Received: 12 July 2022 | Revised: 8 September 2022 | Accepted: 21 September 2022

DOI: 10.1111/jns.12513

WILEY

RESEARCH REPORT

The diagnostic accuracy of the small fiber neuropathy symptoms inventory questionnaire (SFN-SIQ) for identifying pure small fiber neuropathy

Eleonora Galosi | Pietro Falco | Giuseppe Di Pietro | Caterina Leone | Nicoletta Esposito | Gianfranco De Stefano | Giulia Di Stefano | Andrea Truini

Department of Human Neuroscience, Sapienza University, Rome, Italy

Correspondence
Eleonora Galosi, Department of Human Neuroscience, Sapienza University, Viale dell' Università 30, Rome 00185, Italy.
Email: eleonora.galosi@uniroma1.it

Abstract

A definite diagnosis of pure small fiber neuropathy (SFN) relies on specific diagnostic testing, such as skin biopsy, quantitative sensory testing (QST), and nociceptive evoked potentials, which require considerable resources that may not be widely available. Accordingly, diagnostic tools with easy implementation in non-specialist centers are warranted to identify patients who require second-level diagnostic tests. In this study, we aimed to test the accuracy of the Small Fiber Neuropathy Symptoms Inventory Questionnaire (SFN-SIQ) in diagnosing pure SFN. We enrolled 86 patients with suspected pure SFN. In these patients, we calculated the diagnostic accuracy of the SFN-SIQ using a combination of clinical examination, QST, and skin biopsy as a reference standard. We found that the SFN-SIQ showed an excellent ability to discriminate between patients with and without pure SFN, with 86% sensitivity and 70% specificity in the diagnosis of pure SFN. Our study providing the diagnostic yield of the SFN-SIQ for pure SFN diagnosis suggests that this questionnaire might be used to screen patients with suspected SFN and identify those requiring second-level diagnostic tests such as QST, skin biopsy, or nociceptive evoked potentials.

KEYWORDS
neuropathic pain, skin biopsy, small fiber neuropathy

1 | INTRODUCTION

Pure small fiber neuropathy (SFN) is characterized by a selective involvement of small myelinated A-delta and non-myelinated C fibers. Thanks to ongoing advances in small-fiber-related diagnostic testing, pure SFN is an increasingly recognized disease underpinned by heterogeneous etiological conditions.[1] However, limited epidemiological data are available, with an estimated prevalence between 13.3 and 52.9 per 100 000.[2,3]

Pure SFN diagnosis presents several clinical challenges. According to the most widely used diagnostic criteria, a definitive diagnosis of pure SFN relies on clinical assessment and small fiber damage confirmation by specific small-fiber-related diagnostic tests.[4,5] Skin biopsy, thermal threshold assessment with quantitative sensory testing (QST), and nociceptive evoked potentials are considered the reference standard tests for diagnostic confirmation.[4,5] However, these techniques are time-consuming, not widely available in primary healthcare settings and neurological outpatient clinics, and require highly specialized equipment with specially trained medical personnel.[6,7] Therefore, screening tests that can help clinicians select patients who require second-level small-fiber-related diagnostic

testing (ie, QST, skin biopsy, and nociceptive evoked potentials) are needed.

Different questionnaires have been used in previous studies to quantify SFN-related symptoms.[8] The Small Fiber Neuropathy Symptoms Inventory Questionnaire (SFN-SIQ) is one of the most widely used due to the wide spectrum of investigated symptoms, which encompasses autonomic and somatosensory disturbances.[9-12] Although non-invasive, easy to administer and free of cost, only a few studies have assessed the diagnostic accuracy of specific questionnaires in pure SFN diagnosis or evaluated their screening ability.[10,13]

In this prospective study, designed according to Standards for Reporting of Diagnostic Accuracy (STARD) guidelines, we aimed to define the accuracy of the SFN-SIQ in the diagnosis of SFN. To do so, we calculated the sensitivity and specificity of the SFN-SIQ in the definite diagnosis of pure SFN in a population of patients with suspected pure SFN, using widely agreed reference standard criteria for definite pure SFN diagnosis as a comparator.[5]

2 | METHODS

2.1 | Study design and patient cohort

From October 2018 to September 2021, we consecutively screened for polyneuropathy in 1140 patients with sensory disturbances and/or sensory examination abnormalities involving distal extremities of lower limbs and/or autonomic symptoms. Patients were consecutively referred to our Peripheral Neuropathy and Neuropathic Pain Unit of the Human Neuroscience Department at Sapienza University, Rome, by medical personnel of the Policlinico Umberto I University Hospital, Rome. Each screened patient underwent clinical examination and nerve conduction study (NCS).

Age under 18 years, central nervous system diseases, cognitive disturbances, and psychiatric disorders, as assessed with clinical history and examination, were considered a priori exclusion criteria.

We also excluded patients with symptoms and signs meeting the American College of Rheumatology criteria for fibromyalgia syndrome due to the potential influence of fibromyalgia on painful and autonomic symptom evaluation in the SFN-SIQ and the high frequency of small fiber pathology in patients with fibromyalgia.[14,15]

Then we excluded patients with clinical signs of large fiber impairment (reduced/absent tactile and/or vibration sensation) and/or abnormal NCS findings, that is, symmetrically decreased or absent sensory action potentials.

Eventually we included in the study only patients with suspected pure SFN. These patients had distally distributed pain and/or sensory examination abnormalities (thermal-pain hypoesthesia, hyperalgesia, and/or allodynia) and/or autonomic symptoms, with normal NCS findings and no clinical signs of large fiber impairment. Within a single clinical session, patients with suspected pure SFN underwent SFN-SIQ administration, QST from the dorsum of the foot, and skin biopsy at the distal calf. All data were collected in a structured form using a standardized protocol by staff members (clinical examination and SFN-SIQ administration: AT, GDS, CL; NCS and QST: AT, GDP, GDS, NE; skin biopsy collection and analysis: EG, PF).

In line with the widely accepted Besta criteria for pure SFN diagnosis, we diagnosed pure SFN based on the combination of at least two of three of the following criteria: (i) distally distributed sensory signs (decreased thermal-pain sensation and/or hyperalgesia and/or allodynia); (ii) abnormal cold and/or warm detection threshold (CDT and/or WDT) as assessed by QST; and (iii) intraepidermal nerve fiber density (IENFD) reduction at skin biopsy from the distal calf.[5]

In patients with suspected pure SFN, we calculated the accuracy of the SFN-SIQ in the diagnosis of definite pure SFN using the Besta criteria as reference standard diagnostic criteria.[5]

The study was approved by the local institutional review board.

2.1.1 | Clinical examination

All the screened patients underwent a structured interview and were asked about the presence of painful and non-painful distally distributed sensory disturbances and autonomic symptoms.

All the screened patients underwent a detailed neurological examination using bedside tools that was particularly focused on the assessment of sensory disturbances.

Touch was investigated at the dorsum of the foot with a piece of cotton wool and pinprick sensation with a wooden cocktail stick, as recommended.[16] Vibration was assessed with a Rydel Seiffer tuning fork. During vibration investigation at the lateral malleolus, patients were asked to indicate when the vibration ceased; values between 4 and 0, as indicated on the Rydel Seiffer graduated scale, were considered abnormal.[17]

Patients were examined for negative (tactile, vibration, pinprick, and thermal hypoesthesia) and positive symptoms and signs (constant pain, paroxysmal pain, pinprick hyperalgesia, and dynamic mechanical allodynia).

2.1.2 | Nerve conduction study (NCS)

All the screened patients underwent NCS by surface recording electrodes with standard placement. NCS included sensory nerve action potential amplitude and conduction velocity recorded from sural, ulnar, and superficial radial nerves, and compound motor action potential amplitude and conduction velocity of peroneal, tibial, and ulnar nerves. Recording methods adhered to the recommendations of the International Federation of Clinical Neurophysiology.[18,19] Skin temperature was maintained between 34° and 36°C. NCS data were compared with age-adjusted normative ranges.[20]

2.1.3 | SFN-SIQ

All 86 patients were administered the 13-item SFN-SIQ. The questionnaire assessed changes in sweating patterns, diarrhea,

constipation, urinary incontinence or hesitation, dry eyes, dry mouth, orthostatic intolerance, palpitations, flushing, dynamic mechanical allodynia, burning pain distributed to the feet, and restless leg syndrome. A four-point Likert scale was used to grade each disturbance (0 = never present, 1 = sometimes, 2 = often, and 3 = always present).[12,21] The SFN-SIQ score, that is, the sum of the grading scores attributed to each of the 13 items, was used as a main outcome measure for SFN-SIQ diagnostic accuracy calculation, with a 0 to 39 range.[10]

2.1.4 | Quantitative sensory testing (QST)

QST was performed in all 86 patients by trained examiners following the standardized protocol of the German Research Network on Neuropathic Pain.[6,22] We examined the dorsum of the right foot as a "test site" because it is the most painful area in most patients. The radial nerve territory of the left hand was tested before as a practice area.

Using log-transformed raw patient values for each measured variable and a large, widely recognized dataset of normative values,[23] a z-score was calculated for each QST variable (z-score = value of the patient - mean value of control subjects/SD [SD] of control subjects). Negative z-scores indicated a loss of perception, whereas positive z-scores indicated a gain of perception. Z-values below −1.96 or above +1.96 were considered abnormal.[23]

2.1.5 | Skin biopsy

All 86 patients underwent skin biopsy at the distal leg, 10 cm above the lateral malleolus, using a 3-mm disposable circular punch after local lidocaine anesthesia, under sterile conditions.[7] No suture was required. Using indirect immunofluorescence, IENFD was assessed with the pan-neuronal marker PGP9.5.

Briefly, biopsies were fixed for 24 h at 4°C in Zamboni's fixative, then cryoprotected overnight. Cut was performed at −23°C with a cryostat (MEV, SLEE medical) to obtain 50-µm-thick sections. Three non-consecutive free-floating sections were randomly selected for immunostaining from each sample and blocked with 5% normal donkey serum for 1 h. Sections were incubated overnight with a rabbit anti-human PGP9.5 monoclonal antibody (Abcam, 1:500 diluted) and a mouse anti-human collagen IV monoclonal antibody (Millipore, 1:1600). The following day, sections were incubated with anti-rabbit-Cy3 (Jakson, 1:800) and anti-mouse-488 (Jakson, 1:400) secondary antibodies overnight. IENFD was calculated according to the guidelines of the European Federation of Neurological Societies and Peripheral Nerve Society.[10] Epidermal linear length was measured through Image-J to obtain a linear density (number of fibers/mm). Fiber counts were performed by blind operators (EG and PF) through a fluorescence microscope (Leica NB) with appropriate wavelength filters. Normative values from an internationally recognized wide dataset were used.[24]

2.1.6 | Statistical analysis

A preliminary univariate analysis was performed to describe the main demographic, clinical, and diagnostic test variables in patients with definite pure SFN and without SFN by reporting means ± SDs and percentage frequencies for continuous and categorical variables. Normal distribution was assessed for all considered continuous variables through D'Agostino-Pearson omnibus normality test. We used *t*-test and Fisher's exact test, or their non-parametric versions as appropriate, to compare continuous and categorical variables between patients with definite pure SFN and without SFN.

We used a correlation matrix based on the Spearman test to analyze the bivariate relationships between SFN-SIQ score and the main small-fiber-related diagnostic test variables (IENFD, CDT, and WDT). Simple linear regression was used to assess linear relation between correlated variables.

We did not calculate the sample size for SFN-SIQ diagnostic accuracy assessment because pure SFN is a rare, low prevalence condition.[2,3] Nevertheless, our sample size is in line with previous studies assessing the clinical usefulness of SFN-SIQ[11] and the diagnostic yield of this questionnaire in patients with mixed-fiber neuropathy.[10]

We calculated the diagnostic accuracy of the SFN-SIQ in patients with suspected pure SFN. The diagnostic accuracy of the SFN-SIQ score was assessed using receiver operator characteristic (ROC) analysis by comparing patients with definite pure SFN to patients without SFN according to Besta criteria. The area under the ROC curve (AUC) was used to define the ability of the SFN-SIQ to distinguish between the two groups (patients with definite pure SFN and without SFN) independent of cut-off values. An AUC of ≤0.50 was considered to reflect "negative", 0.51 to 0.70 "poor", 0.71 to 0.80 "acceptable", 0.81 to 0.90 "excellent", and >0.90 "outstanding" diagnostic accuracy.[25]

The optimal cut-off diagnostic value for SFN-SIQ score was determined by means of the Youden index (sensitivity + specificity −1).[26] The sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) of the SFN-SIQ score were evaluated using the optimal cut-off diagnostic value. We used Fisher's exact test to calculate SFN-SIQ sensitivity and specificity and 95% confidence intervals (CIs). A positive likelihood (LR+) ratio >10 and a negative LR (LR−) <0.1 were used to identify cut-off values able to respectively predict a large increase and decrease in disease likelihood.[27]

A *P* value <0.05 was considered statistically significant. Prism 8.0 was used for statistical analysis.

3 | RESULTS

Of 1140 screened patients, we excluded 703 patients with clinical and/or NCS findings compatible with large fiber damage, 205 as they fulfilled the American College of Rheumatology (ACR) criteria for fibromyalgia syndrome, 128 due to other exclusion criteria, and 18 who did not consent to skin biopsy (Figure 1).

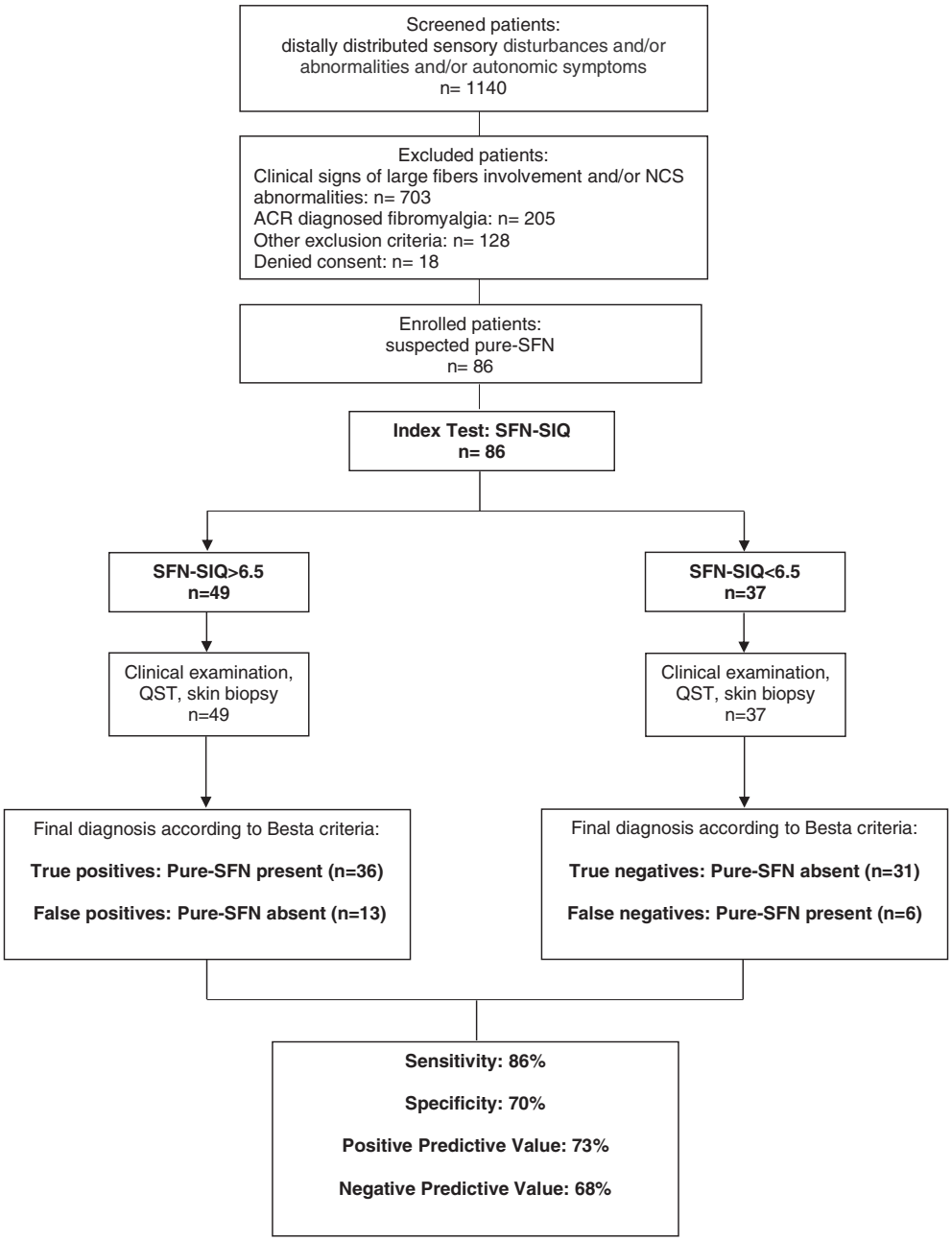

FIGURE 1 Diagram showing standards for reporting diagnostic accuracy. Standards for reporting diagnostic accuracy (STARD) flow diagram for SFN-SIQ diagnostic accuracy in pure small fiber neuropathy (SFN) diagnosis, as defined by Besta criteria, using the optimal SFN-SIQ cut-off (6.5), as calculated by the Youden index after ROC curve analysis

TABLE 1 Symptoms assessed by SFN-SIQ in patients with and without pure small fiber neuropathy

	Suspected pure SFN n = 86	Pure SFN n = 42	No SFN n = 44
Autonomic symptoms	77 (89%)	39 (93%)	38(86%)
Somatic symptoms	56 (65%)	32 (76%)	24 (54%)
Autonomic and somatic symptoms	58 (67%)	36 (86%)	22 (50%)

Note: Autonomic symptoms: number and percentage of patients reporting at least one autonomic symptom among sudomotor impairment, dry eyes, dry mouth, orthostatic intolerance, palpitations, flushing, stypsis, diarrhea, and urinary dysfunction. Somatic symptoms: patients reporting at least one somatic symptom among burning pain, allodynia, pain worsening with sheet contact, and restless leg syndrome. Autonomic and somatic symptoms: patients reporting at least one autonomic and one somatic symptom.
Abbreviation: SFN-SIQ, small fiber neuropathy symptoms inventory questionnaire.

For the diagnostic accuracy analysis, we enrolled 86 patients with suspected pure SFN who had normal NCS findings, distally distributed pain and/or sensory examination abnormalities (thermal-pain hypoesthesia, hyperalgesia, and/or allodynia), and/or autonomic symptoms. Of the 86 patients with suspected pure SFN, 42 patients met the Besta criteria for a diagnosis of definite pure SFN, while

44 did not (Figure 1; Table 1). Distribution of clinical, QST, and skin biopsy abnormalities in patients with definite pure SFN and without SFN is shown in Figure 2.

The SFN-SIQ score was significantly higher in patients with definite pure SFN than in patients without SFN ($P < 0.0001$) (Figure 3; Table 1). The total number of symptoms of the SFN-SIQ, graded on a 0 to 13 scale by attributing 1 point to each symptom, did not significantly differ between patients with and without SFN.

The SFN-SIQ score significantly correlated with IENFD ($P = 0.001$; $r = -0.366$) and WDT ($P < 0.0001$; $r = -0.451$). Linear regression models demonstrated a linear relation between the SFN-SIQ score as a dependent variable and IENFD and WDT as independent variables (IENFD: $P = 0.0014$; r-squared = 0.1259; WDT: $P < 0.0001$; r-squared = 0.2053).

The ROC curve analysis, comparing patients with definite pure SFN and without SFN, showed an AUC of 0.8412 ($P < 0.000001$, 95% CI: 0.7584-0.9240), indicative of an excellent discriminative ability (Figure 3).[25] According to the maximized Youden index (0.5616), an SFN-SIQ score of 6.5 was the optimal cut-off value for distinguishing patients with and without pure SFN. An SFN-SIQ score of 6.5 had 86% diagnostic sensitivity (95% CI: 72.16%-93.28%) and 70% specificity (95% CI: 55.78%-81.84%), with 73% positive and 68% negative predictive values (Table 1).

An LR+ >10, indicating a high likelihood of disease, was achieved for SFN-SIQ scores >12.5 (LR+ 15.73), with 97.73% specificity and 35.71% sensitivity. An LR− <0.1, suggesting a very low disease likelihood, was achieved for scores <3.5 (LR−: 0.09), with 97.62% sensitivity and 25% specificity.

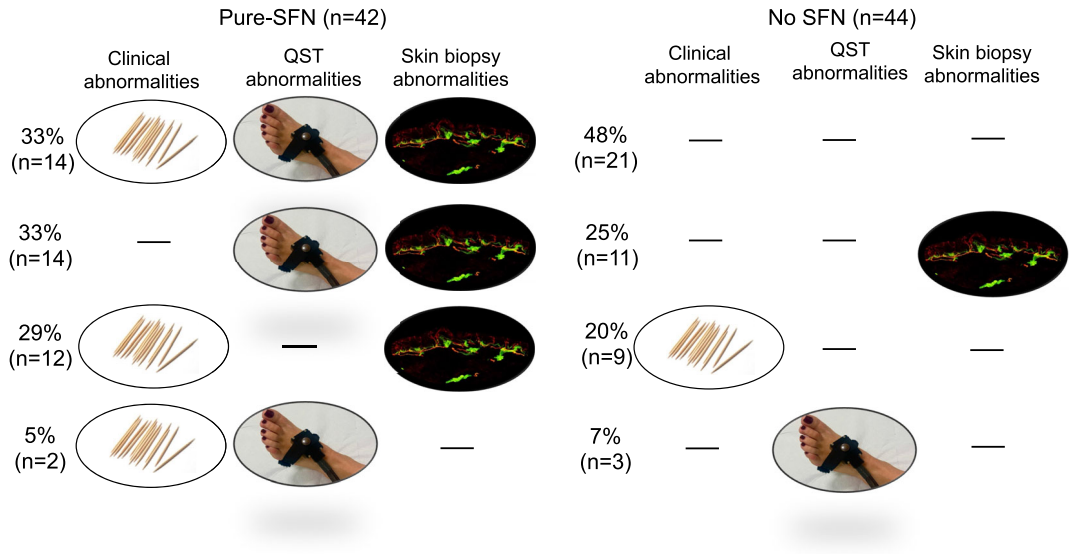

FIGURE 2 Distribution of clinical, quantitative sensory testing (QST), and skin biopsy abnormalities in patients with and without definite pure small fiber (SFN) neuropathy. Clinical abnormalities: thermal-pain hypoesthesia, hyperalgesia, or allodynia; QST abnormalities: warm and/or cold detection threshold impairment at the dorsal foot; skin biopsy abnormalities: intraepidermal nerve fiber density reduction at skin biopsy at the distal calf.

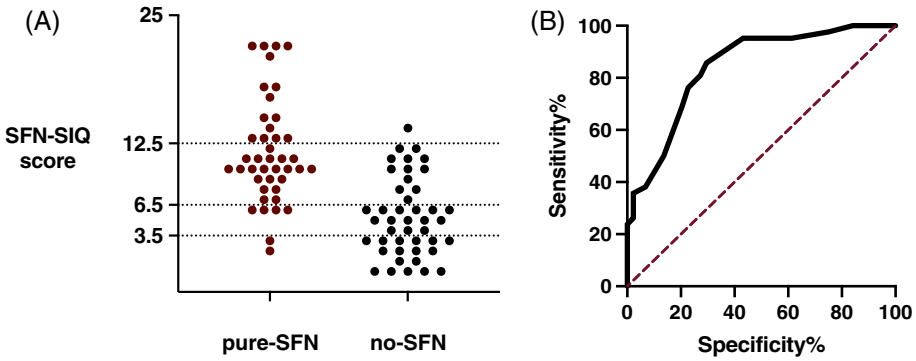

FIGURE 3 Diagnostic accuracy of SFN-SIQ. (A) Graph showing the SFN-SIQ score in the 86 patients with suspected pure small fiber neuropathy (SFN). Red dots represent patients with pure SFN as defined by Besta criteria, and black dots represent patients without SFN. Ticks mark the best cut-off value of SFN-SIQ score as calculated by the Youden index (SFN-SIQ = 6.5), the cut-off with positive likelihood ratio higher than 10 (SFN-SIQ >12.5), and negative likelihood ratio lower than 0.1 (SFN-SIQ < 3.5). (B) Receiver operating characteristic curve of the diagnostic accuracy of SFN-SIQ, calculated in the 86 patients with suspected pure SFN by using Besta criteria. Area under the curve: 0.8412; 95% confidence interval: 0.7584 to 0.9240; *P* value <0.000001.

4 | DISCUSSION

In this prospective study, we showed that the SFN-SIQ has clinically reliable sensitivity (86%) and adequate specificity (70%) in identifying pure SFN, thus suggesting that this questionnaire might be useful to screen patients with suspected SFN for second-line confirmatory diagnostic tests, such as QST, skin biopsy, or nociceptive evoked potentials.

The SFN-SIQ is commonly used as an inventory questionnaire to rate and measure small-fiber-related symptoms in patients with confirmed SFN of distinct etiology.[11,21,28] In this study, however, we tested the accuracy of the SFN-SIQ score (0-39) in identifying patients with pure SFN. We found a diagnostic accuracy comparable with a previous study that tested its diagnostic yield in a heterogeneous sample of patients with mixed-fiber neuropathy, with small and large fiber impairment.[10]

Conversely, we found that the total number of symptoms of the SFN-SIQ, graded on a 0 to 13 scale, did not differ between patients with and without SFN, and thus cannot be considered as a reliable diagnostic index. This finding suggests that the frequency of presentation of the different symptoms, which is evaluated by the SFN-SIQ score, is a crucial factor to distinguish patients with and without definite SFN.

In our study, we specifically tested SFN-SIQ accuracy in identifying patients with pure SFN according to STARD guidelines. We selected the widely accepted Besta criteria[5] as a reference standard for definitively diagnosing pure SFN. Due to the high sensitivity and specificity of these criteria in SFN diagnosis,[29] these criteria represent a reliable comparator able to distinguish between patients with and without SFN and identify the accuracy of the SFN-SIQ in screening patients with suspected SFN.

In our population, we found that an SFN-SIQ score of 6.5, established as the optimal cut-off, had a sensitivity and specificity of 86% and 70%, respectively, and positive and negative predictive values of 73% and 68%, respectively, thus indicating that the SFN-SIQ score has a relatively high probability of correctly identifying patients with SFN. These findings suggest that the SFN-SIQ might be clinically useful to screen patients with suspected SFN. Since the SFN-SIQ is more accessible and less expensive, time-consuming, and physically and psychologically discomforting than QST, skin biopsy, and nociceptive evoked potentials, the SFN-SIQ might be an attractive option to identify patients who require second-level confirmatory diagnostic tests. In particular, for patients with SFN-SIQ scores >12.5, which are associated with a very high likelihood of disease, second-line diagnostic tests are mandatory, whereas in patients with SFN-SIQ scores <3.5, which are associated with a very low likelihood of disease, further diagnostic testing is not required. This clinical practice approach could be used for patients with normal clinical examination, in line with a recent study showing that clinical signs reflect small fiber damage more reliably than sensory symptoms alone.[30]

Our study also showed a significant correlation between the SFN-SIQ score and the main small-fiber-related diagnostic test variables, namely IENFD and WDT. This finding suggests that the questionnaire reliably reflects the impairment of small nerve fibers as assessed by specific diagnostic tests and could be a useful tool to monitor patients with SFN in a clinical and research setting.

We did not consider the specificity and positive predictive values below 80% as limitations. Since the SFN-SIQ may be used as a screening tool, we regarded sensitivity as the critical value. Accordingly, the SFN-SIQ could be an ideal tool to screen patients with suspected SFN in primary care and non-specialist settings.

Our study showing the diagnostic accuracy of the SFN-SIQ might be useful in clinical trials and epidemiological surveys where SFN diagnosis represents a possible issue. The use of the SFN-SIQ might contribute to improving patient screening consistency in multi-center clinical trials enrolling patients with SFN. Additionally, the SFN-SIQ might be particularly suitable for online and mail surveys investigating SFN epidemiology.

Interestingly, despite being mainly based on reports of autonomic complaints, with only a few items dedicated to sensory symptoms, the SFN-SIQ achieved favorable diagnostic accuracy in our patients, who were diagnosed with SFN by skin biopsy and QST, both techniques that measure parameters specifically related to somatic small nerve fibers, rather than autonomic fibers. These findings suggest that although a preferential involvement of somatic rather than autonomic fibers may be reported in some conditions characterized by small fiber impairment,[31,32] in most cases somatic and autonomic nerve fiber subtypes are simultaneously involved.

4.1 | Limitations

In our study, we excluded patients with fibromyalgia due to the potential influence of fibromyalgia on painful and autonomic symptom evaluation in the SFN-SIQ and to the high frequency of small fiber pathology in fibromyalgia patients. Therefore, we cannot exclude that the SFN-SIQ might have a limited validity in distinguishing between patients with fibromyalgia and SFN. Nevertheless, the differential diagnosis between fibromyalgia and pure SFN is particularly challenging. Most studies showed that patients with SFN and fibromyalgia frequently share similar clinical examination, QST, and skin biopsy findings.[14,33]

In our study, we used the widely accepted Besta criteria as a reference standard for definitively diagnosing small fiber neuropathy. It follows that we did not evaluate autonomic nerve fibers with specific diagnostic tests. This approach might be regarded as a potential limitation of our study, because we could have failed to recognize and enroll patients with SFN manifesting with a selective autonomic nerve fiber damage. Therefore, we cannot exclude that our diagnostic criteria for SFN might affect the diagnostic accuracy of SFN-SIQ, which is mainly based on reports of autonomic symptoms.

Although our study indicates that the SFN-SIQ might be effective in screening patients with suspected SFN, our data should be interpreted cautiously. Like all questionnaires, the SFN-SIQ should be used in the diagnostic work-up of patients with suspected SFN as a standardized part of the clinical examination and cannot substitute careful clinical examination or objective diagnostic testing.

5 | CONCLUSIONS

Our study provides previously unreported information on the diagnostic accuracy of the SFN-SIQ in patients with suspected pure SFN. We found that the SFN-SIQ had a sensitivity and specificity of 86% and 70%, respectively, thus indicating that this questionnaire might be reliably used to screen patients with suspected pure SFN and select those needing second-level confirmatory diagnostic tests, such as QST, skin biopsy, or nociceptive evoked potentials.

ACKNOWLEDGEMENT

Open Access Funding provided by Universita degli Studi di Roma La Sapienza within the CRUI-CARE Agreement.

CONFLICT OF INTEREST

The authors whose names are listed immediately below certify that they have no conflicts of interest to declare that are relevant to the content of this article: Eleonora Galosi, Pietro Falco, Giuseppe Di Pietro, Caterina Leone, Nicoletta Esposito, Gianfranco De Stefano, Giulia Di Stefano, and Andrea Truini.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author [EG], upon reasonable request.

ORCID

Eleonora Galosi https://orcid.org/0000-0002-4464-9982
Giuseppe Di Pietro https://orcid.org/0000-0002-9645-3578

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How to cite this article: Galosi E, Falco P, Di Pietro G, et al. The diagnostic accuracy of the small fiber neuropathy symptoms inventory questionnaire (SFN-SIQ) for identifying pure small fiber neuropathy. *J Peripher Nerv Syst*. 2022;1-8. doi:10.1111/jns.12513