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Establishing the patient acceptable symptom state for patient-reported pain outcomes 6 months after breast cancer surgery

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Abstract

Introduction: The patient-acceptable symptom state (PASS) is a threshold score on patient-reported outcome measures beyond which patients consider their symptoms unacceptable (PASS negative). The PASS may guide the interpretation of outcomes associated with persistent pain after breast cancer surgery (PPBCS).

Objectives: This study aimed to identify PASS cut-off values for the numerical rating scale (NRS) on the brief pain inventory (BPI) items for pain at 6 months after breast cancer surgery and describe functional and psychological outcomes associated with an unacceptable (PASS-negative) pain state.

Methods: This prospective cohort study included patients undergoing primary breast cancer surgery. Patients were assessed preoperatively and postoperatively at 2 weeks and 6 months using validated questionnaires. Patient-acceptable symptom state was evaluated at 6 months after surgery. Patients were classified into PASS-positive (acceptable pain state) or PASS-negative groups using a pain-specific anchor question. Patient-acceptable symptom state thresholds for the BPI items were determined using the Youden index on a receiver operating characteristic curve.

Results: Of the 140 included patients, 13.6% reported a PASS-negative state at 6 months after surgery. Compared to PASS-positive patients, PASS-negative patients reported greater pain severity, pain interference, psychological distress, upper limb disability, and neuropathic pain (all $P < 0.008$). Numerical rating scale patient-acceptable symptom state cut-off values for the BPI items were 1.5 (worst pain), 0.5 (average pain), and 0.8 (pain interference).

Conclusion: The NRS scores for the BPI worst pain >1.5, average pain >0.5, and pain interference >0.8 delineated patients with "unacceptable" PPBCS. These values may define clinically meaningful PPBCS and offer pain cut-off values for research.

Keywords: Persistent pain, Breast cancer, Surgery, Risk factors, Patient acceptable symptom state, Impact

1. Introduction

Between 25% and 60% of patients develop persistent pain after breast cancer surgery (PPBCS).[3] Factors contributing to this wide variance in PPBCS prevalence include multiple definitions for PPBCS, various pain assessment tools to define and measure PPBCS,[5,10,20,55] and different empirically determined cut-offs to categorise pain severity ratings.[19,23,44,55] Despite current efforts to incorporate patient perspectives into research, the cut-offs currently used do not consider patient well-being, acceptance, and satisfaction when categorising pain, thus limiting the comprehension of what constitutes clinically meaningful pain.

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Thresholds to categorise pain severity and other patient-reported outcome measures (PROMs) may be contextualised by applying the concept of the patient-acceptable symptom state (PASS). Patient-acceptable symptom state is defined as the symptom threshold below which patients consider themselves "well."[51] There are several established methods to determine PASS.[38,39,52]

These all rely on an anchor question related to the symptom domain of interest (eg, pain) designed to categorise patients into groups based on symptom state acceptability. Patients with an acceptable symptom state are classified PASS-positive, whereas those reporting an unacceptable symptom state are classified PASS-negative. Using these 2 groups, cut-off values for PROMs that correlate with patient satisfaction and symptom acceptability may be determined. Within the context of pain, it would follow that patients in a PASS-negative state are those experiencing clinically meaningful pain.

Patient-acceptable symptom state has been predominantly utilised in rheumatology and orthopaedics to represent a clinical target for symptom management,[32,43,57] but its use in other areas supports its multidisciplinary applicability.[36,47] Patient-acceptable symptom state after orthopaedic surgery has been incorporated in postsurgical pain assessment both in severity[9,15,16,22,38] and interference.[46] However, PASS has not yet been applied to patients undergoing breast cancer surgery and could better identify clinically meaningful levels of pain severity or pain interference in patients suffering from PPBCS. In contrast to rheumatology and orthopaedic patients, cancer survivors may experience chronic pain that is complicated by cancer-related treatments, and the diminished postsurgical quality of life can leave patients feeling a sense of injustice, exacerbating the impact of pain on life domains.[4,7,30] Thus, the identification of PASS in breast cancer surgery patients may help determine thresholds for clinical intervention and improve understanding of patient-specific clinically meaningful pain after breast cancer surgery.

Therefore, this study aimed to (1) estimate the prevalence of patients reporting a PASS-negative state at 6 months after breast cancer surgery, (2) describe the functional and psychological outcomes of PASS-negative patients compared to PASS-positive patients 6 months after breast surgery, (3) determine the PASS cut-off value for the brief pain inventory (BPI) pain severity and BPI pain interference scales 6 months after breast cancer surgery, and (4) internally validate the PASS concept in our breast cancer surgery population.

2. Methods

2.1. Study population and data collection

This is a secondary analysis of data from a previously published prospective cohort study involving 140 patients who underwent primary breast cancer surgery in North Shore Hospital and Elective Surgery Centre, Waitemata Health, Auckland, New Zealand, between October 2016 and August 2020.[10] Ethical approval to conduct the study was granted by the New Zealand Health and Disabilities Ethics Committee (16/NTA/55/AM06). The Awhina Research and Knowledge Centre, WDHB (RM13274) granted locality approval for data collection. The study was registered with the Australia and New Zealand Clinical Trials Registry (ANZCTRN 12616000488404).

Detailed methods are published elsewhere.[10] Briefly, consented patients were assessed at a preoperative clinic (within 14 days before the surgery) and 2 postoperative clinic appointments (at 2 weeks and 6 months after surgery). Patient demographic factors, assessment of PROMs, and preoperative medical history were collected during the preoperative appointment, whereas postoperative medical history and PROMs were collected during postoperative appointments. Persistent pain after breast cancer surgery was defined as pain in the breast, chest wall, axilla, or shoulder on the surgical side at 6 months after breast cancer surgery.[54] Patients were thus directed to complete the pain-related questions regarding pain experienced in the aforementioned sites. Responses to the PASS anchoring question were collected at the 6-month postoperative appointment. There were no missing data for the pain assessment PROMs and PASS response. Intraoperative medical history was also collected during surgery.

2.2. Patient-reported outcome measures

The BPI worst pain, least pain, pain now, average pain, and pain interference items were used to assess pain in breast cancer surgery patients. The BPI worst pain and average pain items are frequently used as single items[14] to assess pain severity in the past 24 hours by scoring on an 11-point numerical rating scale (NRS) between 0 (no pain) and 10 (worst pain imaginable). Brief pain inventory pain interference item is a composite score of 7 subitems, including relationship with others, enjoyment of life, mood, sleep, walking, general activity, and working, collectively addressing the impact of pain on functioning in the past 24 hours. Each interference subitem is scored on an 11-point numerical rating scale to produce an average score between 0 (no interference) and 10 (interferes completely).

The Douleur Neuropathique en 4 interview (DN4 interview) questionnaire was used to screen for signs and symptoms of neuropathic pain at 6 months postoperatively. Patients who reported pain in any of the BPI pain items and had a total DN4 interview score $\geq$3 on a scale of 7 were considered as having likely neuropathic pain.[6] The DN4 interview demonstrates acceptable discrimination in the diagnosis of neuropathic pain after breast cancer surgery (area under the curve [AUC] = 0.77, 69% of patients correctly identified).[1]

The Depression Anxiety Stress Scale 21 (DASS-21) questionnaire was used to measure the severity of psychological distress at 6 months.

The Disabilities of the Arm, Shoulder, and Hand (DASH) 30-item questionnaire assessed a patient's ability to perform upper extremity functional activities and symptoms at 6 months.

2.3. Patient-acceptable symptom state question

An anchoring question was used to classify patients into PASS-positive (acceptable pain state) and PASS-negative (unacceptable pain state) groups and establish an external patient-reported reference to interpret the BPI worst pain, average pain, and pain interference scores at 6 months. These 3 BPI items were selected based on their previous use to assess both acute and persistent pain after breast cancer surgery.[11,20,33,35,42] Patient opinion of their symptom state was collected at 6 months by asking the anchor question, "*Considering all the ways in which the pain associated with your breast surgery affects your life, if you were to remain in this state over the next 6 months, do you consider your current state to be satisfactory?*" for which a dichotomous answer of "yes" or "no" was required. This question was derived from the anchor questions designed by Tubach to estimate the PASS.[52] Patients who answered yes or no were designated in this study as PASS-positive or PASS-negative, respectively. In keeping with

previous studies that have derived pain intensity PASS cut-points for postsurgical pain, all patients were included in this analysis, including those without pain on the BPI.[9,15,16,22,36,38,50]

2.4. Statistical analyses

2.4.1. Description of the study population

The characteristics of the PASS-positive and PASS-negative patients were compared using descriptive statistics. Depending on the data distribution (normal vs nonnormal), independent *t*-tests and Mann–Whitney *U* tests were used to examine between-group differences. The χ^2 and the Fisher exact tests were used to assess categorical variables.

2.4.2. Association between the patient-acceptable symptom state concept and brief pain inventory items

A rank-biserial correlation test was performed to determine the statistical significance and strength of association between the PASS anchor score and the BPI items at postoperative 6 months, including BPI worst pain, least pain, pain now, average pain, and pain interference items.

2.4.3. Derivation of the ideal patient-acceptable symptom state cut-off

The ideal PASS cut-off for the postoperative BPI worst pain, BPI average pain score, and BPI pain interference score was estimated using the receiver operating characteristic (ROC) curve and selecting the plot that maximised sensitivity and specificity. The Youden index approach and the minimal distance from the (0, 1) coordinate approach were used to estimate the ideal PASS cut-offs.[22,32] The area under the ROC curve was used to indicate the accuracy of the prediction.

2.4.4. Internal validation of the patient-acceptable symptom state cut-offs

Bootstrapping was used to internally validate the PASS cut-offs for the postoperative BPI items derived using the ROC curve. Bootstrapping is a method that allows sampling with the replacement of the original data set to simulate new samples, and the resultant sample distribution can be used to estimate various statistical measures.[26] In this study, a bootstrap sample of 1,000 simulations was included. Next, an identical ROC curve analysis was performed to identify the area under the curve and estimate the new PASS cut-offs from the bootstrapped data, which were compared to the original study population data parameters.

IBM SPSS Statistics for Windows, Version 29.0.1.0 (IBM Corp, Armonk, NY) was used to calculate the rank-biserial correlation. GraphPad Prism 10.2 for Windows (GraphPad Software, Boston, MA, www.graphpad.com) was used for all other statistical analyses and figures. A *P*-value of ≤ 0.05 was considered statistically significant throughout.

3. Results

3.1. Description of patient-acceptable symptom state negative and patient-acceptable symptom state positive patients

Of 173 patients recruited, 140 completed the 6-month follow-up and were included in the analysis. Overall, 86.4% (n = 121) reported that they were in an acceptable symptom state (PASS positive), and 13.6% (n = 19) were in an unacceptable symptom state (PASS negative) at 6 months after surgery. All patients who reported an unacceptable symptom state 6 months after surgery reported pain on the BPI. From our previous analysis,[10] any PPBCS (average pain NRS ≥1) was reported in 38.5% of patients (n = 54, 95% CI: 30.5%–47.2%) with a median pain score of 2 (IQR: 1–3). Of the patients with any PPBCS, approximately 68.5% (n = 37) were in a PASS-positive state, and 35.2% (n = 19) were in a PASS-negative state.

There were several differences in characteristics between PASS-negative and PASS-positive patients (**Table 1**). Patients reporting a PASS-negative state differed from those reporting a PASS-positive state with respect to age (mean 49.2 years vs 59.1 years, $P < 0.001$), BPI average pain at postoperative 14 days (median [IQR] NRS 2.5 [2–4] vs 1 [0–3], $P \leq 0.002$), and BPI pain interference at postoperative 14 days (median [IQR] pain interference 3.8 [2.2–4.5] vs 1.1 [0–2.6], $P < 0.001$). Finally, hormone therapy was administered more frequently to PASS-negative patients (100%) compared to PASS-positive patients (82%) ($P = 0.044$).

3.2. Clinical differences at 6 months after surgery between patient-acceptable symptom state negative and patient-acceptable symptom state positive patients

Patients reporting a PASS negative state scored significantly higher than patients reporting a PASS positive state across all BPI items examined in this analysis, worst pain (median [IQR] NRS 3 [2–4] vs 0 [0–2]), average pain (2 [1–4] vs 0 [0–1]), and pain interference (2.9 [1.1–3.9] vs 0 [0–0.2]) (all $P < 0.001$) (**Table 2**). Patient-acceptable symptom state-negative patients also reported greater upper limb disability on the DASH (median [IQR] DASH 22.5 [13.3–35] vs 3.3 [0–11], $P < 0.001$) and greater psychological distress on the DASS-21 total score (median [IQR] score 9 [4–12] vs 2 [0–8.5]), depression subscore (2 [1–4] vs 0 [0–1]), and stress subscore (5 [3–7] vs 1 [0–5]) (all $P \leq 0.008$) when compared to PASS-positive patients. There was no significant difference in the anxiety score ($P = 0.556$) between the 2 groups. Finally, a larger proportion of PASS-negative patients reported likely neuropathic pain (DN4 ≥ 3/7) compared to PASS-positive patients (52.6% vs 15.7%, $P < 0.001$).

There was no significant difference in the use of analgesic medications nor antineuropathic analgesics between the PASS groups (all $P \geq 0.165$).

3.3. Association between different brief pain inventory items and the patient-acceptable symptom state concept

The strength of the association between each BPI item and the PASS concept was estimated to identify the items that represent what matters most to patients.

All BPI items were significantly associated with the PASS concept with moderate to high strength of association (rank biserial correlation coefficient 0.339–0.578, <0.001) (Supplementary Table 1, http://links.lww.com/PR9/A318). Brief pain inventory pain interference item displayed the strongest association (coefficient 0.578), whereas worst pain and average pain displayed similar moderate strength of association (coefficient 0.446 and 0.428, respectively). The BPI worst pain, average pain, and pain interference categories were selected for the subsequent analyses based on their previous use in breast surgery populations (as described in the Methods).

Table 1

Patient characteristics between patient-acceptable symptom state negative and patient-acceptable symptom state positive patients.

Patient characteristics	PASS-negative patients (n = 19)	PASS-positive patients (n = 121)	*P*
Baseline demographic factors			
Mean age (SD) at primary breast surgery; y	49.2 (±8.8)	59.1 (±11.4)	<0.001
Mean height (SD); cm	165.7 (±5.4)	163.2 (±6.7)	0.129
Mean weight (SD) at primary breast surgery; kg	75.7 (±17.3)	76.8 (±17.5)	0.804
Mean BMI (SD); kg/m^2	28 (±6)	29 (±6)	0.488
European ethnicity	15 (79%)	97 (80%)	>0.999
Current smoker	1 (5%)	16 (13%)	0.468
Preoperative medical history			
Depression	3 (16%)	18 (15%)	>0.999
Anxiety	5 (26%)	19 (16%)	0.323
Hypertension	5 (26%)	45 (37%)	0.446
Diabetes mellitus	1 (5%)	10 (8%)	>0.999
Neoadjuvant chemotherapy	0 (0%)	3 (2%)	>0.999
Preoperative patient-reported outcome measures			
Median BPI average pain score (IQR)	0 (0–2)	0 (0–1)	0.672
Median BPI pain interference score (IQR)	0 (0–0.4)	0 (0–0.6)	0.688
Postoperative day 14 patient-reported outcome measures			
Median BPI average pain score (IQR)	2.5 (2–4)	1 (0–3)	0.002
Median BPI pain interference score (IQR)	3.8 (2.2–4.5)	1.1 (0–2.6)	<0.001
Intra- and postoperative medical history			
Breast surgery type			
Breast conserving	11 (58%)	87 (72%)	0.281
Mastectomy	8 (42%)	34 (28%)	
Immediate reconstruction	5 (26%)	103 (10%)	0.057
Axillary lymph node dissection	3 (16%)	18 (15%)	>0.999
Sentinel lymph node biopsy	15 (79%)	102 (84%)	0.518
Nerve transection	5 (26%)	104 (26%)	>0.999
Anaesthetic modality—TIVA	8 (42%)	106 (51%)	0.623
Adjuvant chemotherapy	9 (47%)	107 (50%)	>0.999
Adjuvant radiotherapy	14 (74%)	108 (72%)	>0.999
Hormone therapy	19 (100%)	109 (82%)	0.044

Analyses of statistical significance between mean values were performed using the parametric unpaired *t*test, between median values were performed using the Mann–Whitney test, and between categorical variables were performed using Fischer exact test. Values within brackets indicate percentage unless specified otherwise.
BPI, brief pain inventory; IQR, interquartile range; SD, standard deviation; TIVA, total intravenous anaesthesia.

3.4. Cut-off scores for brief pain inventory items according to patient-acceptable symptom state status

The area under the ROC curve comparing different PASS cut-offs on the BPI worst pain, BPI average pain, and BPI pain interference items demonstrated, overall, a good to excellent accuracy of prediction (AUC = 0.818–0.915; all $P < 0.001$) (**Fig. 1**). On the BPI worst pain item, the ideal cut-off for predicting PASS-negative patients that maximised both sensitivity (89.5%) and specificity (74.4%) was 1.5 (**Fig. 1B**). On the BPI average pain item, the cut-off score that maximised sensitivity (89.7%) and specificity (67.8%) was 0.5. Similarly, on the BPI pain interference item, the cut-off score that maximised sensitivity (89.5%) and specificity (88.4%) was 0.8. Identical ideal cut-off scores were reproducible using the Youden index and the minimal distance from the (0, 1) coordinate approach for all 3 BPI items.

3.5. Internal validity of patient-acceptable symptom state

Finally, a bootstrapped sample of 1,000 simulations was generated to internally validate the previously identified PASS cut-offs. The area under the ROC curves on the bootstrapped sample for BPI worst pain, BPI average pain, and BPI pain interference items with the PASS concept demonstrated good accuracy of prediction (AUC = 0.801–0.899, $P < 0.001$) that was comparable to the AUC of the original study population (Supplementary Figure 1, http://links.lww.com/PR9/A318 and **Fig. 1**). Each cut-off for BPI worst pain, BPI average pain, and BPI pain interference items maintained a sensitivity and specificity that were comparable between the bootstrapped sample and the study population, which indicated 1.5, 0.5, and 0.8, respectively, as the ideal cut-offs that maximised sensitivity (91.9%, 87.5%, and 89.0%) and specificity (73.3%, 67.3%, and 88.3%).

4. Discussion

To our knowledge, this is the first study to evaluate the PASS for persistent pain after breast cancer surgery. Of all patients, approximately 13.6% (n = 19) patients reported a PASS-negative state and 86.4% (n = 121) reported a PASS-positive state at 6 months after breast cancer surgery. Patients who reported a PASS-negative state also reported greater pain severity, pain interference, likely neuropathic pain, upper limb disability, and greater psychological distress (all $P < 0.01$) when compared to patients who reported a PASS-positive state.

Baseline differences were observed in patient characteristics according to PASS status. Patient-acceptable symptom state-negative patients were generally 10 years younger than PASS-positive patients. This is consistent with the literature, which consistently identifies younger age as a risk factor for PPBCS[23,34,44] and may relate to more aggressive disease and/or be due to the comparatively lower pain acceptance and higher pain catastrophising levels in younger patients.[21,31] Patient-acceptable symptom state-negative patients also tended to

Table 2

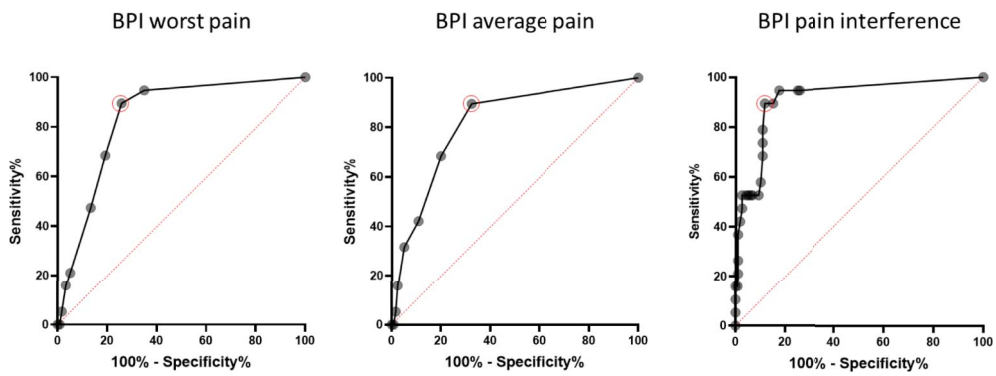
Clinical differences at 6 months after surgery between patient-acceptable symptom state negative and patient-acceptable symptom state positive patients.

Variable	PASS-negative patients (n = 19)	PASS-positive patients (n = 121)	*P*
BPI			
Median BPI worst pain score (IQR)	3 (2–4)	0 (0–2)	<0.001
Median BPI average pain score (IQR)	2 (1–4)	0 (0–1)	<0.001
Median BPI pain interference score (IQR)	2.9 (1.1–3.9)	0 (0–0.2)	<0.001
General activity (IQR)	3 (1–5)	0 (0–0)	<0.001
Mood (IQR)	3 (1–6)	0 (0–0)	<0.001
Walking activity (IQR)	0 (0–2)	0 (0–0)	<0.001
Normal work (IQR)	3 (1–5)	0 (0–0)	<0.001
Relationships with others (IQR)	1 (0–2)	0 (0–0)	<0.001
Sleep (IQR)	3 (2–5)	0 (0–0)	<0.001
Enjoyment of life (IQR)	3 (1–5)	0 (0–0)	<0.001
DASH			
Median total DASH score (IQR)	22.5 (13.3–35)	3.3 (0–11)	<0.001
DASS21			
Median depression score (IQR)	2 (1–4)	0 (0–1)	0.002
Median anxiety score (IQR)	1 (0–2)	1 (0–2)	0.556
Median stress score (IQR)	5 (3–7)	1 (0–5)	0.002
Median total score (IQR)	9 (4–12)	2 (0–8.5)	0.008
DN4 interview			
Likely neuropathic pain, DN4 ≥3	10 (52.6%)	19 (15.7%)	<0.001
Treatment			
Paracetamol	5 (26.3%)	16 (13.2%)	0.165
Ibuprofen	1 (5.3%)	3 (2.5%)	0.446
Diclofenac	0 (0%)	1 (0.8%)	>0.999
Morphine	0 (0%)	1 (0.8%)	>0.999
Gabapentin	2 (10.5%)	4 (3.3%)	0.188
Amitriptyline	0 (0%)	2 (1.7%)	>0.999
Nortriptyline	0 (0%)	1 (0.8%)	>0.999
Overall analgesic use	5 (26.3%)	26 (21.5%)	0.766

Analyses of statistical significance between median values were performed using the Mann–Whitney test, and between categorical variables were performed using Fischer exact test. Values within brackets indicate percentage unless specified otherwise.

BPI, brief pain inventory; DASH, disabilities of the arm shoulder and hand questionnaire; DASS21, depression anxiety and stress scale 21; DN4, Douleur Neuropathique 4 questionnaire; IQR, interquartile range.

A



B

Patient-reported outcome measures	ROC			
	PASS	Sens/Spec (%)	AUC (95% CI)	P-value
BPI worst pain	> 1.5	89.5/74.4	0.838 (0.756 - 0.921)	<0.001
BPI average pain	> 0.5	89.5/67.8	0.818 (0.720 - 0.917)	<0.001
BPI pain interference	> 0.8	89.5/88.4	0.915 (0.843 - 0.987)	<0.001

Figure 1. PASS cut-offs for the BPI worst pain, BPI average pain, and BPI pain interference items at 6 months after surgery. (A) ROC curves outlining individual PASS cut-offs. The red circle indicates the ideal cut-off determined by the maximal sensitivity and specificity, Youden index, and the minimal distance from the (0, 1) coordinate approach. (B) Characteristics of the ROC curve and the sensitivity/specificity associated with the ideal cut-off. AUC, area under the curve; BPI, brief pain inventory; CI, confidence interval; PASS, patient-acceptable symptom state; ROC, receiver operating characteristic; Sens/Spec, sensitivity and specificity.

report greater pain severity and interference at postoperative 14 days but not at preoperative assessment. Since both preoperative pain and early postoperative pain have been associated with PPBCS,[30,41,56] this finding was unexpected but suggests that acute postoperative pain trajectory may be particularly important for 6-month PPBCS outcomes.[37] Finally, a higher administration of adjuvant hormone therapy among PASS-negative patients was found, which is in line with Kudel et al.[29] (2007), who reported similar findings for patients experiencing persistent postmastectomy pain. The common side effects of hormone therapy may contribute to the level of symptomology that the patient is willing to accept.

Patient-acceptable symptom state-negative patients in this study experienced worse pain severity and impact on daily function. Also, they experienced greater upper limb dysfunction and psychological distress (depression and stress) 6 months after surgery, consistent with the literature.[10,13]

Psychological distress affects both the severity and interference aspects of patients' pain.[58] including after breast cancer surgery,[25] which may partly drive patients toward PASS negative status.[46] Surprisingly, worse anxiety scores were not demonstrated in the PASS-negative patients. This finding should be examined further in a larger population and could be consolidated with a parallel assessment of other anxiety assessment scales.

Neuropathic pain is well described after breast surgery and especially reconstructive surgery[53] possibly resulting from nerve damage due to the surgery and the use of adjuvant therapies for cancer management.[18] Although previous publications report that approximately 45% of patients with moderate-to-severe PPBCS describe likely neuropathic pain,[8,10,11] approximately 53% of our PASS-negative patients reported likely neuropathic pain. Distinct from pain severity, this finding emphasises the importance of chronic postsurgical pain quality, especially neuropathic pain, in determining pain acceptability.[28,48] Despite this, there was no difference in the analgesic medications prescribed for patients to manage their pain according to their PASS status, including first-line antineuropathic analgesics such as gabapentinoids and antidepressants. Incorporating multiple dimensions of pain assessment (eg, pain severity, pain quality, and pain interference) and defining PASS as the clinical endpoint may offer improved identification and management of patients with clinically meaningful PPBCS.

Patients who reported a PASS-negative state reported greater upper limb dysfunction ($P < 0.001$). This aligns with the previous findings of studies assessing PPBCS using traditional NRS cut-off values.[10,11] The median total DASH scores in patients who reported PASS-negative pain (22.5) were very similar to the median total DASH scores of patients who experienced moderate to severe pain (20.0) reported in our previous analysis of this cohort.[11] The median BPI average pain score in PASS-negative patients (NRS 2/10) in this analysis, however, was lower than those with moderate to severe PPBCS (4/10) in our previous study.[11] This suggests that the broader context of pain, including its influence on upper limb function, may be important to consider, rather than simply relying on measures of pain severity when determining pain acceptability.

Patient-acceptable symptom state cut-off values were estimated for the BPI NRS pain scores 6 months after breast cancer surgery. Based on the results of this study, the NRS pain scores of 1.5 for worst pain, 0.5 for average pain, and 0.8 for pain interference items should be used as thresholds for PASS for PPBCS. Above these values, it is likely that patients are in an unacceptable, clinically meaningful pain state (PASS-negative).

The cut-offs for the BPI worst pain and average pain items identified in this study contrast with those frequently reported in the literature to describe patients with clinically meaningful PPBCS, which tend to range from 3 to 5 on an 11-point numerical pain severity rating.[19,23,34,44,55] This suggests that conventional cut-offs used to define PPBCS are set too high and exclude a number of patients with clinically relevant, unacceptable pain.

Although numerous studies (mainly orthopaedic) have investigated PASS cut-offs for pain severity measures in various contexts,[17,22,32,38] direct comparison of PASS cut-offs is difficult due to the differing patient populations, variation of pain assessment tools, pain aetiology, and anchor question used. Despite this, the PASS cut-offs for persistent pain after orthopaedic surgery reported by studies that used comparable methodology to this study were still higher (1.5–2.5 on an 11-point NRS),[9,24,49] thus demonstrating the difficulty in generalising cut-off values between surgical populations and highlighting the need to identify PASS cut-off values for each unique surgical population. This is especially relevant to this population as all patients are female, and gender differences are well recognised in pain perception, description, and management.[40]

There are other considerations that may influence the PASS cut-offs in the breast cancer surgery population. Surgery is usually the first therapy associated with breast cancer management, which may include chemotherapy, radiation therapy, and hormone therapy. These, in combination with the psychological burden of a cancer diagnosis and subsequent sequelae of adjunctive therapies, may affect pain reporting and the level of symptomology that a patient may deem acceptable.

Differing levels of preoperative pain among patients undergoing breast cancer surgery compared to other surgical contexts, such as orthopaedic surgery, may create differences in patient-acceptable outcomes. A greater proportion of arthroplasty patients experience high-severity preoperative pain compared to women undergoing breast cancer surgery. This then may influence the acceptance of higher severity persistent post-surgical pain.[12]

The BPI pain interference item alone is rarely used to classify patients with clinically meaningful pain. Despite this, the BPI pain interference item displayed the strongest association with the PASS concept in this study, suggesting that this measure may be as if not more valuable than the BPI worst pain and BPI average pain items when classifying PPBCS patients with clinically meaningful pain. It also aligns with contemporary approaches to defining clinically meaningful persistent postsurgical pain, which place greater emphasis on pain interference, rather than pain severity alone.[27]

Overall, the PASS concept provides a patient-centred and meaningful global description of the effect of unacceptable pain on function. The study has reemphasised the potential factors that may be addressed to limit PPBCS development and progression. This may include closer monitoring of acute pain in the early postoperative period, earlier management of neuropathic pain symptoms with appropriate medication, and contextualising existing outcome scores within this framework specific to the breast surgery population. However, a multivariable risk factor analysis is required to provide a greater understanding of these.

This study has limitations. First, the sample size is small and derived from a single surgical centre in New Zealand. The findings, including the estimated PASS cut-offs, should therefore be considered preliminary until confirmed in larger study populations and other geographical settings. However, the

reproducibility of the cut-off estimations using 3 different statistical approaches and a bootstrapped sample strengthens the confidence in these results.

Second, patients were not followed up beyond 6 months. Although PASS is stable across many years in an orthopaedic population,[22] this must be confirmed in a breast cancer surgery population before stronger conclusions can be made regarding the stability of PASS and appropriate cut-offs for BPI pain severity and pain interference at other time points. This is especially important given that adjuvant therapies may extend beyond 6 months in the breast cancer surgery population.

Third, the PASS negative cut-offs associated with BPI average pain (0.5) and worst pain (1.5) do not align with the discrete values of the 11-point NRS used by the BPI. Logically, however, clinicians managing PPBCS could utilise a cut-off of 1/10 for any pain to guide treatment decisions and not miss any patients in a PASS-negative state.

Fourth, this study did not use the International Association for the Study of Pain definition of chronic postsurgical pain after breast surgery, which requires pain to be of new onset, or of increased intensity, lasting more than 3 months after breast surgery after all other causes have been excluded.[45] This is because this study was designed before the provision of this unifying definition. Despite this, it appears that the incidence of PPBCS is relatively stable up to 1 year after surgery,[2] and the 6-month time frame used in this study allowed time for completion of adjuvant therapies.

Finally, the BPI and the DN4 interview were the only pain assessment tools utilised in this analysis to diagnose and characterise PPBCS. Although these are widely used questionnaires to quantify PPBCS prevalence and screen for signs and symptoms of neuropathic pain, using these 2 questionnaires alone is not adequate to characterise PPBCS, understand aetiology, and target management. The BPI assesses pain severity and interference without assessment of pain quality and temporal characteristics. Furthermore, the DN4 interview screens for neuropathic signs and symptoms but does not replace formal diagnosis based on clinical examination.

The aetiology of PPBCS is likely complex, resulting in characteristic clinical differences in pain distribution, severity, quality, and time course. Understanding and classifying patients according to these clinical characteristics may provide insights into PPBCS aetiology and allow targeted pain management strategies. Although PASS provides an important basis for understanding and defining clinically meaningful pain and focusing management, detailed assessment utilising diagnostic tools that incorporate clinical examination and history, such as the International Association for the Study of Pain neuropathic pain grading system, should be used in future studies to provide the granularity required.

The PASS concept is a useful patient-centric concept when describing the global impact of pain in a breast cancer surgery population and providing cut-off estimates for defining clinically meaningful PPBCS. Estimating PASS cut-off values will provide a clinically relevant outcome that more accurately reflects the multidimensional consequences of pain on patient experience and function than existing unidimensional questionnaires. From this study, PASS cut-off values for NRS BPI worst pain >1.5, BPI average pain >0.5, and BPI pain interference >0.8 best-delineated patients with "unacceptable," PASS negative, persistent pain 6 months after breast cancer surgery. These values are lower than traditional cut-off values defining clinically meaningful pain in numerous research publications and have important implications for PPBCS treatment and research.

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