in UPSS correlated significantly inversely. Their result indicates that sonographic assessment may be a useful tool for therapeutic monitoring.[52]

MMN had higher values of intra- and interne rve CSA variability compared with CIDP and anti-MAG neuropathy.[55] Merola *et al.* found that, compared with CIDP, MMN was associated with greater side-to-side intranerve variability.[39] Grim *et al.* found that detection of enlarged nerves/roots served as a good marker to differentiate MMN from ALS with a sensitivity of 87.5% and a specificity of 94.1%.[56] Loewenbruck *et al.* found that nerve ultrasound may be superior to nerve conduction study in the diagnosis of MMN in patients with a suspected diagnosis of ALS/LMND or MMN.[57]

2.2.2. Vascularity

Hypervascularization of nerves was scarcely seen in MMN. According to Goedee *et al.*, only one out of 22 MMN had hypervascularization at the forearm in an enlarged median nerve.[44]

2.2.3. Fasciculation

By comparing the distribution of fasciculation between MMN and ALS, Tsuji *et al.* found that the absence of fasciculation in the tongue and truncal muscles in MMN patients may help distinguish MMN from ALS.[58] In our study, no fasciculation was detected in bulbar muscles for MMN patients. Both the grade and detection rate of fasciculation were lower in MMN than in ALS patients.[59]

2.3. Vasculitic neuropathies (VN)

There were few studies about nerve ultrasound of vasculitic neuropathies. Nerve enlargement was reported. Grim *et al.* found that patients with vasculitic neuropathies (VN) displayed significantly smaller amplitudes of compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP), and larger CSA compared to healthy control (HC). Nerve ultrasound revealed nerve enlargement in most of the clinically and electrophysiologically affected nerves (22/31) in VN. Nerve enlargement was more often seen in VN than in other axonal neuropathies, but significantly rarer than in demyelinating neuropathies.[60] Goedee *et al.* found that enlargement of arm nerves proximal to nerve compression sites with sparing of the brachial plexus may indicate vasculitic neuropathy. Hyper vascularization was found in 3 out of 11 patients with systemic vasculitis.[61] Ito *et al.* found that tibial nerve appeared enlarged and hypoechoic in 8 patients with vasculitic neuropathy.[62] Nodera *et al.* reported a female patient with rheumatoid arthritis had vasculitic neuropathy. Nerve ultrasound showed diffuse thickening of peripheral nerves, which resolved two weeks after intravenous steroid infusion.[63]

2.4. Guillain-Barre syndrome

Nerve ultrasound has been performed in a small number of GBS patients, demonstrating significantly enlarged peripheral nerve and nerve roots compared to HC, which became normal at follow-up.[64-66] At an early stage of disease, enlargement of nerve roots and proximal nerve predominates.[67-70] Enlargement of nerve roots is more obvious than peripheral nerves.[71] Pure sensory nerves were not obviously enlarged.[38] In a study of a small group of GBS patients, Mori *et al.* found that the patients with AIDP tended to show enlarged nerves in the proximal segments and the cervical roots, whereas the patients with AMAN/AMSAN had greater enlargement in the distal nerve segment.[72] Liu *et al.* found that the CSA in AIDP tended to be larger than in AMAN/AMSAN, especially in cervical nerves.[73] In Miller-Fisher syndrome, ultrasound also showed enlargement of peripheral nerves, as demonstrated by Decard *et al.*[74]

3. Comparison between ultrasound and MRI in inflammatory peripheral neuropathies

Oudeman *et al.* compared the diagnostic accuracy of ultrasound and MRI in chronic immune-mediated neuropathies. For distinguishing CIDP and MMN from SMA, ultrasound had a larger area under the curve (0.870) compared with MR diameter (0.607).[48] Having the best discriminative properties and being widely available and convenient, ultrasound seems to be the most appropriate imaging tool in inflammatory peripheral neuropathies.

CONCLUSIONS

High-resolution nerve ultrasound is complementary in the diagnosis of inflammatory peripheral neuropathies. Most CIDPs have enlarged CSA of peripheral nerve and cervical nerve roots revealed by ultrasound. Heterogeneous enlargement patterns, including moderate enlargement and segmental giant nerve enlargement, exist in CIDP. Since the enlargement patterns are different, ultrasound is useful to help differentiate CIDP from CMT1 and

GBS. Regional enlargement next to normal segments helps to distinguish MMN from ALS. Vasculitic neuropathies and GBS had moderately enlarged CSA. Hyper vascularization was more often seen in vasculitic neuropathies. (Table 1) In conclusion, CSA enlargement and its distribution are the most useful and quantifiable parameters in the evaluation of peripheral nerves. For patients suspected to have inflammatory neuropathies, we advise measuring the CSA of several pre-determined sites in the median, ulnar nerve, C5-8 cervical roots, and brachial plexus. The significance of echogenicity needs further investigation. Evaluation of vascularization should also be performed, since it may help discriminate vasculitic neuropathies, neurolymphomatosis and other peripheral neuropathies.

Acknowledgments

Funding: Study funded by the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-017)

Conflict of interest: None of the authors have potential conflicts of interest to be disclosed.

Author contributions: Jingwen Niu, data acquisition and analysis, manuscript preparation, manuscript editing. Mingsheng Liu, concept and design, manuscript review.

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