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Pain, numbness, or both? Distinguishing the longitudinal course and predictors of positive, painful neuropathic features vs numbness after breast cancer surgery

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Abstract

Introduction: Both positive (burning, stabbing, and allodynia) and negative (numbness) neuropathic symptoms may arise after surgery but likely contribute differently to patients' postoperative pain experience. Numbness has been identified as divergent from positive neuropathic symptoms and therefore excluded from some neuropathic assessment tools (Neuropathic Pain Scale for PostSurgical patients [NeuPPS]).

Objectives: In this prospective longitudinal study of patients undergoing breast surgery, we aimed to delineate the time course of numbness and its coincidence with NeuPPS and to contrast the association of surgical, psychosocial, and psychophysical predictors with the development of negative vs positive neuropathic symptoms.

Methods: Patients reported surgical area sensory disturbances at 2 weeks and 3, 6, and 12 months postoperatively. Association of baseline demographic, surgical, psychosocial, and psychophysical factors with NeuPPS and numbness across time was investigated using generalized estimating equation linear and logistic regression.

Results: Numbness was consistently reported by 65% of patients; positive neuropathic symptoms were less common, often decreasing over time. Neuropathic Pain scale for PostSurgical patients and numbness co-occurred in half of patients and were both associated with greater clinical pain severity and impact, younger age, axillary surgery, and psychosocial factors. More extensive surgery and chemotherapy were only associated with numbness. Conversely, other chronic pain, lower physical activity, perioperative opioid use, negative affect, and lower baseline pressure pain threshold and tolerance were only associated with NeuPPS. Patients reporting numbness alone did not endorse substantial clinical pain.

Conclusions: Differentiation of predictors, prevalence, and time course of numbness vs NeuPPS in breast surgical patients revealed important distinctions, suggesting that their independent assessment is worthwhile in future studies of postsurgical pain.

Keywords: Postsurgical pain, Neuropathic pain, Numbness, Sensory disturbance, Quantitative sensory testing, Psychosocial

1. Introduction

Persistent postsurgical pain (PPSP), defined as the presence of pain in the surgical area >3 months after the surgery, has been recognized as an important problem.[43] The assumption that surgical injury to nerves drives the development of persistent pain underpins many commonly used animal models of persistent pain.[26,62,63,67] In humans, surgeries producing more extensive nerve branch damage are associated with higher rates of PPSP,[39] especially if a neuropathic pain assessment tool is used

to determine PPSP incidence. For example, thoracic surgery (which may damage intercostal nerves) and hernia repair (which may damage ilioinguinal nerves)[1,28,71] are associated with substantial rates of persistent pain.[39] Within the context of persistent postmastectomy pain (PPMP), axillary lymph node sampling may involve nerve stretching, injury, or ligation, especially to the intercostobrachial nerve (ICBN), and has often been associated with greater rates of persistent pain.[3,6,33,46,47,52,59,69]

Although neuropathic symptoms occur commonly after breast cancer surgery,[5,7,11,17,41,64] their time course and correlates vary widely across individuals.[25,31,49,57,61,68] In a comprehensive prospective investigation of a broad array of simultaneously assessed potential predictors, greater surgical extent (which would presumably involve greater nerve injury) played a relatively minor role in explaining pain burden 1 year after surgery,[59] suggesting that variation in the extent of nerve injury cannot account for the variation in pain observed between individuals. Previous studies have distinguished between a predominantly gain-of-function vs loss-of-function phenotype, showing that in some cases therapeutics may work differently between these patient subgroups.[27] It seems possible that individual differences in the response to nerve injury manifest as differences in the nature and quality of postsurgical sensory disturbances (eg, numbness vs hyperalgesia) and may also importantly contribute to the burden of PPSP.

Most neuropathic pain measures in common use[15,16,19,21,34,37,45,47,53] query about both painful, positive and nonpainful, negative sensory disturbances. From the patient's perspective, whether a sensory disturbance is painful or not painful (numb) can make a big difference to quality of life, and therefore, this distinction merits the attention of those who study persistent postsurgical sensory changes. In particular, in the study of persistent pain after breast surgery, a breast surgery–adapted set of questions about neuropathic symptoms has been used by several groups,[4,8,9,35,38,44,47,50,59] with some studies supporting the separate consideration of numbness from other painful neuropathic symptoms.[2,48] Investigations into the construct validity of the sensory disturbance items resulted in explicit omission of numbness because of its limited correlation with other items, resulting in its exclusion from 5-item Neuropathic Pain scale for PostSurgical patients (NeuPPS).[48] However, such exclusion of numbness from scoring is relatively uncommon among most neuropathic pain questionnaires (**Table 1**).

To further probe this question, we explored patient-reported sensory disturbances in our prospective longitudinal cohort of patients undergoing surgery for breast cancer in the United States. Specifically, the aims of this study were to investigate (1) the time course of positive neuropathic symptoms (NeuPPS) vs numbness during the first year after breast cancer surgery, (2) the relationship of NeuPPS vs numbness to persistent clinical pain and pain burden, and (3) potential similarities and differences in the predictors (eg, surgical, psychosocial, and psychophysical factors) of NeuPPS vs numbness in the surgical area. We hypothesized that important differences may exist between "positive" neuropathic symptoms (NeuPPS items) vs the "negative" symptom of numbness in their time course, prevalence, and predictors.

2. Methods

2.1. Study description

Full methods of this prospective, observational longitudinal study have previously been described in an investigation of prediction of clinical PPMP.[59] In this IRB-approved study, patients were recruited from the preoperative clinic between September 2014

and March 2017. Eligible patients were female, aged 18 to 80 years, who were scheduled for breast surgery. Patients completed validated questionnaires through secure email link, and a baseline assessment of general pain sensitivity in nonsurgical areas using quantitative sensory testing (QST) was performed in the preoperative evaluation clinic. Surgical and treatment information was extracted from the patient's electronic medical record 1 year after surgery. Most patients received general anesthesia, with regional anesthesia offered to most patients undergoing total mastectomy, depending on anesthesia and surgical provider preference. Intraoperative and postoperative analgesics were also given per provider preference. Patients self-reported use of radiation, chemotherapy, or endocrine therapy as part of their 12-month survey assessment. Previous reporting from this cohort regarding acute postsurgical pain and opioid use (2 weeks postsurgery),[60,72] 6-month preliminary postsurgical outcomes,[65] and chronic pain 1 year after surgery has been published.[59]

2.2. Clinical pain assessment

Persistent pain in the surgical area was assessed postoperatively at 2 weeks and 3, 6, and 12 months using the extended version of the Breast Cancer Pain Questionnaire (BCPQ). The BCPQ was developed in 2009 by Gartner et al.[36] and has been used in many subsequent studies.[2,4,8,10,35,38,44,47,50] The BCPQ inquiries about the presence of pain in 4 surgically related body areas (breast, axilla, chest wall, and arm), pain severity in the area (on a 0–10 scale), and the frequency of the pain (never = 0 to constantly = 5). The pain severity index (PSI) score is calculated using: PSI = Σ(Pain score at each site [0–10] $\times$ frequency [1–5]).[14,56,58,59]

2.3. Assessment of sensory disturbance: positive neuropathic symptoms and numbness

The BCPQ also queried patients regarding the presence of sensory disturbances, both painful and nonpainful, in the surgical area. Similar to Mejdahl et al.,[48] we used responses in this section to calculate the NeuPPS (range 0–5), which is the sum of responses to 5 questions, with higher scores indicating greater neuropathic pain. Neuropathic Pain scale for PostSurgical patients questions included (1) stabbing or pins and needles, (2) electric shock or jabbing, (3) heat or burning, (4) mechanical allodynia, and (5) cold allodynia (Appendix A, available as supplemental content at http://links.lww.com/PR9/A138). Neuropathic Pain scale for PostSurgical patients has been found to measure the same latent trait as the Self-report Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS).[48] A question about numbness in the surgical area was also asked as part of the BCPQ, and response to this question was evaluated separately.

2.4. Psychosocial assessment

Psychosocial assessments were selected for inclusion based on their strong psychometric properties,[60] brevity, and previous associations with persistent pain in a retrospective cohort.[14] The Pain Catastrophizing Scale (PCS; range 0–52) was used to measure catastrophic thinking associated with pain.[66] The Brief Symptom Index-18 somatization scale (BSI; range 5–30) was used to assess somatization.[29] The NIH PROMIS short forms were used to assess depression (range: 8–40), anxiety (range: 7–35), and sleep disturbance (range: 8–40).[24] Affect was

Table 1

Comparison of neuropathic symptoms across neuropathic pain questionnaires.

	Breast cancer pain questionnaire	Other neuropathic pain questionnaires						
	Sensory disturbance questions	NeuPPS	DN4	S-LANSS	NPSI	PD-Q	NPQ	ID pain
Score range	0–8	0–5	0–10	0–24	0–100	−1 to 38	−21.4 to 60.6	−1 to 5
Numbness part of total?	Yes	No	Yes (+1)	Yes (+3)	No	Yes (up to +5)	Yes (up to +20)	Yes (+1)
Neuropathic symptoms included								
Numbness	X[Q3]		X[Q8,Q9]	X		X	X	X
Hyposthesia	X[Q3]			X				
Stabbing, pins and needles, tingling, falling asleep, or pricking	X	X	X[Q4,Q5]	X	X[Q6,Q11,Q12]	X[Q2,Q3]	X	X
Electric shocks, jabbing, or shooting	X	X	X	X	X	X	X[Q3,Q5]	X
Heat/burning	X	X	X	X	X[Q8,Q9]	X	X	X
Mechanical allodynia	X	X	X	X[Q3,Q6,Q7]	X	X[Q5]	X[Q2,Q11]	X
Cold allodynia	X	X	X		X[Q2,Q3]	X[Q5]		
Painful itch	X							
Pressure/squeezing					X[Q2,Q3]		X	
Painful area changes color or looks different				X				
Freezing pain							X	
Increased pain from weather changes							X	
Pain limited to joints								X

Q, multiple symptoms may be inquired about in a single question or similar symptoms may be represented in multiple questions.

DN4, Douleur Neuropathique 4 questions; NeuPPS, Neuropathic Pain scale for Postsurgical patients; NPQ, neuropathic pain questionnaire; NPSI, Neuropathic Pain Symptom Inventory; PD-Q, PainDETECT questionnaire; S-LANSS, Self-report Leeds Assessment of Neuropathic Symptoms and Signs.

measured using the Positive Affect Negative Affect Scale (PANAS; range for positive and negative affect: 10–50).[70]

2.5. Psychophysical assessment

Psychophysical assessment of general pain sensitivity at non-surgical areas was conducted at baseline and involved 2 brief, portable QSTs.[56,58,60] Using methods discussed in our previous studies[56,58,60] and by Rolke et al.,[54] standardized, weighted mechanical pinpricks were used on the left and right index and middle fingers to assess temporal summation of pain, and these 4 scores were averaged. A handheld pressure algometer (Wagner FDX, Greenwich, CT) with a flat round transducer (probe area 0.785 cm) was used to assess pressure pain threshold and tolerance bilaterally on the dorsal aspect of the proximal forearm, approximately 3 to 4 cm distal to the elbow crease (extremity site) and over the trapezius muscle at the upper back approximately 2 to 3 cm above the scapular spine, midway between C7 prominence and humeral head (truncal site), with averaging across the 2 sides.

2.6. Statistical analyses

Descriptive statistics for patient demographics, psychosocial, psychophysical, and pain outcomes are reported as either frequencies and percentages for categorical variables or means and SDs for continuous variables. Spearman correlations were used to examine the association between clinical pain (PSI) and neuropathic pain (NeuPPS) at the 2-week and 3-, 6-, and 12-month time points. The Mann–Whitney U tests were used to compare PSI in patients who did and did not report numbness.

We used generalized estimating equations to perform univariable analyses (ie, simple regression) assessing the association of baseline demographic, surgical, and psychosocial variables with NeuPPS (linear regression) and numbness (logistic regression) across time. We used an autoregressive correlation structure to account for the correlation between continuous (ie, NeuPPS) and binary (ie, numbness) outcomes collected from the same patient across time. Generalized estimating equation accommodates missing data across time points if the missing values are random (eg, a patient skipped a survey at one of the time points). All analyses were performed using SPSS v27.

3. Results

3.1. Study cohort

A total of 259 patients were enrolled and completed preoperative baseline and 2-week questionnaires, with 228, 216, and 201 patients completing questionnaires at 3, 6, and 12 months after surgery. Details regarding the recruitment and longitudinal follow-up assessment of patients in this cohort, and a report of the predictors of pain severity at 1 year, have been reported previously.[59] Demographic information is reported in **Table 2**.

3.2. Surgical and medical treatment

About half of the patients underwent a lumpectomy, 13% underwent a total mastectomy, and about a third of patients underwent a total mastectomy with reconstruction (**Table 2**). The most common axillary procedure was the sentinel lymph node procedure (64%), whereas 26% of patients underwent axillary lymph node dissection and 20% of patients had no axillary surgery.

Table 2

Patient demographic, surgical, and medical treatment characteristics.

Variable	Mean ± SD, n (%)
Age	55.5 ± 12.4
BMI	27.4 ± 6.2
Education	
High school or less	24 (9.3)
Technical school or some college	37 (14.4)
College graduate	104 (40.5)
Master's degree	68 (26.5)
Doctoral degree	24 (9.3)
Race/ethnicity	
Caucasian	223 (86.4)
African American	7 (2.7)
Hispanic/Latina	5 (1.9)
Asian	11 (4.3)
Mixed race	8 (3.1)
Other	4 (1.6)
Previous breast surgery	66 (25.5)
Bilateral breast surgery	53 (20.6)
Surgery/reconstruction type	
Lumpectomy	136 (52.5)
Mastectomy	34 (13.1)
Mast + recon: tissue expander	68 (26.3)
Mast + recon: autologous	21 (8.1)
Node surgery type	
No axillary surgery	52 (20.1)
Sentinel lymph node procedure	165 (63.7)
Axillary lymph node dissection	42 (16.2)
Chemotherapy	146 (57.3)
Radiation therapy	92 (35.9)
Hormone therapy	126 (49.6)

BMI, body mass index; Mast + recon, mastectomy with reconstruction.

3.3. Sensory disturbances across time

The BCPQ queried patients regarding the presence of positive and negative neuropathic symptoms in the surgical area, including several painful neuropathic symptoms and numbness (**Fig. 1**). Most symptoms remained relatively consistent across time, with some symptoms such as allodynia and burning decreasing over time.
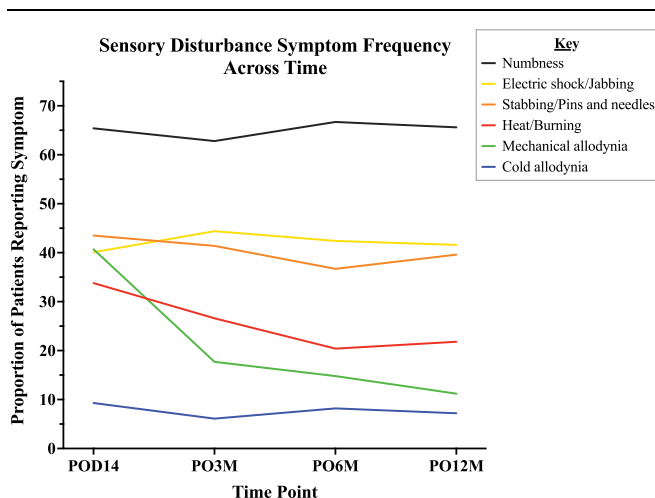

Figure 1. Proportion of patients reporting positive neuropathic symptoms and numbness across time.

Numbness was reported by approximately 65% of patients at all time points measured. Analysis of the consistency of individual-reported symptoms across time points showed relatively high consistency for reported numbness within an individual, with approximately 5% to 8% of participants switching from yes to no numbness at any given time point, and 5% to 8% switching from no to yes at any given time point. Component symptoms of the NeuPPS were somewhat less consistently reported by individuals, with a larger percentage of participants switching from yes to no (8%–16%) than those switching from no to yes (7%–10%) at any given time point (Appendix B, available as supplemental content at http://links.lww.com/PR9/A138).

3.4. Association of clinical pain severity with numbness and Neuropathic Pain scale for PostSurgical patients

As described in our previous work,[59] patients reported a range of clinical pain severity during the first year after surgery, expressed as the PSI. We assessed the association of PSI with numbness as well as PSI with the NeuPPS score. The presence of numbness was associated with significantly higher clinical pain scores throughout the first year after surgery (**Fig. 2A**). Similarly, clinical pain was also significantly correlated with the presence of positive neuropathic symptoms (**Fig. 2B**).

3.5. Assessment of predictors of Neuropathic Pain scale for PostSurgical patients and numbness over time

We examined whether certain baseline patient characteristics and treatment variables were differentially associated with numbness vs positive neuropathic symptoms (**Table 3**). **Figure 3** depicts the overlap of factors that were significantly associated with numbness and NeuPPS over time during the first year after surgery. Many factors were significantly associated with both types of symptoms, including baseline pain in the surgical area, younger age, and more extensive axillary surgery (ALND). Most baseline psychosocial measures (anxiety, depression, pain catastrophizing, sleep disturbance, and somatization) were associated with both NeuPPS scores and numbness. By contrast, factors that were unique predictors of NeuPPS (and not numbness) included other chronic pain, greater perioperative opioid use, lower positive affect, greater negative affect, and lower trapezius pressure pain threshold and tolerance on baseline QST.

Conversely, many surgical factors were associated with numbness, but not greater NeuPPS including previous breast surgery, bilateral surgery, longer surgical duration, sentinel lymph node procedure, and higher forearm pressure pain threshold and tolerance on baseline QST (**Fig. 3**). In particular, mastectomy or mastectomy with reconstruction was associated with greater numbness, but not greater neuropathic pain, compared with lumpectomy (**Fig. 4A, B**). In addition, some medical treatments, including radiation and chemotherapy, were associated with the presence of numbness in the surgical area across time, but not the NeuPPS score (**Fig. 3**).

3.6. Overlap of numbness and painful neuropathic symptoms

Figure 5A depicts the number of subjects at each time point who reported no sensory disturbances (green), numbness only (blue), numbness and at least 1 positive neuropathic symptom (purple), or positive neuropathic symptoms only (red). There was a substantial amount of overlap of negative (eg, numbness) and positive NeuPPS component symptoms, occurring in roughly half
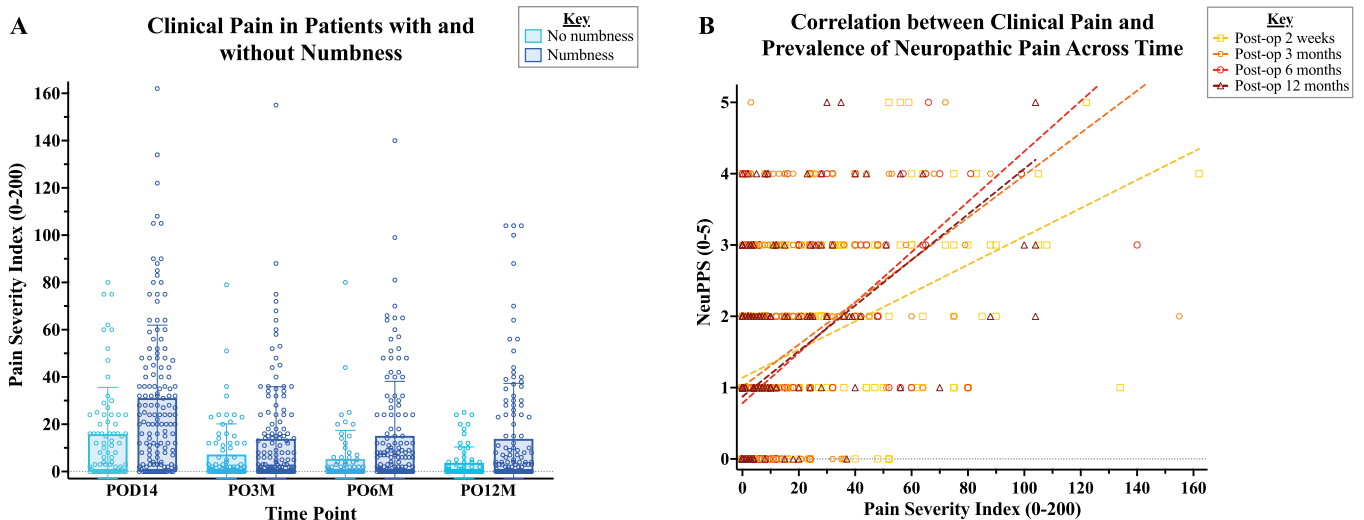
Figure 2. Relationship between clinical pain (pain severity index [PSI]) and numbness or positive neuropathic pain symptoms. (A) PSI scores were significantly higher among women reporting numbness compared with those not reporting numbness throughout the first year after surgery (Mann–Whitney U tests at 14 days: $P < 0.001$, 3 months: $P = 0.018$, 6 months: $P < 0.001$, and 12 months: $P = 0.003$). (B) Positive neuropathic pain symptoms score (NeuPPS) was significantly associated with higher clinical PSI (Spearman correlation at 2 weeks: Rho = 0.473, $P < 0.001$, 3 months: Rho = 0.565, $P < 0.001$, 6 months: Rho = 0.605, $P < 0.001$, and 12 months: Rho = 0.589, $P < 0.001$).

of the patients throughout the first year after surgery. There were also relatively few patients who were completely asymptomatic (green), although this group increased over time. The number of patients in the group with only numbness tended to increase, whereas that in the group with only neuropathic pain tended to decrease over time. Comparing the clinical pain across these groups, there was significantly less pain among patients with numbness only compared with those reporting at least 1 positive neuropathic feature (**Fig. 5B**).

3.7. Association of individual Neuropathic Pain Scale for PostSurgical patient component symptoms with numbness

Of the 5 positive, painful neuropathic symptoms of the NeuPPS, pins and needles or tingling or stabbing was the most consistently associated with report of numbness at each postoperative time point. Electric shocks and burning were associated with numbness at the 3- and 12-month time points, and cold allodynia at 2-week and 12-month time points. Mechanical allodynia was not significantly associated with numbness at any time point (Appendix C, available as supplemental content at http://links.lww.com/PR9/A138).

4. Discussion

This prospective longitudinal study used an augmented, validated version of a surgery-specific BCPQ[2,4,8,10,35,38,44,47,50,59] to investigate the temporal confluence of positive (eg, burning, stabbing, and allodynia) and negative (numbness) sensory disturbances in the surgical area throughout the first year after breast surgery. The presence of numbness was more common, consistent, and longer lasting than most positive neuropathic features. By contrast, many of the positive neuropathic symptoms decreased over time, with less consistency from one time point to another. In our sample, a report of stabbing or pins and needles was significantly associated with numbness at all time points; cold allodynia, heat or burning, and electric shock or jabbing only occasionally coincided with numbness, and

mechanical allodynia was not significantly associated with numbness at any time point.

When we grouped patients based on the presence of numbness and positive neuropathic features (**Fig. 5**), we observed that the total number of patients reporting only numbness tended to increase, whereas those with only positive neuropathic symptoms tended to decrease over time. This mirrors the overall (decreasing) temporal trajectory of clinically reported pain in the first year after surgery.[59] As in previous reports,[49] both numbness and positive neuropathic features were significantly associated with greater clinical pain intensity (**Fig. 2**), whereas the group of patients who reported only numbness reported significantly less clinical pain across time. Notably, the substantial overlap between the occurrence of positive and negative symptoms somewhat confounds this observation. However, an important insight from this study is that numbness, despite an overlap with positive sensory features, diverged from many positive neuropathic features, both in its time course and associated predictors.

Analysis of the predictive association of patient demographic, surgical, treatment, psychosocial, and psychophysical factors with either numbness or positive neuropathic symptoms revealed modest overlap, as well as notable differences. The presence of chronic pain in other parts of the body and indices of greater general pain sensitivity (lower baseline pressure pain threshold and tolerance and larger postoperative opioid requirement) were all associated with positive neuropathic symptoms, but not with greater prevalence of numbness. Other postsurgical studies longitudinally tracking and characterizing sensory disturbance in the surgical area using sensory testing have suggested that minor changes occur over time, especially early after surgery.[28] This is consistent with our finding that subjects switched their report of certain sensory disturbances from one time point to another, although the report of numbness tended to be the most consistent.

Conversely, although most indices of more extensive surgery (ie, total mastectomy with or without reconstruction, surgical duration, bilateral surgery, and reoperation) and more extensive cancer treatment (ie, radiation or chemotherapy) were

Table 3

Generalized estimating equation univariable analyses for outcomes significantly associated with neuropathic pain (NeuPPS) and numbness across the first year after surgery.

Variable	Baseline values		NeuPPS		Numbness	
	n	Mean ± SD, n (%)	0–5, higher is worse		0 = no, 1 = yes	
			β (95% CI)	P	β (95% CI)	P
Demographics						
Age (y)	259	55 ± 12	−0.020 (−0.032 to −0.008)	0.001*	−0.067 (−0.089 to −0.044)	<0.001*
BMI	259	27.44 ± 6.22	0.020 (−0.002 to 0.042)	0.078	−0.029 (−0.068 to 0.010)	0.146
ASA, n (%)	259					
1		5 (1.9%)	Ref.	—	Ref.	—
2		208 (80.3%)	0.217 (−0.781 to 1.214)	0.670	0.555 (−1.075 to 2.184)	0.505
3		46 (17.8%)	0.284 (−0.762 to 1.330)	0.594	0.589 (−1.122 to 2.299)	0.500
College graduate, n (%)	257	196 (76.3%)	−0.226 (−0.583 to 0.130)	0.213	0.340 (−0.188 to 0.869)	0.207
Non-White race, n (%)	258	35 (13.6%)	0.226 (−0.221 to 0.673)	0.322	0.113 (−0.573 to 0.800)	0.746
Other chronic pain	250	106 (42.4%)	0.344 (0.059 to 0.628)	0.018†	−0.216 (−0.683 to 0.251)	0.365
Activity level, n (%)	256					
Sedentary or physically passive		27 (10.5%)	0.166 (−0.342 to 0.673)	0.522	−0.201 (−0.993 to 0.592)	0.620
Light physical activity		114 (44.5%)	Ref.	—	Ref.	—
Moderate physical activity		96 (37.5%)	−0.309 (−0.602 to −0.015)	0.039†	−0.048 (−0.556 to 0.461)	0.854
Hard physical activity		19 (7.4%)	−0.397 (−0.936 to 0.142)	0.149	−0.337 (−1.221 to 0.547)	0.455
Surgical variables						
Previous breast surgery, n (%)	259	66 (25.5%)	−0.167 (−0.468 to 0.135)	0.279	0.604 (0.054 to 1.155)	0.031‡
Bilateral surgery, n (%)	257	53 (20.6%)	−0.009 (−0.340 to 0.322)	0.958	2.563 (1.747 to 3.379)	<0.001‡
Surgery/reconstruction type, n (%)	259					
Breast conserving surgery (Lumpectomy)		136 (52.5%)	Ref.	—	Ref.	—
Mastectomy		34 (13.1%)	0.222 (−0.246 to 0.572)	0.389	2.116 (1.299 to 2.943)	<0.001‡
Mastectomy with reconstruction—tissue expander		68 (26.3%)	0.101 (−0.237 to 0.440)	0.558	2.370 (1.750 to 2.990)	<0.001‡
Mastectomy with reconstruction—autologous		21 (8.1%)	0.163 (−0.283 to 0.727)	0.434	2.918 (1.432 to 4.403)	<0.001‡
Node surgery type, n (%)	259					
No axillary surgery		52 (20.1%)	Ref.	—	Ref.	—
Sentinel lymph node procedure		165 (63.7%)	0.046 (−0.290 to 0.383)	0.787	0.592 (0.044 to 1.140)	0.034‡
Axillary lymph node dissection		42 (16.2%)	0.690 (0.243 to 1.138)	0.002*	2.761 (1.576 to 3.947)	<0.001*
Surgical duration (min)	259	152.63 ± 132.40	0.001 (0.000 to 0.002)	0.112	0.012 (0.007 to 0.016)	<0.001‡
PACU opioid consumption (MME)	257	5.10 ± 5.51	0.034 (0.008 to 0.061)	0.011†	0.037 (−0.010 to 0.084)	0.121
Medical treatment						
Radiation therapy, n (%)	255	146 (57.3%)	0.249 (−0.029 to 0.527)	0.079	−0.827 (−1.309 to −0.344)	0.001‡
Chemotherapy, n (%)	256	92 (35.9%)	0.133 (−0.156 to 0.422)	0.369	1.041 (0.537 to 1.545)	<0.001‡
Hormone therapy, n (%)	254	126 (49.6%)	0.120 (−0.154 to 0.395)	0.390	0.291 (−0.166 to 0.749)	0.212
Baseline pain (BCPQ)						
Pain severity index (PSI: 0–200)	258	4.08 ± 9.28	0.045 (0.026 to 0.065)	<0.001*	0.068 (0.026 to 0.109)	0.001*
Physical impact of pain (0-38)	225	1.03 ± 2.65	0.099 (0.036 to 0.162)	0.002*	0.077 (−0.012 to 0.167)	0.090
Taking opioids before surgery	254	13 (5.1%)	0.203 (−0.469 to 0.875)	0.553	−0.384 (−1.408 to 0.640)	0.462
Psychosocial variables						
Catastrophizing (PCS: 0–52)	259	6.43 ± 7.05	0.028 (0.006 to 0.050)	0.013*	0.048 (0.008 to 0.088)	0.017*
Anxiety (PROMIS-SF: 7–35)	255	16.86 ± 5.29	0.049 (0.024 to 0.073)	<0.001*	0.064 (0.019 to 0.109)	0.005*
Depression (PROMIS-SF: 8–40)	259	12.50 ± 4.63	0.054 (0.026 to 0.082)	<0.001*	0.062 (0.007 to 0.117)	0.028*
Sleep disturbance (PROMIS-SF: 8–40)	259	21.14 ± 7.18	0.049 (0.029 to 0.069)	<0.001*	0.033 (0.001 to 0.065)	0.043*
Negative affect (PANAS: 10–50)	245	17.51 ± 5.87	0.039 (0.014 to 0.063)	0.002*	0.045 (−0.001 to 0.091)	0.053
Positive affect (PANAS: 10–50)	245	34.05 ± 7.37	−0.028 (−0.048 to −0.009)	0.005†	−0.014 (−0.045 to 0.017)	0.385
Somatization (BSI: 6–30)	247	7.50 ± 2.15	0.151 (0.082 to 0.219)	<0.001*	0.110 (−0.010 to 0.231)	0.072
Psychophysical variables (QST)						
Temporal summation of pain (0–10)	257	2.44 ± 1.89	0.067 (−0.005 to 0.138)	0.066	−0.052 (−0.170 to 0.066)	0.388
Painful after sensations (0–10)	256	0.17 ± 0.40	0.114 (−0.200 to 0.428)	0.476	−0.451 (−1.058 to 0.156)	0.145
Forearm pressure pain threshold§	257	5.02 ± 1.88	−0.040 (−0.117 to 0.036)	0.301	0.158 (0.041 to 0.275)	0.008‡
Trapezius pressure pain threshold§	253	7.531 ± 3.24	−0.044 (−0.085 to −0.003)	0.034†	0.047 (−0.023 to 0.116)	0.187
Forearm pressure pain tolerance§	257	7.64 ± 2.94	−0.020 (−0.067 to 0.026)	0.394	0.116 (0.028 to 0.204)	0.010‡
Trapezius pressure pain tolerance§	253	10.48 ± 3.92	−0.041 (−0.077 to −0.006)	0.023†	0.043 (−0.016 to 0.103)	0.154

* Significant predictor of NeuPPS and numbness.

† Significant predictor of NeuPPS only.

‡ Significant predictor of numbness only.

§ Pressure pain threshold and tolerance measured in pounds.

ASA, American Society of Anesthesiologists physical status classification system; BCPQ, Breast Cancer Pain Questionnaire; BMI, body mass index; BSI, Brief Symptom Inventory somatization subscale; GEE, generalized estimating equation; lb, pounds of force with a handheld algometer; MME, morphine milligram equivalent; PACU, postanesthesia care unit; PANAS, Positive and Negative Affect Scale; PCS, Pain Catastrophizing Scale; PROMIS-SF, Patient-Reported Outcomes Measurement Information System short form; QST, quantitative sensory testing.

significantly associated with numbness, they were not associated with greater painful neuropathic symptoms. The exception to this was axillary lymph node dissection, which was associated with increased report of both positive neuropathic symptoms and numbness, along with greater clinical pain.[59] These findings are in agreement with previous studies[6,22,23,30,36,42,49,55] and may be an important consideration to the management of axillary sampling and clearance through surgical or other means.
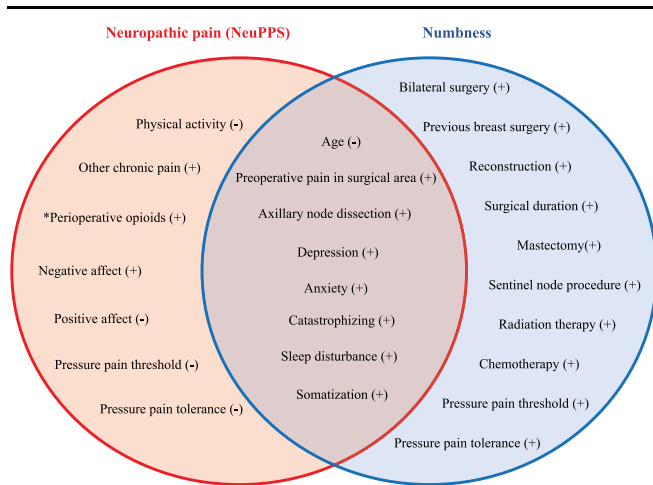
Figure 3. Overlap and divergence of surgical, psychosocial, and psychophysical predictors of positive neuropathic pain symptom score (NeuPPS) vs numbness. (+) signifies a positive relationship between the predictor and outcome, and a (−) signifies a negative relationship between the predictor and outcome. *Perioperative opioids: morphine milligram equivalents (MME) administered to patient in the postanesthesia care unit (PACU) after surgery.

Because surgery injures a number of tissue types,[56] only 1 being nervous tissue, multiple mechanistical categories (nociceptive, neuropathic, nociplastic, and central sensitization) contribute to the totality of PPSP.[1,18,28,71] The idea that PPSP may have more or less of a neuropathic component is not unprecedented.[12,13,18] However, even when nerve injury is carefully diagnosed (ie, known ICBN resection and QST in surgical area documenting nerve injury), other pain modulators, such as other chronic pain, psychosocial factors, and sleep disturbance, are of at least equal importance to predicting interindividual variation in clinical pain.[51]

Traditionally, neuropathic pain screening tests have been used for (1) diagnosis or detection of neuropathic pain, (2) distinction between neuropathic and nonneuropathic pain, and (3) profiling of patients who may respond to a given treatment.[16,37] Inclusion of tools designed to screen for and assess neuropathic aspects of persistent pain after surgery is essential to understanding phenotypic variation, mechanistic underlay, and differential

response to treatment. Expert consensus groups have advocated for use of common, well-validated, and mechanistically based pain measures to allow more direct comparison between studies.[56] Validation of these tools has often involved determining performance of the screen in a sample of patients with a formal clinical diagnosis of neuropathic pain by physical examination.[19,37] Perhaps because of the strong association between painful and nonpainful sensory disturbances in many cases of neuropathy (eg, diabetic neuropathy or lumbar radiculopathy), the symptom of numbness empirically has been included because it contributed to improving the sensitivity and specificity of the tool as a screen for neuropathic rather than nonneuropathic pain. When applied to the postsurgical context, however, these screening tools estimate higher rates of neuropathic pain in surgeries involving injury to larger nerves (thoracic-intercostal, inguinal hernia-ilioinguinal, and breast surgery-ICBN).[39,40]

Previous studies after mastectomy have suggested that the experience of numbness may be separate from other painful neuropathic symptoms. Its presence as a postoperative symptom may, however, be coincidental rather than mechanistically contributory to PPSP.[48] Furthermore, because of its prevalence, inclusion of it as a component to diagnose PPSP may in fact falsely elevated estimated rates of chronic pain after surgery. Several questionnaire-based measures of neuropathic pain have previously been applied to breast surgery patients: The Douleur Neuropathique 4 questions (DN4), neuropathic pain questionnaire, painDETECT, and Self-complete Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS).[19,20,34,45] A systematic review compared the incidence of neuropathic pain across studies and reported varied rates according to the tool used: 55% to 58% of those with pain have neuropathic pain per DN4, 38% for S-LANSS, ID Pain 21% to 38%, and painDETECT 30% to 35%. Studies using a tool in which numbness contributes heavily to the neuropathic pain score (DN4) may report higher rates of neuropathic pain than those using tools in which numbness is less heavily weighted (ID Pain and painDETECT) or does not contribute (NPSI and NeuPPS)[41] (**Table 1**). Some previous studies have separated numbness from other neuropathic symptoms in postmastectomy patients, as in Mejdahl et al.,[48] who tested the validity of neuropathic items on the BCPQ, including (1) stabbing or pins and needles, (2) electric shock or jumping, (3) burning, (4) numbness, (5) allodynia, (6) cold pain,
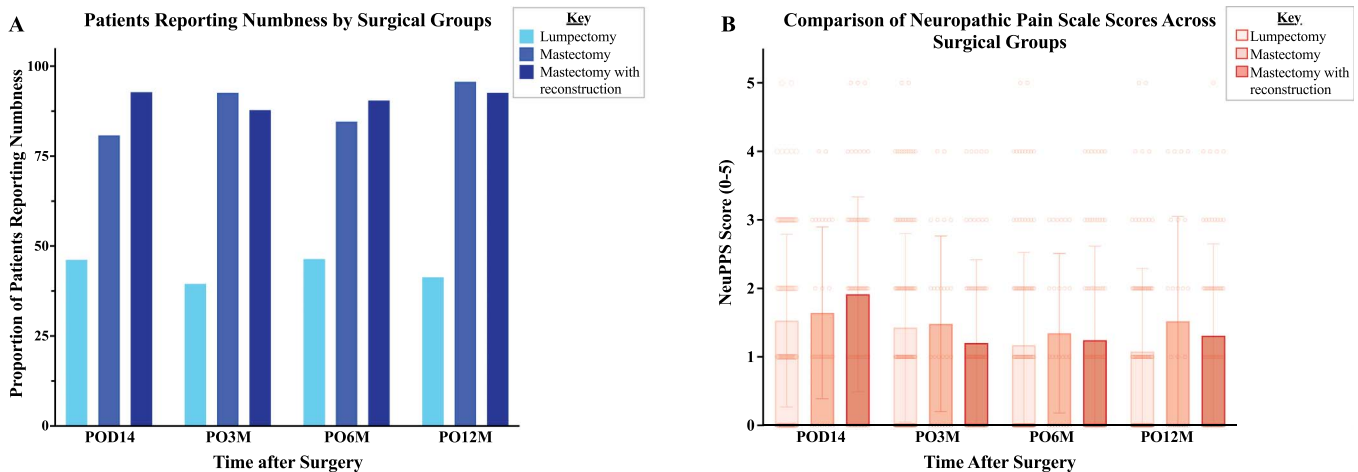

Figure 4. Numbness prevalence (A) and positive neuropathic pain symptom score (NeuPPS) (B) in different surgical subgroups. (A) Proportion of patients in each of the major surgical categories who reported numbness across time; (B) neuropathic pain scores (NeuPPS) (without numbness included) among patients in the major surgical categories.
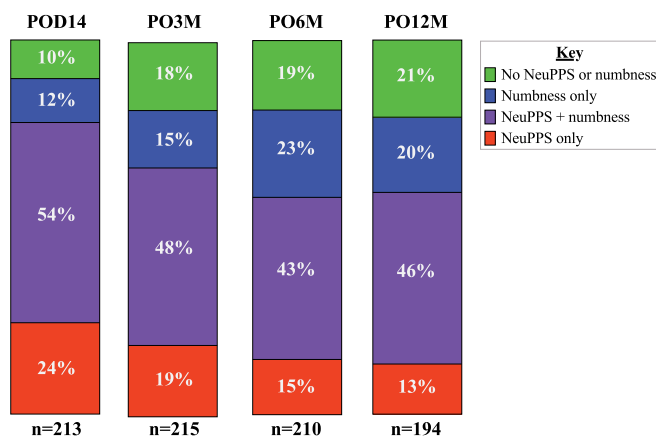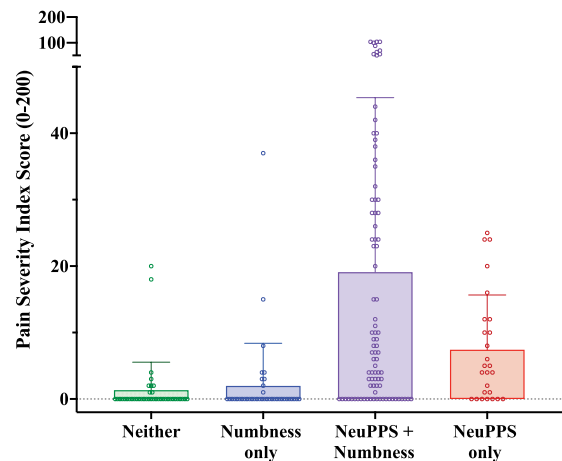
Figure 5. Patients grouped by incidence of painful neuropathic symptoms, numbness, both, or neither. (A) Proportion of patients reporting no symptoms (green), numbness only (blue), numbness and at least 1 positive neuropathic symptom from the NeuPPS (purple), and NeuPPS symptoms only (red). (B) Lower clinical pain ratings (pain severity index) were seen among those with numbness only, compared with those who had at least 1 positive neuropathic symptom, whether these symptoms were accompanied by numbness (numbness only vs both, Kruskal–Wallis H: −58.1, $P < 0.001$) or occurred without numbness (numbness only vs NeuPPS only, H: −46.6, $P = 0.003$).

and (7) painful itch. While painful itch was excluded before analyses because of concerns of construct validity, numbness was omitted from the model after analyses because it decreased the fit of the model and showed disparity with the remaining 5 questions. The investigators also found that 34% of people reported numbness within the pain-free group, which is similar to our observations. Given this insight and the evidence for divergence of positive symptoms vs numbness in the current work, we conclude that counting numbness as a neuropathic pain symptom may not be appropriate and may have contributed to the high variability in previously reported incidence of PPMP.[41]

The differential phenotypic outcomes of persistent neuropathic pain vs numbness may inform different phenotype-based treatment approaches. Previous studies have shown that patients with preserved thermal sensation + positive neurological findings such as allodynia and hyperalgesia (the "irritable nociceptor" phenotype) are more likely to respond to NaV blockers such as oxcarbazepine.[27] In the context of PPMP, the subset of patients with numbness only, with no overtly painful neuropathic symptoms such as allodynia or hyperalgesia, may be a different subset than those who do experience these symptoms, and these 2 groups may respond to treatment approaches differently. Although the findings of the current study merely suggest that there are variable patient symptomatic responses to surgical injury, and cannot address the utility of differential perioperative treatment, they underscore the importance of careful patient phenotyping in future studies and that differential efficacy of treatment approaches may be examined, as has been advocated in previous guidelines.[32]

4.1. Limitations

As a secondary analysis of a prospectively collected, longitudinal data set, the findings should certainly be considered exploratory. We refrained from multivariable regression analyses because of likely underpowering and, therefore, could not take into account the covariance of associated factors with either NeuPPS or numbness. It should also be emphasized that our intent was not to diagnose neuropathic pain in these patients nor to claim that

this can be definitively performed using the NeuPPS. Previous Neuropathic Pain Special Interest Group (NeuPSIG) guidelines for diagnosing neuropathic pain include important recommendations for a diagnosis of neuropathic features, including a detailed history and examination, which were not conducted in this study.[37]

5. Conclusions

The exploration of PPSP not only represents an important and rare opportunity to prevent a chronic pain syndrome but also may represent a key point of translation from the tremendous wealth of preclinical research on the mechanisms underlying the development of chronic pain in humans.

We observed some important distinctions between numbness and positive neuropathic symptoms, which have commonly been combined in previous investigations of chronic postsurgical neuropathic pain. Specifically, we observed important differences in the trajectory, prevalence, predictors, and overlap of numbness with positive pain-related neuropathic symptoms. Greater surgical extent was associated with numbness but not positive symptoms, with the exception of axillary lymph node dissection. Furthermore, the finding that numbness was more commonly reported than positive symptoms at each time point suggests that numbness should be assessed independently of the presence of pain and that it requires consideration as a unique clinical entity and a unique potential contributor to the postoperative experience of patients.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A138.

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