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How Much Pain Will I Have After Surgery? A Preoperative Nomogram to Predict Acute Pain Following Mastectomy

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ABSTRACT

Introduction. Acute postoperative pain affects time to opioid cessation and quality of life, and is associated with chronic pain. Effective screening tools are needed to identify patients at increased risk of experiencing more severe acute postoperative pain, and who may benefit from multimodal analgesia and early pain management referral. In this study, we develop a nomogram to preoperatively identify patients at high risk of moderate–severe pain following mastectomy.

Methods. Demographic, psychosocial, and clinical variables were retrospectively assessed in 1195 consecutive patients who underwent mastectomy from January 2019 to December 2020 and had pain scores available from a post-discharge questionnaire. We examined pain severity on postoperative days 1–5, with moderate–severe pain as the outcome of interest. Multivariable logistic regression was performed to identify variables associated with moderate–severe pain in a training cohort of 956 patients. The final model was determined using the Akaike information criterion. A nomogram was constructed using this model, which also included *a priori* selected clinically relevant variables. Internal validation was performed in the remaining cohort of 239 patients.

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T.-A. Moo, MD e-mail: moot@mskcc.org **Results.** In the training cohort, 297 patients reported nomild pain and 659 reported moderate-severe pain. High body mass index (p = 0.042), preoperative Distress Thermometer score ≥ 4 (p = 0.012), and bilateral surgery (p =0.003) predicted moderate-severe pain. The resulting nomogram accurately predicted moderate-severe pain in the validation cohort (AUC = 0.735).

Conclusions. This nomogram incorporates eight preoperative variables to provide a risk estimate of acute moderate–severe pain following mastectomy. Preoperative risk stratification can identify patients who may benefit from individually tailored perioperative pain management strategies and early postoperative interventions to treat pain and assist with opioid tapering.

Inadequate pain control in the immediate postoperative setting has been associated with various short- and long-term adverse outcomes. Poorly controlled acute pain directly correlates with diminished quality of life in the postoperative period^{1, 2} and increases the risk for development of chronic pain syndromes after breast surgery.^{3, 4} Evidence also suggests that the severity of acute postoperative pain is strongly associated with time to surgical recovery and opioid cessation.⁵ Among the long-term adverse effects of acute postoperative pain is the possibility of prolonged opioid use. Patients with cancer are a particularly vulnerable population; 10% of opioid-naïve patients undergoing cancer-related surgery develop new persistent opioid use, compared with 3-6% in patients undergoing non-cancer-related surgery.^{6–8} Studies examining prolonged opioid use following mastectomy have reported that up to 17% of opioid-naïve patients continue to fill opioid prescriptions up to 1 year after surgery.⁹⁻¹¹

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Prior studies have identified a variety of factors associated with more severe acute postoperative pain, including younger age, female sex, pre-existing depression and anxiety, and surgical procedures associated with intraoperative manipulation or disruption of sensory nerves.^{12, 13} Many of these factors are common among breast cancer patients undergoing surgery; however, there are no assessment tools currently available to predict which patients will be at risk of experiencing more severe acute postoperative pain, or to quantify the magnitude of this risk. The early preoperative identification of patients at high risk of increased pain postoperatively may allow for more timely interventions. In this context, the aim of this study was to develop a nomogram to preoperatively identify patients at high risk of developing moderate-severe acute pain following mastectomy.

METHODS

This was a single-institution, retrospective study of consecutive patients from January 2019 through December 2020 who underwent mastectomy with and without reconstruction, and who completed at least one survey reporting pain severity during postoperative days 1–5. During this period, 2125 patients underwent mastectomy with or without reconstruction, of whom 1195 (56.2%) reported their postoperative pain severity. All reconstruction was implantbased, with tissue expanders placed either in the prepectoral or subpectoral position, at the discretion of the operating plastic surgeon. Patients who underwent autologous tissue reconstruction were excluded. This study was approved by the Memorial Sloan Kettering Cancer Center (MSK; New York, NY, USA) Institutional Review Board.

Patient demographics, disease characteristics, and treatment details were collected from the electronic medical record. Additional psychosocial and pain-related variables were also collected, including history of depression, anxiety, pre-existing pain conditions (which included musculoskeletal pain disorders, peripheral neuropathy, and migraines), preoperative pain level, preoperative pain medication use (which was defined as an opioid listed as an active home medication preoperatively), and preoperative distress. The National Comprehensive Cancer Network (NCCN) Distress Thermometer is a screening tool that is routinely administered in our clinics and asks patients to indicate a number from 0 to 10 (hereafter referred to as a score) that best describes how much distress they have experienced over the past week, including on the day of assessment.¹⁴ The cut-off for clinically significant distress is considered to be a score of four or greater, and patients with elevated scores are asked additional questions to identify their areas of concern and to determine the need for social work and psychiatry referrals.¹⁵

Postoperative pain scores were collected through the MSK Recovery Tracker, an institutional daily postdischarge questionnaire that is sent to patients via email and the patient portal on postoperative days 1 through 10. In this study, we focused specifically on the acute postoperative period of days 1 through 5. Pain scores of 0 through 10 were reported by patients and were categorized as none (score 0), mild (score 1–3), moderate (score 4–6), and severe (score 7–10). When multiple reported scores were available, the highest reported category was used as the representative pain severity score for subsequent analysis.

All patients undergoing mastectomy receive a multimodal pain management regimen as part of our institutional enhanced recovery pathway. Preoperatively, patients undergoing mastectomy with implant-based reconstruction have the option to receive a regional nerve block; however, patients undergoing mastectomy without reconstruction are not routinely offered a nerve block. Patients <65 years of age are routinely administered gabapentin preoperatively. Intraoperatively, acetaminophen is routinely administered intravenously, while postoperatively, patients receive acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids as needed for breakthrough pain. Patients who had reconstruction also receive lorazepam as needed, as well as an additional dose of gabapentin if they are <65 years of age. All patients were admitted for one night postoperatively, as is standard practice in our institution.

The primary outcome of interest in this study was pain of moderate or greater intensity during postoperative days 1 through 5 following mastectomy. The overall cohort was chronologically divided 80:20 into training and validation cohorts, and analysis was performed on complete data. Patient, disease, and treatment characteristics were compared between the training and validation cohorts to ensure there were no significant differences in baseline characteristics between the two groups. Using the training cohort, univariate analysis was performed using Pearson's Chisquare test and Fisher's exact test for categorical covariates and the Wilcoxon rank-sum test for continuous covariates. Significant variables from the univariate analysis were analyzed using multivariable logistic regression. The nomogram was constructed using stepwise model selection by the Akaike information criterion, incorporating variables significant on multivariable analysis as well as clinically relevant variables that were determined a priori based on previous studies examining factors associated with increased acute postoperative pain.^{12, 13, 16-19} These factors included age, history of depression, preoperative pain medication use, neoadjuvant chemotherapy, Distress

Thermometer score, unilateral versus bilateral procedure, and implant-based reconstruction. Decisions regarding potential interactions between covariates were based on clinical input; multicollinearity was assessed using variance inflation factors. The Box-Tidwell test was used to confirm that transformation was not required for continuous covariates in our model. Calibration plots were created for internal validation of the nomogram using the validation cohort. The performance of the nomogram was assessed in both the training and validation cohorts using receiver operating characteristic (ROC) curves, measurement of the area under the ROC curve (AUC), and 95% confidence intervals (CIs) associated with each AUC value, created using 2000 stratified bootstrap replicates. Additionally, bootstrap validation was performed using 2000 replicates from the original dataset in order to obtain average AUC and 95% CIs. All analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) with the boot (v1.3.28), pROC (v1.18.0), and rms (v6.2.0) packages {@r; @boot; @pROC; @rms}. Two-sided p-values <0.05 were considered significant.

RESULTS

Overall, 1195 patients who met the study inclusion criteria were identified; 829 patients (69.4%) had reported pain scores for all 5 postoperative days, 76 patients (6.4%) reported pain scores for 4 of the 5 days, 84 patients (7.0%) for 3 days, 96 patients (8.0%) for 2 days, and 110 patients (9.2%) for 1 day only. The first 956 patients were used as the training cohort and the remaining 239 patients were used for the validation cohort. The training and validation cohorts were well balanced, with no significant differences in their baseline presenting patient, disease, and treatment characteristics (electronic supplementary Table 1). Of the 956 patients in the training cohort, 659 patients (68.9%) reported pain of moderate or greater intensity (Table 1). The distribution of pain scores was similar in the validation cohort; 182 patients (76.2%) in the validation cohort

reported pain of moderate or greater intensity, which was slightly higher than reported in the training cohort but was not statistically significant (p = 0.15).

Within the training cohort, on univariate analysis, patients who reported moderate-severe pain compared to those with mild or no pain were younger (median age 48 years vs. 53 years, p < 0.001), had a higher BMI (median 25.2 vs. 24.6, p = 0.016), more frequently reported current alcohol use (6.5% vs. 2.1%, p = 0.044), had a history of depression (19.3% vs. 7.1%, p < 0.001), and were more likely to have a Distress Thermometer score >4 (53.1% vs. 37.0%, p < 0.001), have pain preoperatively (26.0% vs. 16.6%, p = 0.004), and take pain medications preoperatively (6.5% vs. 2.6%, p = 0.024). Neoadjuvant chemotherapy was received by 32.8% of patients who reported moderate-severe pain compared with 25.9% of those reporting no pain or mild pain (p = 0.033). Patients who reported moderate-severe pain were also more likely to have undergone bilateral mastectomy (54.8% vs. 33.7%, p < 0.001) and to have had reconstruction (p < 0.001). Additional patient, disease, and treatment details are shown in Table 2.

On multivariable analysis, higher BMI (odds ratio [OR] 1.05, 95% CI 1.00–1.10, p = 0.042), Distress Thermometer score ≥ 4 (OR 1.94, 95% CI 1.16–3.30, p = 0.012), and undergoing bilateral mastectomy (OR 2.23, 95% CI 1.31-3.83, p = 0.003) remained associated with an increased likelihood of experiencing moderate-severe pain following mastectomy (Table 3). These three factors were integrated with the *a priori* selected clinically relevant variables-age, history of depression, preoperative pain medication use, neoadjuvant chemotherapy, Distress Thermometer score, unilateral versus bilateral procedure, and implant-based reconstruction-to construct the final model. The model demonstrated an AUC of 0.726 (95% CI 0.687-0.764) in the training cohort and 0.735 (95% CI 0.643-0.827) in the validation cohort (Fig. 1). Bootstrap validation from the original dataset generated an average AUC of 0.729 and a 95% CI of 0.694-0.764.

In the constructed nomogram shown in Fig. 2, variables are organized by row, with points assigned using the scale on the top line of the nomogram labeled 'Points'. A vertical

TABLE 1 Patient-reported
pain severity categories on
postoperative days 1-5

Pain severity category	Training cohort $[n = 956]$	Validation cohort $[n = 239]$	
None	33 (3.5)	6 (2.5)	
Mild	264 (27.6)	51 (21.3)	
Moderate	463 (48.4)	124 (51.9)	
Severe	196 (20.5)	58 (24.3)	

Data are expressed as n (%)

TABLE 2 Patient, disease, and treatment characteristics of the training cohort, stratified by postoperative pain severity

	Overall $[n = 956]$	None–mild pain $[n = 297]$	Moderate–severe pain $[n = 659]$	<i>p</i> -value ^a
Age, years [median (IQR)]	50 (42-60)	53 (45-65)	48 (41–57)	< 0.001
BMI [median (IQR)]	25.1 (22.2–29.5)	24.6 (21.8–28.8)	25.2 (22.4–29.8)	0.016
Race				0.117
White	681 (71.2)	201 (67.7)	480 (72.8)	
Black	86 (9.0)	26 (8.8)	60 (9.1)	
Asian	118 (12.3)	48 (16.2)	70 (10.6)	
Unspecified	71 (7.4)	22 (7.4)	49 (7.4)	
Marital status				0.236
Married	602 (75.6)	183 (75.0)	419 (75.9)	
Divorced	66 (8.3)	25 (10.2)	41 (7.4)	
Widowed	16 (2.0)	7 (2.9)	9 (1.6)	
Single	112 (14.1)	29 (11.7)	83 (15.0)	
Unknown	160 (16.7)	53 (17.8)	107 (16.2)	
Current smoker ^b	35 (4.2)	10 (3.8)	25 (4.3)	0.744
Current alcohol use ^b	23 (5.1)	3 (2.1)	20 (6.5)	0.044
Depression	148 (15.5)	21 (7.1)	127 (19.3)	< 0.001
Anxiety	319 (33.4)	112 (37.7)	207 (31.4)	0.056
Distress Thermometer ≥ 4	460 (48.1)	110 (37.0)	350 (53.1)	< 0.001
Pre-existing pain condition	329 (34.4)	99 (33.3)	230 (34.9)	0.637
Reported pain preoperatively	182 (23.1)	41 (16.6)	141 (26.0)	0.004
Took pain medications preoperatively	40 (5.3)	6 (2.6)	34 (6.5)	0.024
Clinical T stage ^b				0.639
0	206 (21.6)	66 (22.3)	140 (21.3)	
1	329 (34.6)	107 (36.1)	222 (33.8)	
2–4	417 (43.8)	123 (41.6)	294 (44.8)	
Clinical N stage ^b				0.354
0	720 (75.6)	231 (78.0)	489 (74.4)	
1	213 (22.4)	61 (20.6)	152 (23.1)	
2–3	20 (2.1)	4 (1.4)	16 (2.4)	
Neoadjuvant chemotherapy	293 (30.6)	77 (25.9)	216 (32.8)	0.033
Bilateral mastectomy	461 (48.2)	100 (33.7)	361 (54.8)	< 0.001
Reconstruction				< 0.001
None	233 (24.4)	112 (37.7)	121 (18.4)	
Prepectoral	246 (25.7)	62 (20.9)	184 (27.9)	
Subpectoral	477 (49.9)	123 (41.4)	354 (53.7)	
Axillary surgery				0.210
None	70 (7.3)	28 (9.4)	42 (6.4)	
SLNB	661 (69.1)	204 (68.7)	457 (69.3)	
ALND	225 (23.5)	65 (21.9)	160 (24.3)	

Data are expressed as n (%) unless otherwise specified

^aP-value indicates comparison between patients with none-mild pain and patients with moderate-severe pain

^bPercentages were calculated using n as the number of those with known data or values

IQR interquartile range, BMI body mass index, SLNB sentinel lymph node biopsy, ALND axillary lymph node dissection

line can be drawn from each variable to the 'Points' scale to calculate the number of points per variable. Once this has been done for each individual variable in the nomogram, all the points are summed to calculate the total points generated by the individual patient. This number is identified along the 'Total Points' line and a vertical line is

OR 95% CI *p*-value 0.99 0.97-1.01 0.359 Age BMI 1.05 1.00 - 1.100.042 Depression 1.45 0.67-3.33 0.352 Took pain medications preoperatively 2.37 0.59-16.00 0.242 Distress Thermometer >4 1.94 1.16-3.30 0.012 Neoadjuvant chemotherapy 1.40 0.79-2.52 0.253 2.23 1.31-3.83 Bilateral mastectomy 0.003 Reconstruction (Ref: None) 0.596 Prepectoral 1.25 0.60-2.63 Subpectoral 1.38 0.74-2.56

OR odds ratio, CI confidence interval, BMI body mass index

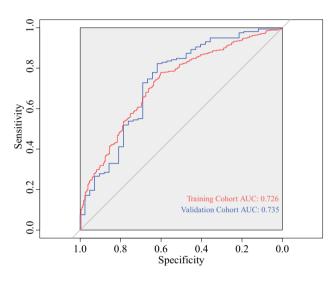


FIG. 1 Receiver operating characteristic curves of the nomogram for the training (*red line*) and validation cohorts (*blue line*)

then drawn to the bottom row of the nomogram labeled 'Risk of Moderate–Severe Pain' to provide the individualized risk estimate of the patient's likelihood of experiencing moderate–severe pain

DISCUSSION

This study identified preoperatively known patient and treatment factors associated with increased acute pain after mastectomy. We found higher BMI, increased preoperative distress, and bilateral mastectomy to be associated with increased likelihood of moderate–severe pain postoperatively. Integrating these three factors with *a priori* selected, preoperatively known clinically relevant factors of age, history of depression, neoadjuvant chemotherapy,

preoperative pain medical use, and use of reconstruction, we constructed a nomogram that can provide an individualized risk estimate of a patient's likelihood of experiencing moderate or greater acute pain following mastectomy. This nomogram performed well, with an AUC of 0.726 in the training cohort and 0.735 on internal validation.

Prior studies have identified similar factors to be associated with increased postoperative pain. Obesity and increased BMI may affect the pharmacokinetics and pharmacodynamics of analgesic regimens.²⁰ As a result, these patients may have more difficulty achieving adequate pain control postoperatively and may require higher dosages of analgesic medications. In a series of 601 patients who underwent autologous breast reconstruction, Nelson et al. reported increased postoperative opioid consumption in patients with increased BMI.¹⁶ We also identified bilateral mastectomy as a risk factor for more severe postoperative pain, likely related to the increased extent of surgery. Similarly, in a series of 2207 women undergoing postmastectomy reconstruction with either implant- or flapbased techniques, Kulkarni et al. also reported bilateral surgery as an independent predictor of more severe acute postoperative pain.¹³

Patient-reported preoperative distress level, as measured by the NCCN Distress Thermometer, also emerged as an independent risk factor for increased postoperative pain. The Distress Thermometer has been validated in cancer patients, and in a meta-analysis of 42 studies and 14,808 cancer patients was shown to have a high sensitivity (0.81, 95% CI 0.79-0.82) and specificity (0.72, 95% CI 0.71-0.72) for detecting distress in cancer patients using a cut-off score of 4.15 While one of the advantages of the Distress Thermometer lies in its brevity and ease of administration, it also provides a comprehensive picture of the patient's overall emotional state. In a survey study of 418 women scheduled to undergo breast surgery, Schnur et al. reported an association between preoperative patientreported distress and the patient's expectation of postoperative pain.¹⁷ Similarly, Pinto et al. reported presurgical anxiety as a predictor of increased acute pain severity following hysterectomy.²¹ The experience of pain is complex and is determined by more than just a physical reaction to surgery. Our study finding of an elevated Distress Thermometer score as an independent risk factor for more severe postoperative pain further highlights the multifaceted nature of the pain experience and the importance of psychosocial interventions in pain control.

The early, preoperative identification of patients at increased risk of having more pain postoperatively can allow for tailored interventions, including multimodal analgesia. This is often incorporated into enhanced recovery pathways, which have been shown to improve pain

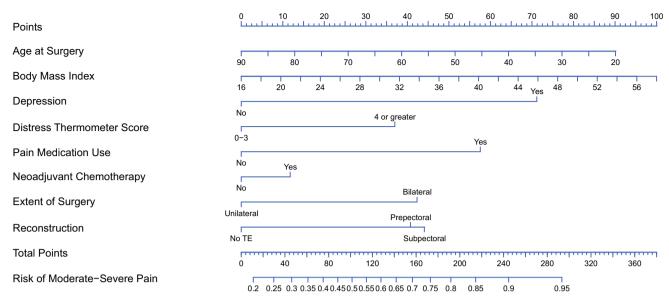


FIG. 2 A nomogram to predict moderate to severe pain on postoperative days 1 through 5 following mastectomy. For each variable, draw a straight line from the patient's variable to the 'Points' axis. The points for all the variables are added to calculate the 'Total

control while also reducing opioid consumption. In a metaanalysis of 10 studies comparing enhanced recovery after surgery (ERAS) versus traditional standard-of-care pathways following breast reconstruction, ERAS pathways were significantly associated with decreased opioid consumption during the postoperative period, as well as decreased pain scores.²² In a single-institution study focusing on patients undergoing total mastectomy with implant-based reconstruction, patients in the ERAS pathway were treated with a similar multimodal pain regimen as in our institutional pathway, including regional nerve block, preoperative acetaminophen, preoperative gabapentin, and postoperative lorazepam.²³ In this study, the 96 patients treated in the ERAS pathway had lower total perioperative opioid consumption (111.5 mg vs. 163.8 mg oral morphine equivalents, p < 0.001) as well as a 2-point decrease in their highest pain score (median 4 vs. 6, p <0.001) when compared with historical controls. Although this nomogram was developed in a population of patients treated on an enhanced recovery pathway protocol, our results suggest potential actionable points of modification in our institutional pathway for these high-risk patients. For example, nerve blocks are not routinely offered to patients undergoing mastectomy without reconstruction. Previous studies have shown the benefit of regional nerve blocks to improve postoperative pain and reduce opioid consumption.^{24–26} Thus, our institutional protocol could be modified accordingly if a patient is preoperatively identified by the nomogram to be at high risk of moderate-severe pain postoperatively.

Points' for the patient. Draw a straight line from the 'Total Points' axis to the 'Risk of Moderate–Severe Pain' axis to obtain the risk estimate

Preoperative risk assessment can also be used to tailor preoperative patient education regarding the recovery process. Several studies have demonstrated the positive impact of preoperative education as a targeted intervention for setting appropriate expectations postoperatively and normalizing the pain experience. Egan et al. demonstrated the effectiveness of a brief, preoperative educational intervention on postoperative pain expectation and multimodal pain management in a randomized, single-center trial of patients undergoing mastectomy with implantbased reconstruction.²⁷ All patients were prescribed the same median number of oxycodone tablets, but the patients who received preoperative education consumed 33% fewer oxycodone tablets than the control group. In a similar randomized controlled trial using a digital education package, Darnall et al. provided breast surgery patients with information on behavioral tools to assist them with managing their postoperative pain.²⁸ Patients who received this intervention had significantly accelerated opioid cessation (5-day difference) without any difference in patientreported pain. These studies highlight the effectiveness of preoperative educational interventions. Such interventions could be focused on high-risk patients identified by our nomogram.

Attention to appropriate tapering and timely opioid cessation is particularly critical in the setting of the current opioid epidemic in the US. In a study of 23,440 opioid-naïve patients who underwent surgery for early-stage breast cancer, which included lumpectomy, mastectomy alone, and mastectomy with reconstruction, 18% continued to be

prescribed opioids at 3–6 months postoperatively, and 9% continued to be prescribed opioids at 6-12 months postoperatively.¹⁰ Similar findings were reported in a study by Marcusa et al. in which 10% of opioid-naïve patients continued to fill opioid prescriptions beyond 3 months after undergoing mastectomy with immediate reconstruction.¹¹ As surgeons also comprise one of the top opioid-prescribing specialties, second only to pain management specialists, clinical alertness to the potential transition from acute opioid use to prolonged or chronic use is important.²⁹ Use of predictive tools such as the opioid risk assessment tool³⁰ and this nomogram could identify patients who are not only at risk of having acute post-surgical pain but also those at risk of continued opioid use beyond the immediate postoperative period. Identification of these patients will allow for early multidisciplinary referrals to ensure timely opioid tapering and cessation without compromising pain management.

This nomogram can also identify patients with a very low likelihood of acute moderate-severe pain and may be candidates for alternate clinical pathways. Low-risk patients can be evaluated for opioid-sparing pain management strategies, thus eliminating the potential adverse effects and dependency risk for these appropriately selected patients.^{10, 31} Previous studies have reported that up to 30% of patients who undergo mastectomy with implantbased reconstruction do not use any opioids postoperatively,³² and, when prescribed, the median prescribed quantity significantly exceeds the reported consumed amount.³³ We, and other institutions, have previously demonstrated the success of eliminating routine discharge opioid prescriptions following breast lumpectomies and excisional biopsies.^{34, 35} The study nomogram also presents an opportunity to translate this to mastectomy patients.

The results of our study must be interpreted in the context of its limitations. First, this was a retrospective, single-institution study. As our study only included patients who responded to the MSK Recovery Tracker, it may not have adequately captured and represented those patients with limited access to the technology used to administer surveys. Second, our institution utilizes an enhanced recovery pathway, which includes use of multimodal analgesia, therefore results may not be applicable in clinical settings where similar pathways are not available. Third, part of our study period also overlapped with the unprecedented coronavirus disease 2019 (COVID-19) pandemic. While no differences were seen in the comparison of the baseline patient, disease, or treatment characteristics between the chronologically divided training and validation groups, there may be other confounders related to the pandemic that are not captured in the current data. Fourth, our study did not evaluate the long-term effects and outcomes associated with more severe acute postoperative pain; however, this is the focus of an ongoing study examining the correlation between acute and chronic pain following mastectomy. Lastly, external validation is necessary to further validate our findings.

CONCLUSIONS

This nomogram incorporates eight preoperative variables to provide an individualized risk estimate of acute moderate–severe pain following mastectomy and can be used for preoperative risk stratification. Identification of patients at high risk of moderate–severe postoperative pain may allow for tailored pain management strategies and early interventions targeted at patient education and appropriate opioid cessation.

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