Cross-Sectional Study

The Assessment of Neuropathic Pain in Patients with Lymphedema Secondary to Breast Cancer

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Background: Lymphedema is a chronic, progressive condition characterized by excessive fluid retention due to impaired lymphatic drainage. While neuropathic pain is known to affect a significant proportion of chronic pain sufferers, the frequency of neuropathic pain in patients with breast cancer–associated secondary lymphedema remains unclear. This study investigates the prevalence and characteristics of neuropathic pain in women with secondary lymphedema caused by breast cancer treatments.

Objective: To determine the prevalence of neuropathic pain in female patients diagnosed with breast cancer–associated secondary lymphedema and to explore that pain's association with lymphedema severity.

Study Design: A cross-sectional study.

Setting: A tertiary hospital physical medicine and rehabilitation center.

Methods: This cross-sectional study included 100 women aged 18 to 65 diagnosed with secondary lymphedema related to breast cancer. Neuropathic pain was assessed using the Self-reported Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and Douleur Neuropathique 4 (DN-4) questionnaires. Lymphedema was staged according to the International Society of Lymphology classification. Data on pain levels and quality of life were collected using the Numeric Rating Scale (NRS-11) and the Lymphedema Life Impact Scale (LLIS).

Results: Neuropathic pain was identified in 14% of patients through the DN-4 and 17% through the S-LANSS. A significant correlation was found between higher lymphedema grades and increased neuropathic pain scores ($P < 0.001$). Patients with Grade 3 lymphedema reported significantly higher pain levels than did those with lower grades.

Limitations: Cross-sectional nature of the study and the single-center design.

Conclusion: Neuropathic pain is prevalent in patients with breast cancer–associated secondary lymphedema, especially in more advanced cases of cancer. Early identification and targeted pain management strategies are crucial to improving the quality of life for these patients.

Key words: Breast cancer, neuropathic pain, prevalence, quality of life, secondary lymphedema

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Lymphedema is a localized tissue swelling caused by impaired lymphatic drainage, leading to fluid retention in the interstitial compartment while capillary function remains unaffected (1). The condition, which is more common in women, is classified into primary and secondary lymphedema. Primary lymphedema results from developmental anomalies or mutations in lymphatic vessels, whereas secondary lymphedema arises from systemic diseases, trauma, or surgical interventions. Most lymphedema cases are secondary and related to breast cancer, particularly among women. This chronic and progressive condition significantly reduces patients' quality of life by causing functional limitations and psychosocial challenges (2).

Neuropathic pain, a debilitating symptom caused by somatosensory system lesions or diseases, affects 20-25% of chronic pain patients. General population studies estimate that 7-8% of adults have neuropathic pain (3). Pain is also a frequent complaint in lymphedema, reported in 20-50% of patients with breast cancer–related secondary lymphedema (4,5). This pain, often described as burning, aching, or squeezing, is thought to result from the compression of nerves by an increased amount of interstitial fluid pressure. Neuropathic pain symptoms, such as numbness and tingling, may arise, further exacerbating the patient's discomfort and limiting daily activities. Despite the significant impact of neuropathic pain, its prevalence and characteristics in lymphedema remain poorly defined, creating a critical gap in the literature (6).

Pain management is an integral component of lymphedema treatment, since the pain affects the patient's quality of life directly. Although the relationship between fluid retention and nerve compression has been hypothesized, studies specifically addressing neuropathic pain in lymphedema are scarce. Existing research highlights the need for a deeper understanding of how lymphedema severity correlates with neuropathic pain (6). Comprehending this phenomenon is especially essential for patients with breast cancer–related lymphedema. In these patients, surgical interventions such as mastectomy and axillary lymph node dissection may contribute to tissue trauma and nerve damage (4).

This study aims to determine the prevalence and characteristics of neuropathic pain in women with breast cancer–related secondary lymphedema. Secondly, we aim to evaluate the association between the severity of lymphedema and the presence of neuropathic pain. The primary hypothesis is that neuropathic pain is common in this patient group, especially in patients with severe lymphedema. Findings are expected to enhance the understanding of neuropathic pain in secondary lymphedema, providing clinicians with evidence-based insights to improve pain management strategies and ultimately improve patient outcomes.

Methods

This cross-sectional study aimed to evaluate the prevalence and characteristics of neuropathic pain in female patients diagnosed with breast cancer–related secondary lymphedema. The study was conducted at a tertiary care center over a year-long period, and the sample consisted of patients who met the inclusion criteria.

Patients

After the approval of the İstanbul Atlas University Ethics Committee, 100 women who were between 18 and 65 years old and diagnosed with breast cancer–associated secondary lymphedema were included in the study. The diagnosis of lymphedema was confirmed through a combination of clinical evaluation and imaging methods such as magnetic resonance imaging, computed tomography, or ultrasound.

Eligible patients were required to have a histopathologically confirmed diagnosis of breast cancer documented in their medical records. The study included only patients with breast cancer classified as early or locally advanced (Stages I-III) based on clinical or imaging-based staging. Patients also needed to have a documented history of surgical interventions such as mastectomy, lumpectomy, or axillary lymph node dissection, as well as detailed records of oncological treatments, including radiation therapy to the breast or axillary region, chemotherapy, or both. The onset of lymphedema had to occur within 5 years of completing breast cancer treatment, with swelling localized to the upper extremities consistent with breast cancer–related lymphedema.

Patients who expressed a willingness to participate and provided informed consent were included in the study. Those with neuropathic pain caused by conditions unrelated to breast cancer, such as peripheral neuropathies, post-herpetic neuralgia, traumatic brain injuries, radiculopathies, syringomyelia, or spinal cord injuries, were excluded. Additionally, patients who did not meet breast cancer criteria or declined to provide informed consent were excluded.

By focusing solely on breast cancer–related secondary lymphedema, the study ensured that findings were specific to this subgroup, enhancing the validity and clinical applicability of the results.

Data Collection

Data collection was conducted using structured patient follow-up forms and validated questionnaires. The forms consisted of detailed demographic information, including age, weight, height, body mass index, educational level, occupation, and comorbid conditions. Specific data on breast cancer-related surgical or treatment history, such as mastectomy, axillary lymph node dissection, radiotherapy, or chemotherapy, were also included.

The diagnosis of breast cancer was confirmed through histopathological examination documented in

the medical records. Clinical or imaging-based staging was used to categorize the cancer as early or locally advanced (Stages I-III). Details of surgical interventions and oncological treatments, including radiation therapy to the breast or axillary region and chemotherapy regimens, were recorded thoroughly.

The duration of lymphedema was recorded for each patient. The specific site affected by lymphedema was noted, including whether it involved the upper or lower extremities or the face/neck region. Additionally, the side of the body that was impacted—right, left, or bilateral—was documented. The stage of lymphedema was classified from 0 to 3 according to the International Society of Lymphology system (7).

Assessment of Pain and Function

Patients rated their lymphedema-associated pain, tension, and heaviness on a numeric rating scale (NRS-11) from 0 (no symptom) to 10 (worst possible symptom). They also evaluated their general health and lymphedema-related health on a Likert scale from 1 to 5, with higher scores indicating worse health status. Additionally, the impact of lymphedema on daily activities was assessed using the Lymphedema Life Impact Scale, which measured physical, psychosocial, and functional concerns on a scale from 1 (no impact) to 5 (severe impact) (9).

Volume Measurements

Lymphedema of the limbs was evaluated with the circumferential method. The circumferential upper limb measurements were performed with the arm abducted at 30°, starting at the level of the carpometacarpal joint, every 5 cm proximal to this point along both limbs. Limb volumes were calculated in milliliters using Limb Volumes Professional version 5.0 (BioScience Research Institute), which converted the circumference measurements into volume estimates (10).

Lymphedema Grading

Lymphedema was classified according to the International Society of Lymphology grading system. Grade 0, also referred to as the latency stage, indicates that there is no visible swelling even though lymph transport is impaired. Grade 1, considered mild, involves fluid accumulation that diminishes with limb elevation. This grade also includes the presence of pitting edema. In Grade 2, which is classified as moderate, the swelling persists despite limb elevation, and pitting may or may not be observed. Finally, Grade 3, or severe lymphedema, is characterized by lymphostatic elephantiasis, marked by significant swelling and skin changes such as fibrosis (11).

Pain Assessment

Neuropathic pain was assessed using 2 validated questionnaires: the Self-Report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and the Douleur Neuropathique 4 Questions (DN-4). The S-LANSS questionnaire consists of 7 items that evaluate pain quality and sensory symptoms, with a score of 12 or higher indicating probable neuropathic pain (12). The DN-4 questionnaire includes 10 items that assess pain descriptors and sensory examination findings, with a score of 4 or higher suggesting neuropathic pain (13).

Ethical Considerations

The study protocol was approved by the institutional ethics committee. Informed consent was obtained from all patients after the study's purpose, procedures, and potential risks were explained. Patient confidentiality was maintained throughout the study, and the patients were assured that their information would be used solely for research purposes.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. The prevalence of neuropathic pain was calculated based on S-LANSS and DN-4 scores. Associations between lymphedema stages and neuropathic pain scores were analyzed using chi-square tests and correlation coefficients. Statistical significance was set at $P < 0.05$. The other values and the purposes for which they were used were as follows: mean and standard deviation (mean ± SD) to summarize the central tendencies and distributions of continuous variables (e.g., age, symptom duration, pain scores); mean and range (mean (range)) to show the central tendency and range of some variables (e.g., S-LANSS and DN-4); the independent samples t-test to compare means between 2 groups; one-way ANOVA to compare means among 3 or more groups; and the chi-square test to compare categorical data.

Results

This study evaluated 100 individuals diagnosed with secondary lymphedema. The mean age of the patients was calculated to be 60.69 years, with a standard deviation of 7.7 years. The duration of symptoms reported by the patients averaged 25.37 months, with

a range spanning from 12 to 48 months, as detailed in Table 1. The assessment of pain, conducted using the NRS-11, yielded an average pain score of 5.41, with a standard deviation of 1.6. Neuropathic pain assessment through the DN-4 questionnaire identified that 14% of the patients (n = 14) had neuropathic pain, whereas the S-LANSS scale indicated a slightly higher prevalence, with 17% (n = 17) of the patients reporting such symptoms (Table 1).

The study revealed a strong association between the severity of clinically graded lymphedema and both the presence and intensity of neuropathic pain. Patients suffering from Grade 3 lymphedema reported significantly higher pain levels, with a mean NRS-11 pain score of 8.00 and a standard deviation of 0.64. These figures were markedly higher than for the patients with Grade 1 lymphedema, who reported a mean pain score of 4.14 (SD = 1.21) or for those with Grade 2, who reported a mean pain score of 5.90 (SD = 1.19), as shown in Table 2. These differences were statistically significant, with *P*-values less than 0.001. Furthermore, Grade 3 lymphedema was also associated with higher scores on neuropathic pain scales; the mean DN-4 score for this group was 6.33 (SD = 1.63), and the mean S-LANSS score was a notably elevated 16.66 (SD = 2.42), both of which differed significantly from the scores associated with less severe grades of lymphedema, confirming that the severity of neuropathic symptoms increased as the lymphedema grade worsened (Table 2).

Table 1. *Patients' demographic and clinical characteristics.*

Variable		Value (n = 100)
Age (years)		60.69 ± 7.7
Symptom duration (months)		25.37 (12-48)
BMI		28.9 ± 1.85
NRS-11 (pain)		5.41 ± 1.6
NRS-11 (tension)		4.83 ± 1.4
NRS-11 (heaviness)		5.01 ± 1.5
S-LANSS		7.80 (0-19)
DN4		2.59 (0-9)
S-LANSS neuropathic pain + (n)		17 (17%)
DN-4 neuropathic pain + (n)		14 (14%)
Lymphedema grading	Grade 1	35 (35%)
	Grade 2	59 (59%)
	Grade 3	6 (6%)

BMI: Body Mass Index, NRS: Numeric Rating Scale, S-LANSS: Self-reported Leeds Assessment of Neuropathic Symptoms and Signs, DN-4: Douleur Neuropathique 4.

The pairwise comparisons among the grades confirmed that each increase in lymphedema grade was associated with significant elevations in the NRS-11, DN-4, and S-LANSS scores, all yielding *P*-values less than 0.001. These results demonstrate the correlation between the progression of lymphedema and the intensification of neuropathic pain symptoms among the afflicted individuals (Table 3).

Discussion

The present study focuses exclusively on patients with breast cancer–associated secondary lymphedema. Although neuropathic pain is expected to be a common symptom in cases of lymphedema related to breast cancer, no study has investigated the prevalence of neuropathic pain in this patient group. In the current study, we assessed the prevalence of neuropathic pain in female patients with breast cancer–related lymphedema, using the S-LANSS and DN-4 questionnaires. This study demonstrates that neuropathic complaints are frequently observed in patients with breast cancer–related secondary lymphedema and highlights a correlation between pain scores/neuropathic symptoms and the severity of lymphedema.

Some recent studies have estimated the prevalence of moderate to severe chronic pain at 15% to

Table 2. *Demographic and clinical data regarding different stages of lymphedema.*

	Grade 1 (n = 35)	Grade 2 (n = 59)	Grade 3 (n = 6)	*P*
Age (years)	62.48 ± 7.83	59.37 ± 7.20	63.16 ± 10.06	0.118
BMI (kg/m^2)	28.64 ± 1.75	28.86 ± 1.43	29.6 ± 1.9	0.454
Symptom duration (months)	25.17 ± 6.70	25.08 ± 6.92	29.33 ± 6.05	0.337
NRS-11(pain)	4.14 ± 1.21	5.90 ± 1.19	8.00 ± 0.64	< 0.001
NRS-11(tension)	4.34 ± 1.23	4.81 ± 1.00	7.83 ± 1.47	< 0.001
NRS-11 (heaviness)	4.37 ± 1.39	5.06 ± 0.96	8.16 ± 1.72	< 0.001
S-LANSS	5.34 ± 2.97	8.35 ± 3.23	16.66 ± 2.42	< 0.001
DN-4	1.54 ± 0.85	2.83 ± 1.83	6.33 ± 1.63	< 0.001
S-LANSS neuropathic pain positive	0 (0%)	11 (18.6%)	6 (100 %)	< 0.001
DN-4 neuropathic pain positive	0 (0%)	9 (15.63%)	5 (83.3 %)	< 0.001

BMI: Body Mass Index, NRS: Numeric Rating Scale, S-LANSS: Self-reported Leeds Assessment of Neuropathic Symptoms and Signs, DN-4: Douleur Neuropathique 4.

25% (14-17). A 2008 study by Bouhassira et al (3) used the DN-4 questionnaire to evaluate the prevalence of neuropathic pain and reported a prevalence of 6.9% among individuals with chronic pain; the figure among those with moderate to severe chronic pain was 5.1%. Similarly, Torrance et al (15) found the overall prevalence of chronic pain with neuropathic features to be 8.2% in the British population. Both studies by Bouhassira et al and Torrance et al (15) identified specific sociodemographic profiles, such as gender (women), rural residence, middle age, and occupations involving physical labor, as factors associated with higher neuropathic pain prevalence (3,15). In contrast, the present study revealed that 14% of patients had neuropathic pain according to the DN-4 questionnaire and 17% according to the S-LANSS questionnaire, highlighting a notably higher prevalence in patients with secondary lymphedema. Additionally, the results showed significant associations between higher lymphedema grades and increased neuropathic pain scores, emphasizing the impact of disease severity on pain experiences.

The high prevalence of neuropathic pain in our cohort underscores the necessity for targeted pain management strategies in patients with secondary lymphedema, particularly because neuropathic pain may impair their quality of life severely. Therefore, the present study supports the need for comprehensive assessment and tailored interventions to address neuropathic pain in this patient group effectively, contributing to enhanced clinical practices and improved patient outcomes.

Pain in breast cancer-related lymphedema (BCRL) has been reported by 20% to 50% of patients who have the condition, with contributing factors including mastectomy, axillary lymph node dissection, tissue trauma during surgery, and dissection of intercostobrachial and axillary nerve branches. These interventions, like radiotherapy and chemotherapy, may result in direct nerve damage, thereby increasing the risk of neuropathic pain. Patients often describe the pain as burning, aching, squeezing, wound-site tenderness, restlessness, or sensitivity. Excessive interstitial fluid pressure on nerves can lead to neuropathic pain with such symptoms as numbness and tingling, potentially limiting daily activities (5,6). Our findings revealed that 14% of patients with breast cancer–associated secondary lymphedema experienced neuropathic pain, according to the DN-4 questionnaire; according to the S-LANSS questionnaire, 17% of the patients were so affected. These results align with those described in the aforementioned 2006 and 2008 studies, highlighting the significant role of surgical trauma and cancer treatment in the development of lymphedema and associated neuropathic pain (5,6).

Table 3. *Comparison of NRS-11, DN4, and S-LANSS scores among patients at different stages of lymphedema.*

			Mean (SD)	Mean (SD)	*P*
NRS-11	Grade 1	Grade 2	4.14 ± 1.21	5.90 ± 1.19	< 0.001
	Grade 1	Grade 3	4.14 ± 1.21	8.00 ± 0.64	< 0.001
	Grade 2	Grade 3	5.90 ± 1.19	8.00 ± 0.64	< 0.001
DN-4	Grade 1	Grade 2	1.54 ± 0.85	2.83 ± 1.83	0.001
	Grade 1	Grade 3	1.54 ± 0.85	6.33 ± 1.63	< 0.001
	Grade 2	Grade 3	2.83 ± 1.83	6.33 ± 1.63	< 0.001
S-LANSS	Grade 1	Grade 2	5.34 ± 2.97	8.35 ± 3.23	< 0.001
	Grade 1	Grade 3	5.34 ± 2.97	16.66 ± 2.42	< 0.001
	Grade 2	Grade 3	8.35 ± 3.23	16.66 ± 2.42	< 0.001

NRS: Numeric Rating Scale, DN-4: Douleur Neuropathique 4, S-LANSS: Self-reported Leeds Assessment of Neuropathic Symptoms and Signs.

Previous studies have reported varying degrees of the relationship between secondary lymphedema and neuropathic pain. Forte et al examined the relationship between BCRL and peripheral neuropathies, but no clear conclusion was reached regarding whether the condition increased the risk of neuropathic pain (17). However, Hong and Kim presented a case report of a patient whose secondary lymphedema and complex regional pain syndrome type I were treated successfully with spinal cord stimulation (18). This case highlights the potential of innovative approaches in managing lymphedema when neuropathic pain is present and underscores the importance of using comprehensive strategies to diagnose and manage neuropathic pain in secondary lymphedema (18).

The present study focuses on patients with breast cancer–associated secondary lymphedema, ensuring that the findings are directly relevant to this specific population. Nevertheless, this specificity limits the generalizability of the results to other causes of secondary lymphedema, such as trauma or filariasis. The distinct pathophysiological mechanisms and clinical features of secondary lymphedema from causes unrelated to cancer were not addressed in this study. Further studies focusing on these patient groups are needed to gain better understanding of secondary lymphedema and its management across different causes.

Limitations

This study has several limitations that should be acknowledged. First, the cross-sectional design restricts

the ability to establish causal relationships between lymphedema severity and neuropathic pain development, since the study captures data at a single time point. Second, the study was conducted on 100 patients in a single tertiary care center, potentially limiting the generalizability of the findings to populations with varying access to health care. Third, while validated self-reported questionnaires such as the DN-4 and S-LANSS were used, subjective biases could still have influenced the accuracy of the data, since patients might have overreported or underreported symptoms based on individual pain thresholds or recall biases. While efforts were made to control for confounding variables such as age and comorbidities, unmeasured factors, including psychological influences (e.g., anxiety or depression), could have affected pain perception. Lastly, we did not include a healthy control group with similar demographic features. Nonetheless, to the best of our knowledge, this study is the first to inquire into the prevalence of neuropathic pain in BCRL patients. The main strengths of the study are the inclusion of a homogeneous population and the evaluation of neuropathic pain on 2 different widely used questionnaires.

Conclusion

These results demonstrate that neuropathic pain may be a significant component of BCRL, so treatment strategies should also aim to alleviate this type of pain. Although this study provides valuable insights into neuropathic pain in patients with breast cancer–associated secondary lymphedema, the scope is limited to this specific population. Clinicians should avoid extrapolating these findings to other causes of secondary lymphedema. Future research should address these limitations by incorporating longitudinal design, objective pain assessment, and evaluation of psychological factors to provide more comprehensive understanding of neuropathic pain in patients with BCRL.

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