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Personalized Approach to The Diagnosis of Neuropathic Pain in Metastatic Breast Cancer: Development of A Multicomponent Questionnaire

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Abstract: Objective: To validate the specialized questionnaire "NEURO-RMZh" for the differential diagnosis of neuropathic pain in patients with metastatic breast cancer and to compare its psychometric properties with existing validated instruments.

Materials and Methods: A single-center prospective validation study was conducted, enrolling 111 patients with metastatic breast cancer. A comprehensive methodological approach was employed, including assessment of internal consistency, test-retest reliability, construct and criterion validity. Statistical methods included factor analysis, correlation analysis, ROC analysis, and multiple logistic regression. The DN4, BPI, SF-36, and Visual Analogue Scale (VAS) questionnaires were used as comparators.

Results: The "NEURO-RMZh" questionnaire demonstrated high internal consistency (Cronbach's α = 0.89) and test-retest reliability (ICC = 0.94). Its four-factor structure explains 73.6% of the total variance. The diagnostic performance of the questionnaire exceeds that of existing tools: sensitivity 89.7%, specificity 82.4%, area under the ROC curve 0.92. Likelihood ratios (LR+ = 5.10, LR- = 0.13) indicate the clinical significance of the test. Strong correlations were observed with SF-36 quality of life domains (r from -0.44 to -0.74).

Conclusion: The "NEURO-RMZh" questionnaire is a valid, reliable, and highly informative tool for the differential diagnosis of neuropathic pain in patients with metastatic breast cancer. Its implementation may contribute to the optimization of diagnostics and personalization of therapeutic strategies in palliative oncology.

Keywords: Neuropathic pain, breast cancer, questionnaire, validation, palliative care.

Introduction: Breast cancer remains one of the leading causes of cancer morbidity among women worldwide, accounting for 24.5% of all malignant neoplasms in women [1]. Pain syndrome of various etiologies develops in 75–90% of patients with advanced forms of the disease, significantly reducing quality of life and necessitating a differentiated approach to therapy [2,3].

The pathogenesis of pain syndrome in breast cancer is characterized by pronounced heterogeneity of underlying mechanisms. Nociceptive pain is caused by the direct effect of the tumor on tissues, inflammatory processes, and mechanical compression of structures [4]. Neuropathic pain develops as a result of peripheral nerve injury due to tumor progression, neurotoxicity of chemotherapeutic agents (taxanes, platinum

compounds, vinca alkaloids), or radiotherapy [5,6]. The mixed type of pain, which combines both mechanisms, is observed in 39–65% of patients and presents the greatest diagnostic challenges [7].

Current Approaches to Pain Assessment in Oncology

The visual analogue scale (VAS) remains the gold standard for assessing pain intensity in clinical practice due to its ease of use and high reproducibility (r=0.94) [8]. However, the VAS does not allow differentiation of pain types based on pathophysiological mechanisms, limiting its use in selecting targeted therapies for neuropathic pain [9].

The DN4 is a validated screening tool for neuropathic pain that includes 10 dichotomous questions [10]. DN4 demonstrates a sensitivity of 82.9% and a specificity of 89.9% at a cut-off value of ≥4 points [11]. Despite its wide application, the DN4 has significant limitations in the oncological population: insufficient validation in patients with chemotherapy-induced polyneuropathy, low specificity for mixed pain types (67.3%), and the need for physical examination, which complicates telemedicine consultations [12,13].

The Brief Pain Inventory (BPI) assesses pain intensity and its impact on patient functional activity using an 11-point scale [14]. The questionnaire demonstrates high internal consistency (Cronbach's α = 0.85–0.95) and is validated in the oncological population [15]. However, the BPI does not include specific descriptors of neuropathic pain and does not allow differential diagnosis between types of pain syndromes [16].

The SF-36 is a universal instrument for assessing quality of life, including a bodily pain domain [17]. In oncological research, the SF-36 has shown adequate reliability (α = 0.78–0.93) and construct validity [18]. Nevertheless, the questionnaire is not intended for differential diagnosis of pain types and has low sensitivity to changes in neuropathic symptoms [19].

A review of the literature reveals critical gaps in current approaches to the diagnosis of neuropathic pain in breast cancer:

- Insufficient specificity of existing tools for the oncological population, particularly in cases of chemotherapy-induced polyneuropathy [20];
- Lack of consideration for the temporal characteristics of pain syndrome related to cycles of anticancer therapy [21];
- Limited applicability in palliative care settings for patients with marked asthenia and cognitive impairment [22].

The aim of this study is to validate a novel specialized questionnaire—the "Oncology Neuropathic Pain Differential Diagnosis Scale" (NEURO-RMZh)—for the assessment of neuropathic pain in patients with breast cancer and to compare its psychometric properties with existing validated instruments (VAS, DN4, BPI, SF-36).

METHODS

In response to the identified shortcomings of current methodologies, we have developed an innovative diagnostic tool that integrates the advantages of contemporary questionnaires while minimizing their limitations. The developed questionnaire comprises 20 items: 16 for self-completion by the patient and 4 for clinical assessment by a specialist.

This diagnostic package is adapted to the specific features of neuropathic pain manifestations in oncology and is equipped with a detailed data analysis system. This ensures the optimization of diagnostic procedures and enhances the reliability of differential diagnosis of various pain types in clinical oncology.

Such a multicomponent methodology allows for the most detailed characterization of pain sensations and their impact on the patient's daily life. The information obtained forms the basis for developing personalized therapeutic programs, which is especially relevant for managing patients with persistent pain syndromes and malignant neoplasms.

Questionnaire for the Differential Diagnosis of Neuropathic Pain in Patients with Metastatic Breast Cancer (NEURO-RMZh)

Part I: Patient Section (16 items)

Section A: Pain Intensity and Localization (4 items)

1. Please rate the intensity of your pain at this moment on a scale from 0 to 10, where 0 means no pain and 10 means unbearable pain. *Numerical scale: 0–10*

2. Please rate the intensity of your most severe pain over the past 7 days on a scale from 0 to 10. *Numerical scale: 0–10*

3. Mark on the body diagram the areas where you experience pain, and circle the area of most intense pain. *Schematic front and back view for marking*

4. Does the pain extend beyond the area of the tumor or metastases?

□ No

□ Yes, slightly

□ Yes, significantly

□ Difficult to answer

Section B: Pain Characteristics (6 items)

5. Do you experience any of the following sensations in the area of pain? (select all that apply)

□ Burning

□ Tingling

□ Electric shock sensation

□ Numbness

□ Crawling sensation

□ None of the above

6. How intense are these unusual sensations on a scale from 0 to 10? *Numerical scale: 0–10*

7. Does the pain occur suddenly, without an obvious cause?

□ Never

□ Rarely

□ Often

□ Constantly

8. Does the pain get worse with:
□ Light touch to the painful area

□ Pressure on the painful area

□ Cold

□ Heat

□ None of the above

9. Is there pain in an area with reduced sensitivity?

□ No

□ Yes, slightly

□ Yes, significantly

□ Difficult to answer

10. Does the nature of your pain change during the day?

□ No, the pain is constant

□ Yes, it worsens in the evening

□ Yes, it worsens at night

□ Yes, it worsens in the morning

□ Other: _____

Section C: Impact of Pain on Quality of Life (6 items)

11. How does pain affect your sleep?

□ No effect

□ Slightly hinders falling asleep

□ Significantly disrupts sleep

□ Makes restful sleep impossible

12. How does pain affect your daily activity?

□ Does not limit

□ Slightly limits

□ Significantly limits

□ Makes activity impossible

13. Does pain affect your mood?

□ No effect

□ Causes occasional irritability

□ Causes constant irritability or depression

□ Causes marked anxiety or depression

14. How effective are pain medications in relieving your pain?

□ Completely eliminate

□ Significantly reduce

□ Slightly reduce

□ Hardly help at all

15. Which methods, besides medication, help you reduce pain? (select all that apply)

□ Cold

□ Heat

□ Massage

□ Change of body position

□ Distraction

□ Nothing helps

□ Other: _____

16. To what extent does pain interfere with your communication with loved ones?

□ Does not interfere

□ Slightly interferes

□ Significantly limits communication

□ Makes communication impossible

Part II: Physician Assessment (4 items)

17. Objective signs of nervous system damage in the area of pain:

□ None

□ Local muscle atrophy

□ Trophic skin changes

□ Skin discoloration

□ Edema

□ Other: _____

18. Assessment of tactile sensitivity in the area of pain:

□ Normal

□ Hypoesthesia (decreased)

□ Hyperesthesia (increased)

□ Allodynia (pain from non-painful stimuli)

□ Anesthesia (absent)

19. Assessment of thermal sensitivity in the area of pain:

□ Normal

□ Decreased to cold

□ Decreased to heat

□ Absent

□ Paradoxical (heat perceived as cold or vice versa)

20. Correspondence of pain localization to the anatomical distribution of nerves or dermatomes:

□ Does not correspond

□ Partially corresponds

□ Fully corresponds

□ Corresponds to the innervation zone of several nerves

Scoring System

For Part I (Patient Section):

- Questions 1, 2, and 6: direct score calculation (0–10 points each)
- Questions 3 and 15: not scored, used for qualitative assessment
- Questions 4, 7, 8, 9, 10, 11, 12, 13, 14, and 16: 0 to 3 points each, depending on symptom severity
- Question 5: 1 point for each symptom indicated (maximum 5 points)

For Part II (Physician Assessment):

- Questions 17–20: 0 to 3 points each, depending on the degree of clinical findings

Interpretation of Results:

- 0–15 points: low probability of neuropathic pain
- 16–30 points: moderate probability of neuropathic pain
- 31–45 points: high probability of neuropathic pain
- 45 points: very high probability of neuropathic pain

The NEURO-RMZh was developed with consideration for the specific characteristics of oncology patients and includes:

- Adapted neuropathic pain descriptors for the oncological population
- Temporal assessment of symptoms in relation to anticancer therapy
- A simplified algorithm for use in palliative care
- Feasibility for remote application without physical examination

The study hypothesis is that the NEURO-RMZh will demonstrate superior diagnostic performance compared to existing questionnaires in differentiating neuropathic pain from nociceptive and mixed pain in patients with breast cancer, thus optimizing targeted therapy selection and improving the quality of palliative care.

A single-center prospective validation study was conducted to assess the psychometric properties of the new NEURO-RMZh questionnaire for evaluating neuropathic pain in patients with metastatic breast cancer. The study included women who met the following criteria:

- Age 18–75 years
- Histologically confirmed metastatic breast cancer
- Presence of pain syndrome with an intensity of ≥3 on the visual analogue scale (VAS)
- Ability to independently complete questionnaires
- Signed informed consent to participate in the study

Exclusion criteria:

- Severe comorbidities that could affect pain perception (e.g., diabetes mellitus with polyneuropathy, systemic connective tissue diseases, chronic renal failure)
- History or presence of psychiatric disorders at the time of enrollment
- Use of psychotropic medications (antidepressants, neuroleptics, tranquilizers) within 2 weeks prior to enrollment
- Cognitive impairment interfering with adequate comprehension of the questionnaires
- Inability to independently complete the questionnaires for any reason
- Refusal to participate

The sample size was calculated using a formula for validation studies of diagnostic tests. Assuming a planned sensitivity of 85%, specificity of 80%, 95% confidence interval, and study power of 80%, the minimum sample size was 98 patients. Taking into account potential attrition (15%), the target sample size was set at 115 patients.

Potential participants were identified among patients undergoing treatment at the Palliative Care Department of the Samarkand Interregional Hospice. The study physician conducted a preliminary eligibility

assessment based on medical records and clinical examination.

After obtaining informed consent, a standardized pain assessment was performed by an anesthesiologist with at least 5 years' experience in palliative oncology. Based on clinical data, disease history, and neurological examination, a preliminary diagnosis of pain type was established: nociceptive pain, neuropathic pain, or mixed pain (nociceptive + neuropathic).

This clinical assessment was considered the "gold standard" for subsequent analysis of the diagnostic properties of the questionnaires.

Questionnaire completion was carried out in standardized conditions in the presence of a research nurse to prevent missing data and ensure proper understanding of the questions.

To assess the test-retest reliability of the NEURO-RMZh questionnaire, 30 patients were randomly selected to complete the questionnaire a second time 48–72 hours later, provided there were no changes in pain management.

Statistical analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). The significance level was set at $p<0.05$.

Reliability of the Questionnaire:

- Internal consistency was assessed using Cronbach's alpha coefficient
- Test-retest reliability was evaluated using the intraclass correlation coefficient (ICC)
- Temporal stability was measured using the Pearson correlation coefficient between initial and repeated test results

Validity of the Questionnaire:

- **Construct validity:** Assessed using factor analysis by the principal components method with Varimax rotation;
- **Criterion validity:** Evaluated by correlation analysis with the clinical assessment of pain type (the "gold standard");
- **Convergent validity:** Assessed by Pearson correlation analysis with the results of the DN4, BPI, and SF-36 questionnaires.

For each questionnaire, the following were calculated:

- Sensitivity (Se) and specificity (Sp);
- Positive predictive value (PPV) and negative predictive value (NPV);
- Positive (LR+) and negative (LR−) likelihood ratios;
- Area under the ROC curve (AUC) with a 95% confidence interval.

Optimal cut-off values were determined using the Youden index ($J = Se + Sp - 1$).

The study included women who met the following criteria:

- Age 18–75 years;
- Histologically confirmed metastatic breast cancer;
- Presence of pain syndrome with an intensity of ≥3 points on the visual analogue scale (VAS);
- Ability to complete questionnaires independently;
- Signed informed consent to participate in the study.

Exclusion criteria:

- Severe comorbidities that could affect pain perception (e.g., diabetes mellitus with polyneuropathy, systemic connective tissue diseases, chronic renal failure);
- History or presence of psychiatric disorders at the time of enrollment;
- Use of psychotropic medications (antidepressants, neuroleptics, tranquilizers) within two weeks prior to enrollment;
- Cognitive impairments precluding adequate understanding of the questionnaires;
- Inability to complete questionnaires independently for any reason;
- Refusal to participate.

The sample size was calculated using a formula for validation studies of diagnostic tests. Assuming a planned sensitivity of 85%, specificity of 80%, a 95% confidence interval, and a study power of 80%, the minimum required sample size was 98 patients. Allowing for a potential dropout rate of 15%, the target sample size was set at 112 patients.

The study was conducted in accordance with the principles of Good Clinical Practice (GCP) and national regulatory requirements. Data confidentiality was ensured by de-identification and coding of information. Participants retained the right to withdraw consent at any stage of the study without explanation and without affecting the quality of medical care received.

RESULTS

A total of 111 patients with metastatic breast cancer were enrolled in the study. The mean age of participants was 58.4 ± 11.2 years (range, 34–74 years).

The majority of patients (67.9%, n=76) had invasive ductal carcinoma, 23.2% (n=26) had invasive lobular carcinoma, and the remaining 8.9% (n=10) had other histological variants.

Here is the full translation of your section, including the table and the accompanying explanation, in scientific English suitable for publication:

Table 1.

Demographic and Clinical Characteristics of the Study Sample (n=111)

Variable	Value
Age, years	
Mean ± SD	58.4 ± 11.2
Median (IQR)	59.0 (50.0–66.0)
Range	34–74
Histological type, n (%)	
Invasive ductal carcinoma	76 (67.9)
Invasive lobular carcinoma	26 (23.2)
Other types	10 (8.9)
Molecular subtype, n (%)	
Luminal A	28 (25.0)
Luminal B HER2-	34 (30.4)
Luminal B HER2+	21 (18.8)
HER2-positive	16 (14.3)
Triple-negative	13 (11.6)
Site of metastases, n (%)	
Bone	67 (59.8)
Liver	43 (38.4)
Lungs	38 (33.9)
Brain	12 (10.7)
Prior therapy, n (%)	
Anthracyclines	89 (79.5)
Taxanes	34 (30.4)
Radiotherapy	78 (69.6)
Pain type (gold standard), n (%)	
Nociceptive	48 (42.9)
Neuropathic	39 (34.8)
Mixed	25 (22.3)
Pain intensity (VAS)	
Mean ± SD	6.2 ± 1.8

Variable	Value
Median (IQR)	6.0 (5.0–8.0)

The study cohort consisted of middle-aged and elderly women with various histological and molecular subtypes of breast cancer. The predominance of invasive ductal carcinoma and luminal subtypes corresponds to the general breast cancer patient population. The high frequency of bone metastases (59.8%) explains the substantial proportion of patients with pain syndrome.

According to the clinical assessment by an anesthesiologist ("gold standard"), 48 patients (42.9%) were diagnosed with predominantly nociceptive pain, 39 (34.8%) with neuropathic pain, and 25 (22.3%) with mixed pain. The mean pain intensity by VAS was 6.2 ± 1.8.

Psychometric Properties of the NEURO-RMZh Questionnaire

The internal consistency of the NEURO-RMZh questionnaire demonstrated high values: Cronbach's alpha coefficient was 0.89 (95% CI: 0.85–0.92), which significantly exceeds the recommended minimum level of 0.70. For comparison, the Cronbach's alpha for the DN4 was 0.76 (95% CI: 0.69–0.82), and for the BPI – 0.81 (95% CI: 0.76–0.85).

Table 2

Questionnaire	Cronbach's α (95% CI)	ICC (95% CI)*	r test-retest**
NEURO-RMZh	0.89 (0.85–0.92)	0.94 (0.88–0.97)	0.92
DN4	0.76 (0.69–0.82)	0.87 (0.75–0.94)	0.85
BPI	0.81 (0.76–0.85)	0.91 (0.82–0.96)	0.88

*Note: ICC – Intraclass correlation coefficient for assessment of test-retest reliability; **All correlations are significant at p<0.001.

Test-retest reliability was assessed in 30 patients 48–72 hours after initial testing. The intraclass correlation coefficient (ICC) for the NEURO-RMZh questionnaire was 0.94 (95% CI: 0.88–0.97), indicating excellent temporal stability. The Pearson correlation coefficient between the first and repeat test was r=0.92 (p<0.001).

Construct validity was confirmed by factor analysis. Principal component analysis with Varimax rotation revealed a four-factor structure, accounting for 73.6% of the total variance. The factors corresponded to the domains embedded in the questionnaire: qualitative pain characteristics (28.4% of variance), temporal characteristics (18.7%), provoking factors (14.2%), and associated symptoms (12.3%). All factor loadings exceeded 0.60, confirming the adequacy of the questionnaire structure.

Criterion validity was evaluated by comparing the questionnaire results with the clinical assessment of pain type. The correlation between the total NEURO-RMZh score and the clinical assessment of the neuropathic pain component was r=0.78 (p<0.001), which was significantly higher than the corresponding value for the DN4 (r=0.64, p<0.001).

Here is a complete, scientific English translation of your tables and explanatory text for publication:

Table 3.

Results of Factor Analysis of the NEURO-RMZh Questionnaire

Factor	Eigenvalue	% Variance Explained	Cumulative %
1. Qualitative pain characteristics	4.26	28.4	28.4
2. Temporal characteristics	2.81	18.7	47.1
3. Provoking factors	2.13	14.2	61.3
4. Associated symptoms	1.85	12.3	73.6

The four-factor structure of the questionnaire explains 73.6% of the total variance, confirming the adequacy of the theoretical model. The high KMO value (0.84) indicates the suitability of the data for factor analysis.

Convergent validity was confirmed by significant correlations with validated questionnaires: with DN4 r=0.71 (p<0.001), with the "pain intensity" domain of BPI r=0.58 (p<0.001), and with the "physical functioning" domain of SF-36 r=–0.52 (p<0.001).

Table 4.

Comparative Diagnostic Characteristics of Questionnaires for Identifying Neuropathic Pain

Parameter	NEURO-RMZh (≥7 points)	DN4 (≥4 points)	VAS (≥6 points)	p-value*
Sensitivity, % (95% CI)	89.7 (82.1–94.8)	76.9 (67.2–84.7)	84.6 (76.8–90.5)	0.042
Specificity, % (95% CI)	82.4 (74.6–88.5)	71.2 (62.1–79.1)	45.2 (36.4–54.3)	0.049
PPV, % (95% CI)	85.4 (77.9–91.1)	71.4 (62.8–78.9)	58.9 (51.2–66.3)	0.021
NPV, % (95% CI)	87.7 (80.5–92.8)	76.8 (68.4–83.8)	75.8 (64.7–84.8)	0.038
LR+	5.10 (3.42–7.61)	2.67 (1.89–3.77)	1.54 (1.21–1.97)	<0.001
LR–	0.13 (0.07–0.22)	0.32 (0.21–0.48)	0.34 (0.21–0.55)	0.003
AUC (95% CI)	0.92 (0.87–0.96)	0.79 (0.72–0.86)	0.68 (0.59–0.76)	0.004**

p-value for comparison of NEURO-RMZh vs DN4 (McNemar's test for sensitivity/specificity); ** p-value for AUC comparison (DeLong's Z-test).
PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR–: negative likelihood ratio.

Sensitivity and Specificity:

- NEURO-RMZh (≥7 points): sensitivity 89.7% (95% CI: 82.1–94.8%), specificity 82.4% (95% CI: 74.6–88.5%)
- DN4 (≥4 points): sensitivity 76.9% (95% CI: 67.2–84.7%), specificity 71.2% (95% CI: 62.1–79.1%)
- VAS (≥6 points): sensitivity 84.6% (95% CI: 76.8–90.5%), specificity 45.2% (95% CI: 36.4–54.3%)

Differences in sensitivity and specificity between NEURO-RMZh and DN4 are statistically significant (χ^2=4.12, p=0.042 for sensitivity; χ^2=3.89, p=0.049 for specificity).

Predictive Value:

- Positive predictive value (PPV): NEURO-RMZh – 85.4% (95% CI: 77.9–91.1%), DN4 – 71.4% (95% CI: 62.8–78.9%)
- Negative predictive value (NPV): NEURO-RMZh – 87.7% (95% CI: 80.5–92.8%), DN4 – 76.8% (95% CI: 68.4–83.8%)

Likelihood Ratios:

- LR+ for NEURO-RMZh: 5.10 (95% CI: 3.42–7.61)
- LR+ for DN4: 2.67 (95% CI: 1.89–3.77)
- LR– for NEURO-RMZh: 0.13 (95% CI: 0.07–0.22)

The NEURO-RMZh questionnaire demonstrates statistically significantly higher diagnostic performance compared to DN4 and VAS. Especially important are the high LR+ (5.10) and low LR– (0.13), indicating clinically meaningful diagnostic value.

Table 5. Mean Total Questionnaire Scores by Pain Type

Pain Type	NEURO-RMZh (M±SD)	DN4 (M±SD)	VAS (M±SD)	BPI Intensity (M±SD)
Nociceptive (n=48)	3.2 ± 1.8[a]	1.9 ± 1.2[a]	5.8 ± 1.9	5.4 ± 1.7
Neuropathic (n=39)	9.1 ± 1.6[b]	5.8 ± 1.4[b]	6.8 ± 1.6	6.9 ± 1.8
Mixed (n=25)	6.8 ± 2.1[c]	4.1 ± 1.7[c]	6.2 ± 2.1	6.1 ± 2.0
F-statistic (p)	142.8 (<0.001)	89.4 (<0.001)	3.2 (0.045)	8.7 (<0.001)

Different letter indices indicate statistically significant differences between groups (Tukey post hoc test, p<0.05).

The NEURO-RMZh questionnaire shows the strongest discriminative ability between pain types (F=142.8), significantly exceeding DN4 (F=89.4). The clear separation of mean values among groups confirms the instrument's ability to differentiate pain syndromes.

Table 6.

Results of Multiple Logistic Regression for Predictors of Neuropathic Pain

Predictor	OR	95% CI	p-value
NEURO-RMZh ≥7 points	12.4	4.8–32.1	<0.001
Taxane chemotherapy	3.2	1.4–7.3	0.006
Bone metastases	2.1	1.1–4.2	0.031
Age >60 years	1.8	0.9–3.6	0.089
Prior radiotherapy	1.4	0.7–2.8	0.342

A NEURO-RMZh score ≥7 is the strongest independent predictor of neuropathic pain (OR=12.4), confirming its high diagnostic value in clinical practice.

Table 7.

Correlations of the NEURO-RMZh Total Score with SF-36 Quality of Life Domains

SF-36 Domain	Pearson's r	95% CI	p-value
Physical functioning	–0.68	–0.77 to –0.56	<0.001
Role-physical functioning	–0.61	–0.72 to –0.47	<0.001
Bodily pain	–0.74	–0.82 to –0.64	<0.001
General health	–0.52	–0.65 to –0.36	<0.001
Vitality	–0.58	–0.70 to –0.43	<0.001
Social functioning	–0.55	–0.67 to –0.40	<0.001
Role-emotional functioning	–0.49	–0.63 to –0.33	<0.001
Mental health	–0.44	–0.59 to –0.27	<0.001

Here is your translated section (Results, Discussion, and Conclusion) in scientific, fluent English suitable for publication:

Strong negative correlations were found between the severity of neuropathic pain and all quality of life domains. The strongest association was observed with the "bodily pain" domain (r = –0.74), further supporting the construct validity of the questionnaire.

The presented tables and their interpretation demonstrate the comprehensive validation of the NEURO-RMZh questionnaire and its superiority over existing tools in the diagnosis of neuropathic pain in patients with metastatic breast cancer.

DISCUSSION

This study presents the first comprehensive validation of the specialized NEURO-RMZh questionnaire for the diagnosis of neuropathic pain in patients with metastatic breast cancer. The obtained results demonstrate excellent psychometric properties of the new instrument and its significant advantages over existing questionnaires in this specific population.

The internal consistency of the NEURO-RMZh questionnaire (Cronbach's α = 0.89) exceeds the recommended threshold of 0.70 for clinical instruments [1] and is comparable to the best indicators of validated pain questionnaires. The intraclass correlation coefficient (ICC = 0.94) indicates excellent temporal stability, which is critical for monitoring pain dynamics. These indicators surpass those found for DN4 in our study (α = 0.76, ICC = 0.87) and are consistent with results from large international validation studies [2,3].

The four-factor structure of the questionnaire, explaining 73.6% of the total variance, confirms the theoretical rationale for the included domains. The

identified factors—"qualitative pain characteristics," "temporal characteristics," "provoking factors," and "associated symptoms"—align with current concepts of the multidimensional nature of neuropathic pain [4]. The KMO value of 0.84 demonstrates the high suitability of the data for factor analysis, confirming both the adequacy of the sample size and the quality of the data collected.

The most significant result of the study is the demonstration of the superior diagnostic characteristics of the NEURO-RMZh compared to the widely used DN4. Sensitivity (89.7%) and specificity (82.4%) are substantially higher than those of DN4 in our sample (76.9% and 71.2%, respectively) and are comparable to the best results obtained for DN4 in other populations [5,6].

Particularly important are the likelihood ratios: LR+ = 5.10 and LR– = 0.13. According to evidence-based medicine criteria, LR+ > 5 and LR– < 0.2 indicate clinically significant diagnostic value [7]. These values significantly surpass those of DN4 (LR+ = 2.67, LR– = 0.32), indicating that a positive NEURO-RMZh result increases the probability of neuropathic pain fivefold, while a negative result reduces this probability by 7.7 times.

A fundamental advantage of the NEURO-RMZh is its specific adaptation to the features of pain syndrome in metastatic breast cancer. Unlike universal tools such as DN4, the new questionnaire considers specific mechanisms of neuropathic pain in this population, including chemotherapy-induced peripheral neuropathy, compression syndromes in bone metastases, and post-mastectomy pain syndrome [10,11].

The results of multiple logistic regression confirm the clinical relevance of the questionnaire: a score ≥7 is the strongest independent predictor of neuropathic pain (OR = 12.4), outweighing even established risk factors such as prior taxane therapy (OR = 3.2). This suggests that the questionnaire captures not only obvious cases of neuropathic pain but also more complex clinical scenarios.

It is especially important that the high diagnostic performance is maintained across all studied subgroups. The stability of the results in patients of different ages, metastatic sites, and prior therapies demonstrates the questionnaire's universal applicability in the heterogeneous population of metastatic breast cancer patients.

Strong correlations between the NEURO-RMZh score and SF-36 quality of life domains (r from –0.44 to –0.74) further support the construct validity and clinical relevance of the tool. The strongest association with "bodily pain" (r = –0.74) is expected and confirms that the questionnaire accurately measures pain perception. Significant correlations with other domains, including mental health and social functioning, reflect the multidimensional impact of neuropathic pain on patients' lives [12].

These results are consistent with data from Gärtner et al., who showed that neuropathic pain in breast cancer patients is associated with a more pronounced reduction in quality of life compared to nociceptive pain [13]. The ability of the NEURO-RMZh to identify these differences confirms its potential value for patient stratification and personalized therapeutic approaches.

Direct comparison with DN4 in our study showed that the NEURO-RMZh outperforms DN4 in all key parameters. The sensitivity of DN4 in our sample (76.9%) was lower than that reported in the original study by Bouhassira et al. (82.9%) [15], which may be due to the specific features of the oncology population. Similar findings were observed by Pérez et al., who reported reduced diagnostic accuracy of DN4 in cancer patients [16].

The use of the visual analogue scale (VAS) alone for pain assessment showed unsatisfactory results (sensitivity 84.6%, specificity 45.2%), confirming the need for specialized tools for the differential diagnosis of pain types. These findings align with international expert recommendations highlighting the inadequacy of assessing only pain intensity for optimal pain management [17].

This study has several limitations that should be considered when interpreting the results. First, it was conducted in a single center, which may limit external validity. Differences in clinical practice, population characteristics, and treatment approaches in other centers may affect the diagnostic performance of the questionnaire.

Second, the relatively small sample size (n=111) may limit the statistical power for subgroup analyses. Although the sample size meets recommendations for validation studies of diagnostic instruments [18], larger studies are needed to confirm the stability of these findings.

Third, the use of clinical assessment as the "gold standard," despite the involvement of two independent experts, introduces some subjectivity. The absence of objective biomarkers for neuropathic pain remains a fundamental challenge in this field [19].

Fourth, the cross-sectional design does not allow for assessment of the tool's ability to detect changes in pain characteristics over time. Longitudinal studies are required to assess responsiveness and prognostic

value.

Clinical implications: These findings have important clinical implications for palliative oncology. Accurate diagnosis of pain type is critical for selecting optimal therapeutic strategies, as neuropathic pain requires specific treatment approaches [20]. The NEURO-RMZh can facilitate earlier detection of neuropathic pain and timely administration of appropriate therapy.

Integration of the questionnaire into routine clinical practice may improve the quality of palliative care and treatment outcomes. Its simplicity and high diagnostic accuracy make it suitable for both specialized centers and primary healthcare settings.

Future research should include multicenter validation studies, assessment of responsiveness in longitudinal studies, and investigation of the impact of using the questionnaire on clinical outcomes and cost-effectiveness. Promising directions include adaptation for other oncological diseases and development of digital versions for integration into electronic medical records.

CONCLUSION

This study presents the first comprehensive validation of the specialized NEURO-RMZh questionnaire for the diagnosis of neuropathic pain in patients with metastatic breast cancer. The results demonstrate excellent psychometric characteristics and significant advantages over existing diagnostic methods in this specific population.

The NEURO-RMZh questionnaire showed excellent internal consistency (Cronbach's $\alpha = 0.89$) and high temporal stability (ICC = 0.94), confirming its reliability as a diagnostic tool. The four-factor structure, explaining 73.6% of total variance, aligns with modern understanding of the multidimensional nature of neuropathic pain and provides a solid theoretical basis for the included domains.

The most significant achievements are the sensitivity of 89.7%, specificity of 82.4%, and area under the ROC curve of 0.92. These indicators substantially surpass those of the widely used DN4 in the study population (sensitivity 76.9%, specificity 71.2%, AUC = 0.79) and indicate the high clinical value of the new tool. The likelihood ratios (LR+ = 5.10, LR– = 0.13) meet criteria for clinically significant diagnostic tests.

A key advantage of the NEURO-RMZh is its specific adaptation to the features of pain syndrome in metastatic breast cancer, including chemotherapy-induced peripheral neuropathy, compression syndromes in bone metastases, and post-mastectomy pain syndrome. The stability of diagnostic characteristics across all subgroups confirms its universal applicability in a heterogeneous population.

The high practical utility of the questionnaire is ensured by a short completion time (4.2 ± 1.1 minutes), the possibility of self-administration by patients, and high acceptability. Strong correlations with SF-36 quality of life domains confirm construct validity and the tool's ability to reflect the multidimensional impact of neuropathic pain on patients' functional status.

The clinical value of the NEURO-RMZh questionnaire lies in its ability to enable more accurate and timely diagnosis of neuropathic pain, which is critically important for optimal therapeutic strategies in palliative oncology. Integration of the questionnaire into routine clinical practice may improve the quality of palliative care, optimize pharmacotherapy for pain, and ultimately enhance quality of life for patients with metastatic breast cancer.

Further research should include multicenter validation to confirm external validity, longitudinal studies to assess responsiveness, and evaluation of the impact of the questionnaire on clinical outcomes and cost-effectiveness. Promising directions include adapting the approach for other oncological diseases and developing digital versions for integration into electronic health systems.

In summary, the NEURO-RMZh questionnaire is a valid, reliable, and practical tool that may become an important addition to the diagnostic and monitoring toolkit for pain syndrome in palliative oncology, contributing to personalized therapeutic approaches and improved quality of life for oncology patients.

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