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Featured Article

Applying the Rapid OPPERA Algorithm to Predict Persistent Pain Outcomes Among a Cohort of Women Undergoing Breast Cancer Surgery

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Abstract: **Persistent postmastectomy pain after breast surgery is variable in duration and severity across patients, due in part to interindividual variability in pain processing. The Rapid OPPERA Algorithm (ROPA) empirically identified 3 clusters of patients with different risk of chronic pain based on 4 key psychophysical and psychosocial characteristics. We aimed to test this type of group-based clustering within in a perioperative cohort undergoing breast surgery to investigate differences in postsurgical pain outcomes. Women (N = 228) scheduled for breast cancer surgery were prospectively enrolled in a longitudinal observational study. Pressure pain threshold (PPT), anxiety, depression, and somatization were assessed preoperatively. At 2-weeks, 3, 6, and 12-months after surgery, patients reported surgical area pain severity, impact of pain on cognitive/emotional and physical functioning, and pain catastrophizing. The ROPA clustering, which used patients' preoperative anxiety, depression, somatization, and PPT scores, assigned patients to 3 groups: Adaptive (low psychosocial scores, high PPT), Pain Sensitive (moderate psychosocial scores, low PPT), and Global Symptoms (high psychosocial scores, moderate PPT). The Global Symptoms cluster, compared to other clusters, reported significantly worse persistent pain outcomes following surgery. Findings suggest that patient characteristic-based clustering algorithms, like ROPA, may generalize across diverse diagnoses and clinical settings, indicating the importance of "person type" in understanding pain variability.**

Perspective: ***This article presents the practical translation of a previously developed patient clustering solution, based within a chronic pain cohort, to a perioperative cohort of women undergoing breast cancer surgery. Such preoperative characterization could potentially help clinicians apply personalized interventions based on predictions concerning postsurgical pain.***

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Key Words: *Pain, Postsurgical, Clustering, Psychosocial, Psychophysical.*

Introduction

Breast cancer is the most diagnosed form of malignancy in the United States,[31] and advancements in breast cancer treatments (ie, early detection, improved surgical interventions) have contributed to an increased number of patients experiencing disability-adjusted life years. One important aspect of the morbidity and disability resulting from surgical treatments of breast cancer is the development of persistent postmastectomy pain (PPMP).[4,12,24,28,34] Though these surgical procedures are relatively standard and integral in treating the malignancy and preventing metastasis, they lead to a variable duration and severity of postoperative pain.[1,4,5,23] Studies of postoperative pain trajectory suggest that there may be multiple importantly different pain trajectories experienced by different patients based on their demographic characteristics (ie, age, race) and psychological co-morbidities.[7,26,27,37,39,41] Despite these profound differences in the postoperative

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trajectories of patients' pain, the current trend in perioperative pain practice has been towards developing a uniform, protocolized treatment for all patients having a given procedure, essentially administering identical perioperative and preventive analgesia to all patients.[35]

The biopsychosocial model of pain offers a multidimensional framework for understanding individual differences in chronic pain, acknowledging the impact of various underlying biological, psychological, and social factors that have the potential to contribute substantially to pain-related disability and severity.[11,22] Research suggests that differences in an individual's biological, psychological, and social situation may better explain the variance observed with regards to different trajectories in PPMP severity and impact, even more than variations in the surgical procedure itself.[33] Several psychosocial factors have been consistently associated with PPMP, including anxiety, depression[25] and somatization.[4,36] Similarly, baseline differences in the psychophysical processing of nociceptive stimuli, as measured using quantitative sensory testing (QST), have also been associated with persistent postsurgical pain.[21,42] In the specific case of PPMP, lower pressure pain thresholds (PPTs)[34] were associated with worse pain. Psychosocial and psychophysical assessments of these variables in the preoperative period could potentially inform a less standardized, more personalized treatment plan of individual patients.

The discernment of individuals' psychosocial and psychophysical characteristics has proven useful in understanding the variation in the development of other types of chronic pain,[2] including temporomandibular disorder (TMD).[3] Specifically, derivation of a predictive algorithm (Rapid OPPERA Algorithm or ROPA) was accomplished by empirically identifying clusters, or groups, of individuals based on psychosocial (anxiety, depression, and somatization) and psychophysical (trapezius PPT) characteristics.[3] These 4 factors entered into ROPA were selected based on an initial supervised clustering method by Bair et al, which indicated that these factors were most strongly associated with chronic pain when compared to several other potential important factors (eg, number of comorbid conditions, neuroticism, heat pain tolerance).[3] The variables used in the algorithm are based on factors of mechanistic predisposition to pain, exemplifying pro-nociceptive processes such as centralized pain amplification and psychological distress (doi: 10.1016/j.pain.2006.04.015), rather than on specific clinical characteristics, to enable it to be used both in classifying patients and predicting risk of developing chronic pain.

Using ROPA, Bair et al found that chronic pain patients were grouped into 3 clusters based on these 3 psychosocial factors and 1 psychophysical factor. The *Adaptive* cluster was characterized by patients with high PPT and low psychological distress. Patients in the *Pain Sensitive* cluster presented with low PPT and moderate levels of psychological distress. The *Global Symptoms* cluster was characterized by patients with low PPT and high psychological distress. Moreover, these 3 clusters of patients differed substantially in several pain outcomes, including pain intensity and pain interference.[3] The ROPA clustering technique has since been extended beyond the OPPERA cohort to patients with other sources of chronic pain (eg, Fibromyalgia, episodic migraines),[13] allowing discrimination of differential risk of other types of chronic pain. However, the algorithm has yet to be tested within a perioperative cohort of patients to understand differences in the development of postsurgical pain.

The primary objective of this secondary analysis was to test this type of group-based clustering within a different sample of patients (perioperative cohort) and at a different institution (Brigham and Women's Hospital). We aimed to apply ROPA to cluster our prospectively collected cohort of breast surgery patients and examine group differences in postoperative clinical pain severity, impact of surgical area pain on cognitive/emotional and physical functioning, and pain catastrophizing.

Methods

Participants and Procedure

Patients scheduled to undergo breast cancer surgery were recruited from the preoperative anesthesia clinic at Brigham and Women's Hospital. The details of this prospective, observational longitudinal cohort have been reported previously in the primary paper, which examined predictors of pain 1 year after breast surgery.[36] The study was approved by the Partners Human Research Committee/Institutional Review Board. All patients were female (N = 228), aged 18 to 85, proficient in English, and had no cognitive impairment that interfered with their ability to complete questionnaires. After providing informed consent, patients in the clinic underwent brief Quantitative Sensory Testing (QST). Prior to their surgery, all patients were emailed a secure link and completed validated questionnaires via REDCap, an electronic data entry system. Questionnaires assessed psychosocial and demographic characteristics, as well as pain at surgical sites. Patients completed follow-up questionnaires at 2-weeks, 3, 6, and 12-months after surgery. A flow chart for recruitment and retention is provided in Supplemental Figure S1.

Measures

Psychosocial Assessments

The Patient Reported Outcome Measurement Information System (PROMIS)[6] short form was used to measure depression and anxiety. Eight items (eg, "I felt worthless") assessed depression over the past week (1 = never, 5 = always; range 8–40). Scores were summed, and higher scores indicated greater severity of depression. Seven items (eg, "I felt uneasy") assessed anxiety over the past week (1 = never, 5 = always; range 7–35). Scores were summed, and higher scores indicated more severe anxiety. The PROMIS short forms have shown to be valid and reliable assessments in prior pain samples,[6] and demonstrated good reliability in the

current study (αs = 0.91–0.93). The 6-item Brief Symptom Index (BSI) 18-Somatization Scale[9] was used to measure somatization, or distress about bodily sensations. Patients rated how much each item (eg, "Numbness or tingling in parts of your body") had bothered them over the past week (1 = not at all, 5 = extremely; range 6–30), with higher scores reflecting greater somatization. The BSI-18 has been validated and used in several pain samples, and showed adequate reliability in the current study (α = 0.65).[9,36,37]

Psychophysical Assessments

A digital pressure algometer with a flat round transducer was used to assess pressure pain threshold (PPT) over the trapezius muscle of the upper back. As in previous studies,[29,32,34,37] we tested approximately 2 to 3 cm above the scapular spine, midway between the C7 prominence and humeral head. Pressure was increased at a steady rate of approximately 1 lb/s, and the patient indicated when the pressure first became painful. A PPT score was created by averaging the scores for the right and left trapezius muscle. Higher scores indicate higher PPT (ie, less pain sensitivity).

Pain Outcomes

The Breast Cancer Pain Questionnaire (BCPQ)[12] included subsets of items that measured pain severity related directly to the surgical area, as well as the impact of pain on both physical and cognitive/emotional functioning. The BCPQ has been validated and used in several samples of patients with breast cancer and pain.[12,36,37] A pain severity index was calculated by summing items measuring pain severity (eg, "Please indicate the severity of your breast pain"; 0 = no pain, 10 = worst possible pain) at each of the 4 surgical locations (breast, axilla, chest wall, and arm), multiplied by the frequency of pain at each location (0 = never, 1 = monthly, 2 = weekly, 3 = occasionally, 4 = daily). Pain severity = $\sum$ [pain severity at each site X frequency] (range: 0–200). Higher scores reflect greater surgical area pain severity. Ten items assessing physical impact (eg, "Bending down or kneeling") queried about how pain from breast cancer surgery affected daily activities, with higher scores indicating greater impact of pain on physical functioning (range: 0–38). Fourteen items (eg, "I feel that I don't have the energy to solve problems") assessed the cognitive/emotional impact of pain, with higher scores indicating greater impact of pain on cognitive/emotional functioning (range: 14–56). The 14-item Pain Catastrophizing Scale (PCS), which has been validated in pain samples[38,40] and showed good reliability in the current study (α = 0.92), was used to measure negative pain-related cognitions (eg, "I keep thinking about how much it hurts"; 0 = not at all, 4 = all the time).[38] Items were summed for a total score, and higher scores reflected greater pain catastrophizing (range: 0–56).

Demographic and Surgical Characteristics

Patients reported their age, race/ethnicity, education, and marital status. Breast surgery type was extracted from patient medical records including whether the patient had a lumpectomy, mastectomy, or mastectomy with reconstruction. Nodal surgery was also extracted from medical records, including sentinel node biopsy and axillary lymph node dissection.

Data Analysis

Sample Size Estimation

To determine the sample size for the longitudinal parent study,[36] we used data from our previous cross-sectional studies,[4,34] in which roughly 35% of patients experienced PPMP beyond 1 year after mastectomy (defined as pain >3/10). We calculated the effect size for candidate psychosocial or psychophysical predictor variables, determining that 200 patients would provide 80% power at a 2-sided alpha level of 0.05 to detect effect sizes of 0.40 or greater. At baseline, 228 participants had complete data for the 4 clustering factors of interest (depression, anxiety, somatization, PPT) and were used in the main analyses (Supplementary Fig S1).

Cluster Derivation

The ROPA clustering technique was derived from a sample of both patients with chronic TMD (n = 1,031) and "controls" (ie, initially TMD-free participants; n = 3,247), with the intent of agnostically clustering groups of individuals in a way that minimized within-cluster heterogeneity, while maximizing between-cluster heterogeneity. The resultant clustering solution (ROPA) required 4 variables: the BSI-18 subscales for anxiety, depression, and somatization, and the pressure pain threshold at the trapezius. The algorithm uses these features to assign new observations to clusters previously established in the OPPERA study based on a variable selection exercise that identified the 4 characteristics most strongly associated with chronic pain.[3] Nearest centroid models represent each of the 3 clusters by a centroid or the mean of each feature for all patients within the cluster. The algorithm assigns patients to the cluster that minimizes the distance from the patient to its respective centroid.

Of note, in this PPMP cohort, somatization was the only psychosocial factor assessed utilizing the equivalent scale used when deriving the original ROPA cluster estimation. The present study used the PROMIS to assess depression, whereas the ROPA cluster estimation was based on the BSI-18 as an assessment of depression. For this reason, we used a recommended and validated conversion "cross-walk" table to rescore PROMIS depression scores into BSI-18 depression subscale scores.[16] Similarly, the present study used the PROMIS to assess anxiety, whereas the ROPA cluster estimation was based on the BSI-18 as a measurement of anxiety. In contrast to depression, no prior conversion method has been published for transforming between PROMIS anxiety and

BSI-18 anxiety. Using data from which the original ROPA cluster estimation was based, we performed an equipercentile linking method with score smoothing via the software package Linking with Equivalent Groups or Single Group Design (LEGS) in the ANSI C program.[19] This statistical approach matches scores with equivalent ranks on the score distributions of the 2 anxiety assessments. As our sample of PPMP patients are all female, we used female-only TMD cases for this conversion. For the PPT measurement, the values which were recorded as pounds force were converted from pounds/cm2 to kilopascals (kPa), which was the unit of measurement used in the ROPA algorithm. Therefore, PPMP patient clustering was performed using the ROPA technique based on the same 4 features: trapezius PPT, somatization, and anxiety and depression scores transformed to BSI-18 subscales.

Group Comparisons

To investigate differences in demographic and surgical characteristics between clusters, we used chi-squares and Analysis of Variance (ANOVA). Similarly, to examine differences in acute pain outcomes (2-weeks postoperatively) between the clusters, we conducted several ANOVAs. To investigate persistent pain outcomes longitudinally over 3, 6, and 12 months, we conducted generalized estimating equations (GEE), using an autoregressive correlation structure because of the correlation between repeated measurements in the same patient, also allowing for data that is missing at random across timepoints. We report effect sizes as GEE model beta coefficients (B) and confidence intervals (CI).

Results

Clusters

Using the ROPA cluster estimation, which was derived to identify groups that minimize within-cluster heterogeneity and maximize between-cluster heterogeneity for desired characteristics,[3] individuals were categorized into one of 3 clusters based on their preoperative scores of anxiety, depression, somatization and trapezius PPT (Fig 1). The "Adaptive" cluster comprised 26.8% of the sample (n = 61) and was characterized by relatively low levels of psychological distress and high PPT (ie, less pain sensitive). Over half (54.8%, n = 125) of the patients were clustered into the "Pain Sensitive" group. This group reported relatively low levels of psychological distress, although higher than the Adaptive group, as well as low PPT (ie, more pain sensitive). The smallest proportion of patients (18.4%, n = 42) were clustered into the "Global Symptoms" cluster. These patients reported high levels of psychological distress and relatively low PPT (ie, more pain sensitive), although scores were higher than the Pain Sensitive cluster.

Patient Characteristics of the Clusters

Demographic and surgical characteristics of patients within each of the 3 clusters are reported in Table 1. Patients in the Pain Sensitive cluster were significantly older than patients in the Adaptive and Global Symptoms clusters. There were no significant age differences between the Adaptive and Global Symptoms clusters. The 3 clusters did not significantly differ based on

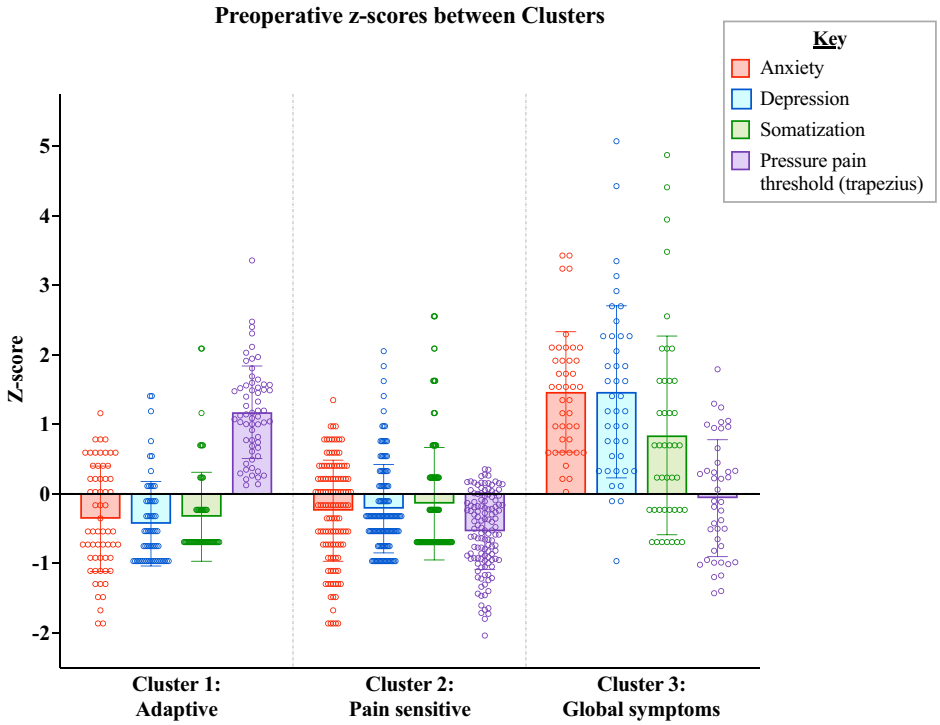

Figure 1. Preoperative Z-scores of the 3 empirically identified subgroups of patients. The height of the bars represents the mean, and the error bars represent the standard deviation (+/- 1SD).

Table 1. Patient Characteristics and Acute Pain between Clusters

	Full Sample (n = 228)	*Global Symptoms (n = 42)*	*Pain Sensitive (n = 125)*	*Adaptive (n = 61)*	
Variables	*M(SD)* or N(%)	M(SD) or N	M(SD) or N	M(SD)	*P*-value
Demographics					
Age	55.81 (12.37)	52.31 (14.07)$_a$	57.90 (12.41)$_b$	53.93 (10.18)$_a$	.015
Race					.957
White	197 (87%)	38 (91%)	108 (87%)	51 (84%)	
Black	6 (3%)	1 (2%)	3 (2%)	2 (3%)	
Asian	10 (4%)	1 (2%)	5 (4%)	4 (7%)	
Hispanic/Latina	3 (1%)	1 (2%)	2 (2%)	-	
Mixed race	8 (4%)	1 (2%)	4 (3%)	3 (5%)	
Other	3 (1%)	-	2 (2%)	1 (2%)	
Marital Status					.787
Single	21 (9%)	5 (12%)	14 (11%)	2 (3%)	
Married	167 (73%)	31 (74%)	90 (72%)	46 (75%)	
Living with partner	5 (2%)	1 (2%)	2 (2%)	2 (3%)	
Separated	2 (1%)	-	1 (1%)	1 (2%)	
Divorced	23 (10%)	4 (10%)	11 (9%)	8 (13%)	
Widowed	10 (4%)	1 (2%)	7 (6%)	2 (3%)	
Education					.200
Some high school	3 (1%)	2 (5%)	1 (1%)	-	
High school grad/GED	20 (9%)	5 (12%)	14 (11%)	1 (2%)	
Tech school	2 (1%)	1 (2%)	1 (1%)	-	
Some college	30 (13%)	6 (15%)	12 (10%)	12 (20%)	
College graduate	94 (42%)	16 (39%)	52 (42%)	26 (43%)	
Master's degree	57 (25%)	8 (20%)	34 (27%)	15 (24%)	
Doctorate degree	20 (9%)	3 (7%)	11 (9%)	6 (10%)	
Surgical characteristics					
Extent of surgery					.116
Lumpectomy	136 (53%)	16 (38%)	74 (59%)	31 (51%)	
Mastectomy	34 (13%)	10 (24%)	13 (10%)	9 (15%)	
Mastectomy with reconstruction	89 (34%)	16 (38%)	38 (30%)	21 (34%)	
Nodal surgery					.153
No node surgery	52 (20%)	7 (17%)	32 (26%)	10 (16%)	
Sentinel node biopsy	165 (64%)	23 (55%)	74 (59%)	42 (69%)	
Axillary node dissection	42 (16%)	12 (29%)	19 (15%)	9 (15%)	
Clustering variables (perioperative)					
Depression	0.56 (0.55)	1.32 (0.69)	0.43 (0.32)	0.31 (0.32)	
Anxiety	0.53 (0.59)	1.45 (0.74)	0.33 (0.27)	0.30 (0.27)	
Somatization	0.25 (0.37)	0.58 (0.52)	0.20 (0.29)	0.13 (0.23)	
Pressure pain threshold(kilopascals)	336.70 (139.45)	330.27 (119.45)	257.28 (79.45)	503.89 (95.86)	
Acute Outcomes (14 d postop)					
Pain severity	25.41 (29.01)	36.22 (31.13)$_a$	22.62 (27.69)$_b$	23.51 (28.86)$_b$	.045
Cognitive/emotional impact of pain	22.56 (6.78)	28.13 (7.10)$_a$	21.46 (6.29)$_b$	21.26 (5.83)$_b$	<.001
Physical impact of pain	7.88 (8.35)	11.03 (8.63)$_a$	7.00 (7.91)$_b$	7.42 (8.59)$_b$	.048
Pain catastrophizing	4.78 (6.48)	9.47 (10.20)$_a$	3.71 (4.94)$_b$	3.89 (4.71)$_b$	<.001

Note. ANOVAs were conducted for continuous variables and chi-squares for categorical variables. Means with different subscripts indicate significant differences between the clusters ($P < .05$).

demographic characteristics of race, education, or marital status, nor on surgical characteristics.

Acute Experience of Postsurgical Pain Outcomes

Between cluster comparisons of acute postsurgical pain 2 weeks after surgery are reported in Table 1. Patients in the Global Symptoms cluster reported greater pain severity, greater impact of surgical area pain on both cognitive/emotional and physical functioning, as well as higher levels of pain catastrophizing compared to patients in the Adaptive and Pain Sensitive clusters (Fig 2). No meaningful differences in these outcomes were observed between patients in the Adaptive and Pain Sensitive clusters.

Longitudinal Experience of Persistent Postsurgical Pain Outcomes

To assess persistent postsurgical pain over time, questionnaire responses were collected throughout the first year after surgery (3, 6, and 12 months) and compared longitudinally between groups using GEEs (Table 2). As

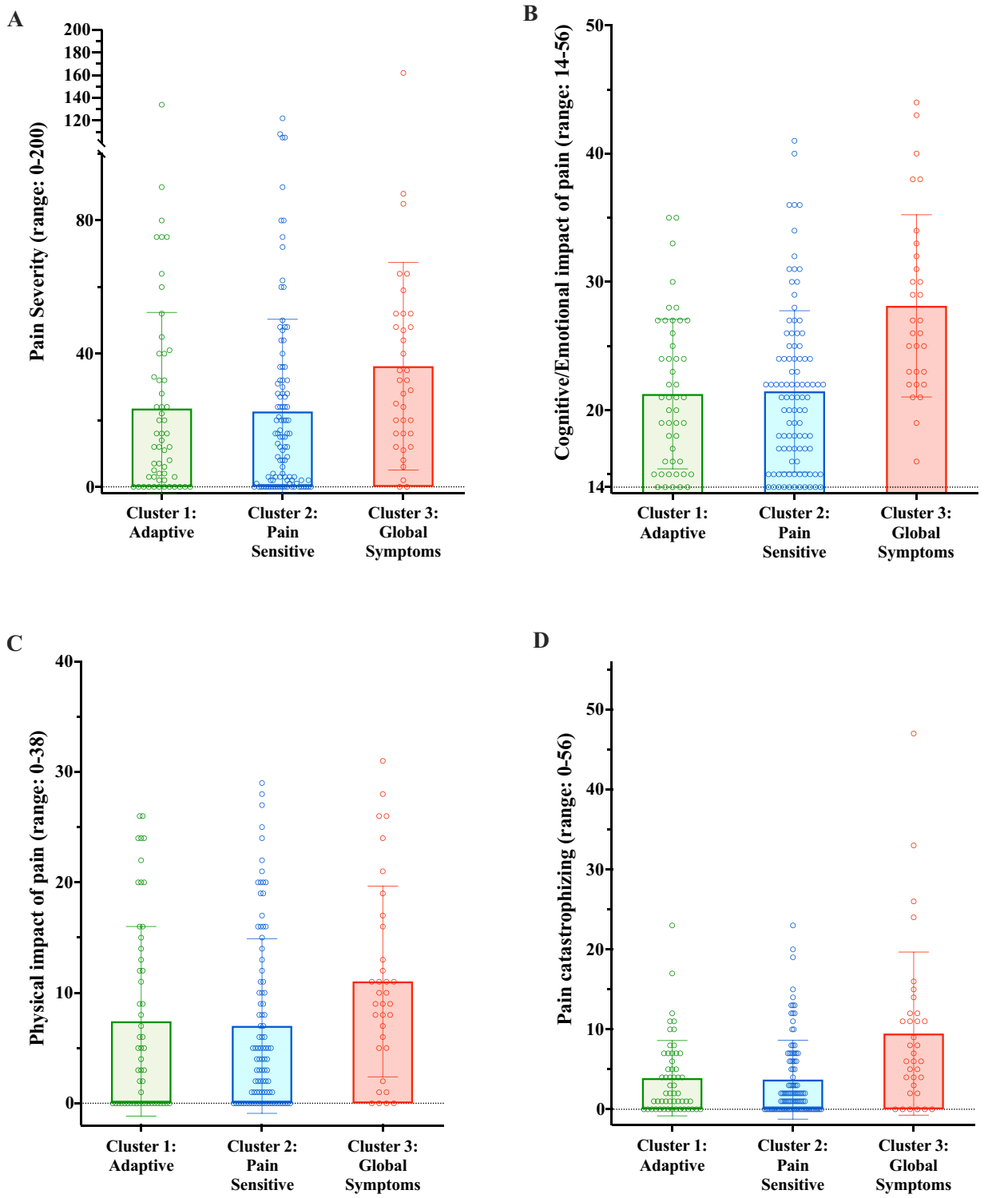

Figure 2. Bar charts of the acute experience of postsurgical pain outcomes. The height of the bars represents the mean, and the error bars represent the standard deviation.

with acute pain, patients in the Global Symptoms cluster reported significantly greater pain severity, greater impact of surgical area pain on both cognitive/emotional and physical functioning, and higher levels of pain catastrophizing compared to patients in the Adaptive and Pain Sensitive clusters (Fig 3). There were no significant differences in longitudinal pain outcomes between patients in the Adaptive and Pain Sensitive clusters.

Discussion

While many previous pain prediction models have been derived and implicate various combinations of risk factors, these models rarely undergo any external validation by separate groups, in different contexts, or across different patient samples. The current analysis is thus novel, giving insight in 3 ways.

Table 2. GEE analyses of Longitudinal Pain Outcomes

Outcome	*Cluster*	*B (Confidence Interval)*	*SE*	*Test Statistic*	P-*Value*
Pain severity	Global symptoms	*Ref*	*Ref*	*Ref*	*Ref*
	Pain sensitive	−15.66 (−24.22, −7.10)	4.37	12.86	<.001
	Adaptive	−15.86 (−24.92, −6.80)	4.62	11.78	<.001
Physical functioning	Global symptoms	*Ref*	*Ref*	*Ref*	*Ref*
	Pain sensitive	−4.13 (−6.34, −1.93)	1.12	13.48	<.001
	Adaptive	−3.95 (−6.35, −1.56)	1.22	10.47	.001
Cognitive/emotional functioning	Global symptoms	*Ref*	*Ref*	*Ref*	*Ref*
	Pain sensitive	−6.77 (−9.38, −4.17)	1.33	25.98	<.001
	Adaptive	−7.30 (−9.95, −4.65)	1.35	29.18	<.001
Pain catastrophizing	Global symptoms	*Ref*	*Ref*	*Ref*	*Ref*
	Pain sensitive	−3.24 (−5.64, −0.84)	1.22	7.00	.008
	Adaptive	−3.14 (−5.68, −0.60)	1.30	5.85	.016

Firstly, our analysis provides evidence of ROPA's generalizability by extending the utility of this algorithm beyond outpatient chronic pain patients to a perioperative, surgical cohort. Within the postsurgical pain literature, most prediction models are procedure specific, with only rare exceptions of prediction models being applied across perioperative categories. With the recognition that risk may depend more on the person rather than the surgical injury itself, non-specific procedure models seem more plausible. More broadly, the extent to which these models can extend across diagnoses (chronic TMD vs fibromyalgia vs postoperative pain) is encouraging for application in future research and clinical practice.

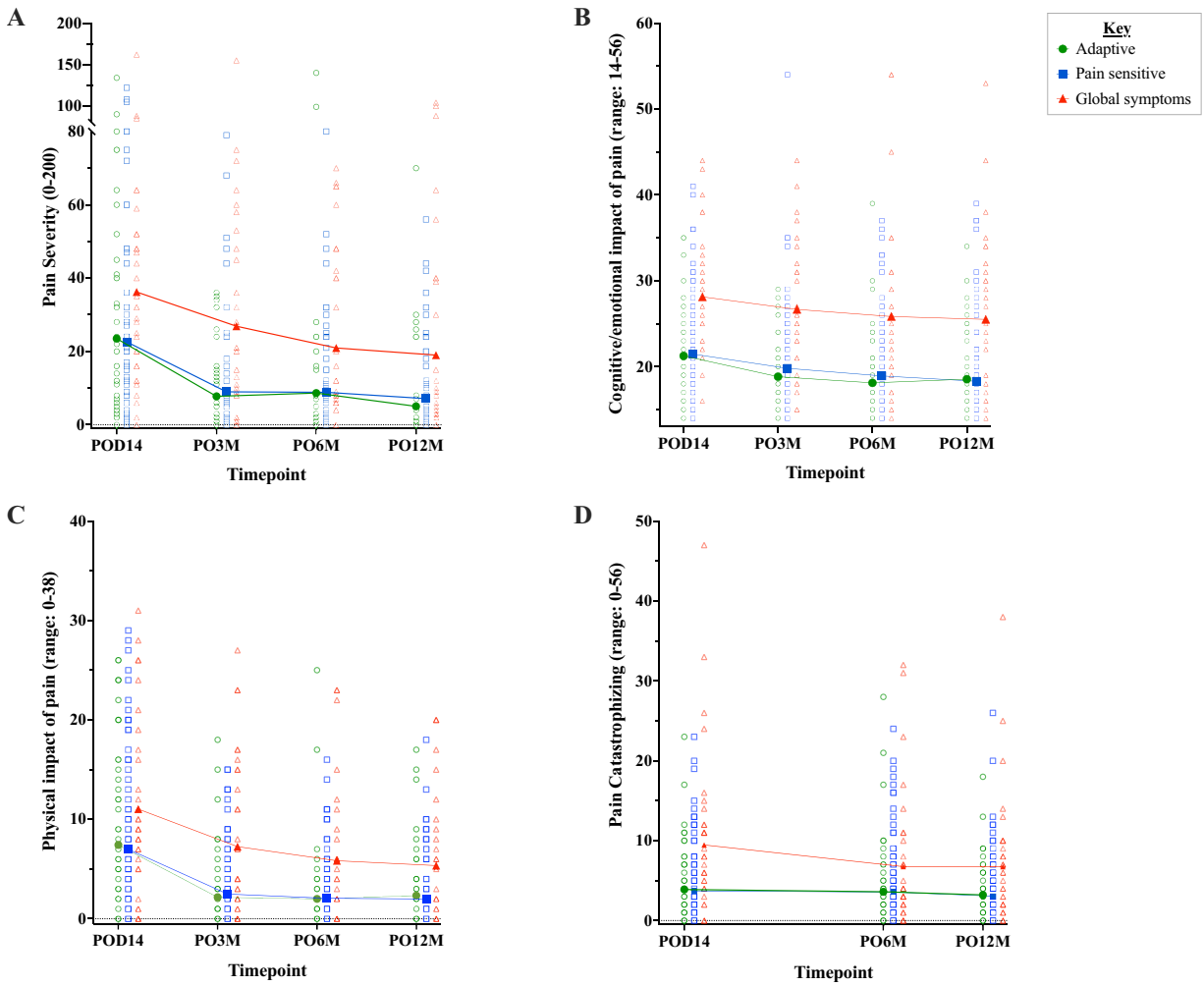

Figure 3. Longitudinal experience of postsurgical outcomes. POD14= postoperative day 14; PO3M= postoperative month 3, PO6M= postoperative month 6, PO12M= postoperative month 12. Pain catastrophizing was not assessed at PO3M.

Secondly, despite the fact that the cluster solution was derived[3] using individuals who developed a different type of chronic pain and using slightly different assessments for several psychosocial factors, it was able to discriminate clusters of individuals who were at differential risk of persistent postsurgical pain. This could suggest that the underlying psychosocial constructs used for clustering are important predictors, even when being measured by slightly different scales. However, it is important to note that we transformed scores for anxiety and depression to more closely match the assessments used in the original ROPA technique. Defining an infrastructure and common taxonomy in which to define and measure pain and its modulators has been the focus of the AAPT and AAAPT,[10,18,32] which has encouraged the measurement of a consistent set of variables in studies across institutions.

Third, this analysis demonstrates the relatively practical and pragmatic use of phenotyping. Although the original set of OPPERA studies and the derivation of the cluster solution[3] involved a large sample and sophisticated statistical analysis, the application over to a heterogenous cohort using 4 relatively straightforward preoperative measures suggests the potential utility of this approach. Whether these findings might inform a more patient-centered version of enhanced recovery after surgery (ERAS) protocols should be the topic of future studies. For example, using a 3-way clustering of patients with this model, multiple ERAS pathways might reasonably be derived, rather than forcing care of patients into a 1-size-fits-all pathway. Multidisciplinary transitional pain services have had success in tailoring management during the postoperative period among patients at high risk,[17] speaking to the feasibility and potential efficacy of multiple clinical pathways based on risk. Other studies suggest that behavioral interventions directed at psychological factors may improve pain.[14,15] However, given the potential negative connotation to some of these psychosocial factors (eg, somatization), it is critical that clinicians and physicians avoid potential unconscious stigmatization of patients based on these categorizations.

The fact that the Global Symptoms cluster of patients, who had elevated preoperative scores of psychological distress and pain sensitivity, had a distinctly higher risk of persistent postoperative pain suggests an additive elevation of risk for these 2 domains. Interestingly, similar proportions of individuals fell into each of the 3 groups when applying the algorithm across different samples. Previous studies observed difference across clusters according to sex and age, and a non-significant trend towards racial differences, although these patterns of findings differed across samples.[3,13] In our all-female sample, patients in the Pain Sensitive cluster were significantly older than those in the Global Symptoms and Adaptive clusters. We did not observe differences in cluster membership according to race/ethnicity, though this may be due to the lack of racial diversity in our sample. Given that previous research suggests an imbalance of burden of cancer outcomes across socioeconomic and racial groups,[7,27] more research focusing on demographically diverse samples is necessary to determine whether these risk factors/phenotypes are similarly distributed across groups.

Finally, the present results may eventually have implications for the implementation of precision pain medicine approaches to pain management. Current precision pain treatment studies generally focus on a single phenotypic variable (eg, high mechanical pain sensitivity[8] or high pain catastrophizing[43]) when considering differential treatment effectiveness. Given that many biopsychosocial "risk" factors tend to intercorrelate and cluster together (as we observe in the present study), in the future it may be desirable to study cluster membership, rather than scores on individual measures, as a predictor of responses in controlled trials of putative analgesic treatments. Given the emerging evidence for the consistency and replicability of the current cluster structure across samples and pain conditions, these ROPA clusters may represent a reasonable starting point for such potential precision pain medicine studies.

Limitations and Future Directions

There are a number of limitations to this study. The OPPERA study deriving the cluster solution[3] employed different validated assessments of anxiety and depression than those used in this perioperative cohort. There are several validated measures of anxiety and depression that are in common use, including the BSI (derivation cohort), the PROMIS (present cohort), as well as others (eg, Patient Health Questionnaire[20]). It was a relatively straightforward conversion from PROMIS to BSI, but it is possible that this may have impacted the fit of the cluster solution within our cohort. On the other hand, this may indicate that these underlying constructs are relatively robust and may be adapted between validated scales. This also raises the consideration that other psychophysical assessments may be more feasible within the perioperative context, such as the use of the Pain Sensitivity Questionnaire[30] in place of QST testing for assessing pain sensitivity. Similarly, the 4 variables used to cluster individuals may not be widely available in clinical practice. While the validated questionnaires are brief and easy to collect from patients through online preoperative assessments, the brief in-person assessment of pressure pain threshold might be more challenging to instrumentalize in the case when patients do not come in person to be evaluated before surgery.

Additionally, the timeframe of assessment for cluster derivation and assessment of outcomes was not the same between the derivation cohort and the current study, potentially further introducing variability between the cohorts. However, the finding that the cluster solution could predict acute and persistent pain across several timepoints, which was not investigated in previous studies, also speaks to the robustness of this cluster solution and is an advantage of prospective longitudinal outcome collection that this cohort offered. A related limitation of ROPA is that the stability of the clusters over time is not yet known. Environmental or peri-morbid factors in this clinical population may distinctively affect cluster membership at the assessed time

point but not maintain consistency longitudinally. Notably, the Adaptive and Pain Sensitive clusters did not meaningfully differ in acute or chronic pain outcomes, which also raises questions regarding the utility of including PPT in the clustering algorithm for predicting postsurgical pain, but more research is necessary.

Conclusion

The application of the ROPA clustering technique, which uses 4 simple measures, to a perioperative cohort undergoing surgery allowed distinction of groups of patients who were at higher risk of acute and persistent postsurgical pain. This cross-institutional exercise suggests that clustering of patients may be useful across different diagnoses and clinical settings, and may be an important tool for personalized medicine in the future.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2022.07.012.

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