

Prevalence of postmastectomy pain syndrome and associated risk factors

A large single-institution cohort study

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Abstract

Postmastectomy pain syndrome (PMPS) is a frequent complication of breast surgery, and is considered a chronic neuropathic pain in the side of surgery which persists more than 3 months. We conducted a retrospective analysis of the largest reported cohort to investigate the prevalence of PMPS and to analyze its associated risk factors as well as the influence on quality of life (QoL). Two thousand thirty-three surgically-treated female patients diagnosed between 2012 and 2017 with early-stage breast cancer were asked to complete a questionnaire survey about their current chronic neuropathic pain problems and quality of life. Multivariate logistic regression analyses were applied to determine the associated risk factors of PMPS. Results have shown that 1983 (97.5%) patients responded and completed a questionnaire survey. Among them, PMPS was found in 28.2% of patients. In univariate analysis, age ≤ 35 years, tumor staging, history of chronic pain, total mastectomy, and axillary lymph node dissection (ALND) were significantly correlated with PMPS ($P < .05$). Multivariate analysis showed that age ≤ 35 years, history of chronic pain, total mastectomy, and ALND were the independent risk factors of PMPS. QoL outcomes have shown that the global QoL score, physical function score, role function score, and social function score in the PMPS group were reduced in the PMPS group ($P < .05$), while the difference in emotional function score and cognitive function score showed no statistical significance ($P > .05$). Besides, patients with PMPS have worse body image, sexual enjoyment, and more breast symptoms. In conclusion, PMPS is linked with a high incidence among breast cancer patients, and has a considerable negative influence on the quality of life. In addition, age, total mastectomy, ALND, and history of chronic pain are the independent risk factors of PMPS.

Abbreviations: ALND= axillary lymph node dissection, BMI = body mass index, CI = confidence interval, HR= hazard ratio, PMPS = postmastectomy pain syndrome, QoL= quality of life.

Keywords: breast cancer, chronic pain, mastectomy, postmastectomy pain syndrome

1. Introduction

Breast cancer is the most common cancer among women worldwide.^[1] The treatment of this condition depends on its

staging, and surgical resection constituting an important step in an attempt to cure the disease.^[2] A variety of complications may occur after surgical treatment for breast cancer, one such complication is chronic pain, which may last months to years after surgery,^[3] and may affect around 20% to 50% of women submitted to mastectomy.^[4]

Persistent pain following mastectomy was reported as early as 1978 and this phenomenon has been named postmastectomy pain syndrome (PMPS),^[5] which is defined as the chronic pain occurring in the chest, armpit, upper arm, and shoulder after mastectomy for over 3 months.^[4] The International Association for the Study of Pain (IASP) defines PMPS as persistent pain soon after mastectomy/lumpectomy affecting the anterior thorax, axilla, and/or medial upper arm.^[6] It usually describes as feeling of burning, stabbing, and pulling around the treatment side.^[7] Despite its name, the term PMPS may also be used when discussing patients who underwent breast-conserving surgery.^[8] According to epidemiologic investigation, the morbidity of PMPS may reach 20% to 68%.^[9,10]

In women who survived after mastectomy, chronic pain can be extremely burdensome, reducing the quality of life and overall functional ability.^[11,12] Like other neuropathic pain conditions, the treatment for PMPS is a difficult task.^[13] The amount of research on the treatment of PMPS is very limited and no consensus of the treatment of PMPS has yet been made. The etiology and mechanism of PMPS remain incompletely clear yet. It is regarded as a neuropathic pain condition that might be generated due to the damage to nervous system in the axilla or the

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chest wall, because of surgical treatment of breast cancer.^[4,13] Some risk factors are believed to be associated with PMPS, including the presence and intensity of postoperative pain,^[14] the type of surgery,^[15] younger women,^[15–19] body mass index,^[20] education level,^[21] marital status,^[3] individual susceptibility, and prior history of other types of pain.^[22] Also, it has been demonstrated that pre or postoperative adjuvant therapies like chemotherapy and radiotherapy can develop acute and chronic pain after breast cancer surgery.^[16,23]

In China, the incidence of breast cancer is increasing year by year; however, research on PMPS is lagging and neglected. With the increasing development of medical technology, the overall survival time of breast cancer patients after treatment in China is markedly extended, and the requirements on quality of life have been enhanced accordingly. Therefore, PMPS has been gradually brought to the forefront. Consequently, we present the largest single-institute study on PMPS. The purpose of this study was to determine the prevalence of PMPS and the factors associated with its occurrence in women submitted to surgical treatment for breast cancer, and to determine the effect of PMPS on quality of life.

2. Methods

2.1. Patient selection

Two thousand thirty-three women with breast cancer who consulted and underwent surgical treatment in our hospital from February 2012 to November 2017 were selected. The age of the enrolled patients ranged from 23 to 82 years, with the average age of (49.3 ± 8.2) years. Inclusion criteria: all patients were confirmed with breast cancer through pathology and had undergone surgical resection, with tumor stage, nodal stage, metastasis stage Tis-T3N0-3M0, at American Society of Anesthesiologists grade I to II, and with no severe medical disease. Meanwhile, all patients had no cognitive disorder, were informed of the disease diagnosis, and agreed with the investigation. Exclusion criteria: patients combined with other malignant tumors, bilateral breast cancer, breast cancer recurrence, and distal organ metastasis; those undergoing breast implants; those combined with other diseases inducing pain (such as chronic infection); and those previously taking analgesics for a long time. The study was approved by the Ethics Committee of Guangxi Medical University Cancer Hospital, China.

2.2. Definition of PMPS

In this study, PMPS should be judged conforming to the following criteria based on the chronic pain criteria of the IASP: pain duration exceeding the normal tissue healing time after breast surgery (3 months); and pain site locating at the ipsilateral armpit, arm, shoulder, or chest wall.

2.3. Medical record collection

The general patient conditions, such as age, height, weight, and body mass index (BMI), were recorded, together with tumor site, surgical method, chemotherapy, radiotherapy, and endocrine therapy. Meanwhile, the patients were followed up through telephone and asked to complete a questionnaire survey, the site, nature, inducing or aggravating factors, interval, and attacking characteristics of postoperative chronic pain were recorded. All patients were followed up until March 2019.

2.4. Assessment of QoL

The patients were invited to finish a questionnaire, consisting of the questionnaires of the EORTC QLQ-C30 (the European Organization on the Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0)^[24] and QLQ-BR23 (the EORTC Breast Cancer Module).^[25] All the scales were converted linearly to a scale of 0 to 100 according to the standard scoring procedures of EORTC. Higher scores stand for better health status and functioning for the scales that evaluate the global health and functioning. The outcomes of mean QoL were compared between different regimens of treatment and were compared with the reference values of EORTC.

2.5. Statistical method

Statistical analysis was carried out using SPSS20.0 software (SPSS Inc, Chicago, IL), enumeration data were compared using χ^2 test, and measurement data were compared by *t* test. The relationship between PMPS and the related variables was analyzed through univariate analysis, and variables displaying difference in univariate analysis were performed logistic multivariate regression analysis. A difference of $P < .05$ was deemed as statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 2033 women with breast cancer who underwent mastectomy procedures were enrolled in this study and sent questionnaires. Among them, 1983 cases had completed the questionnaires. So, the following analysis was based on the 1983 cases. The flowchart of study selection process was shown in Fig. 1. The age of subjects ranged from 23 to 82 years, with the average age of (49.3 ± 8.2) years, and 190 (9.6%) patients were at young age (≤ 35 years). The obese ($BMI \geq 30$) patients were 74 (3.7%), and the nonobese ($BMI < 25$) patients were 1909 (96.3%). Eight hundred ninety-eight (45.3%) patients were at early stage, while 1085 (54.7%) were at advanced stage. Fifty-two (2.6%) patients had depression and 222 (11.2%) patients had a history of chronic pain. One thousand five hundred thirty-three (77.3%) patients received total mastectomy and 450 (22.7%) received breast-conserving surgery. For axillary surgery, 793 (40.0%) received sentinel lymph node biopsy, while 1190 (60.0%) received axillary lymph node dissection (ALND). One thousand two hundred six (60.8%) patients received chemotherapy, 1149 (57.9%) received radiotherapy, and 1207 (60.9%) received endocrine therapy. One hundred fifty-six (7.9%) patients had lymphedema, 86 (15.4%) patients accompanied with other diseases. The characteristics of the study population were given in Table 1.

3.2. Epidemiologic features of PMPS

Of the 1983 patients followed up successfully, 560 (28.2%) cases had developed PMPS. Pain frequently occurred in the ipsilateral armpit ($n=356$, 63.6%), followed by ipsilateral chest wall ($n=243$, 43.4%), ipsilateral arm ($n=158$, 28.2%), and other sites ($n=23$, 4.1%). The pain nature was mostly numbness ($n=433$, 77.3%), followed by stabbing pain ($n=285$, 50.9%), swelling pain ($n=180$, 32.1%), and electric overstress pain ($n=126$, 22.5%). It was discovered during follow-ups on patients that

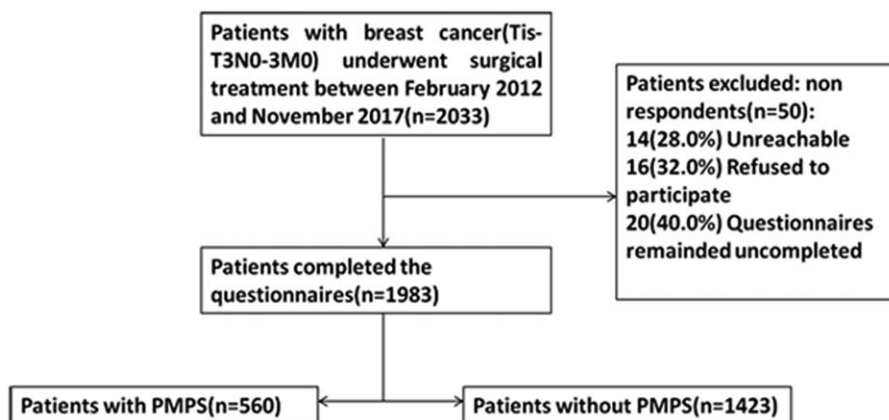


Figure 1. Flowchart of study selection process. T=tumor stage, N=nodal stage, M=metastasis.

some patients had developed other pain symptoms, such as throbbing pain ($n=50$, 8.9%), weakness ($n=32$, 5.7%), and phantom pain ($n=18$, 3.2%). In addition, 28 cases (5.0%) had severe and above (Numeric rating scale score of ≥ 4) pain in terms of pain intensity. Twenty-three patients had taken analgesics by themselves, and 5 had received physiotherapy. The initial occurrence of pain varied from 2 weeks to 3 months after surgery, which was usually intermittent attack.

3.3. Risk factors for PMPS

Of the various variables included in the univariate analysis, the following were associated with PMPS: age ≤ 35 years, advanced tumor stage, history of chronic pain, total mastectomy, and ALND and normal radiotherapy method. No association was found between PMPS and BMI, advanced tumor stage, depression, chemotherapy, chemotherapy cycles, radiotherapy, radiotherapy method, endocrinotherapy, lymphedema, and comorbidity. Next the variables were performed by logistic multivariate regression analysis, and the results suggested that age ≤ 35 years, history of chronic pain, total mastectomy, and ALND were the independent risk factors of the incidence of PMPS. The results were shown in Table 2.

3.4. QoL outcomes

Based on the questionnaires of EORTC QLQ-C30, the global QoL score, physical function score, role function score, and social function score in the PMPS group were reduced, compared with the non-PMPS group ($P < .05$), while the difference in emotional function score and cognitive function score showed no statistical significance ($P > .05$), as shown in Table 3. Based on the questionnaires of EORTC QLQ BR23, the PMPS group reported significantly worse body image, sexual enjoyment, and more breast symptoms, which were statistically different ($P < .001$). There was no significant difference for other QoL domains, as shown in Table 4.

4. Discussion

Postmastectomy pain syndrome is a major clinical challenge, affecting an increasing number of women worldwide.^[4] The postmastectomy chronic pain belongs to the subjective feeling,

which together with the lack of uniform standard of pain and different follow-up time, has resulted in great fluctuation of its incidence. In the present study, we present the largest single-institute study on PMPS, consisting of 2033 patients followed for up to 7 years. All patients were followed up for over 1 year after surgery, among them, 1983 cases had actually completed the follow-up, and 67 were lost to follow-up. According to the definition, PMPS was found in 28.2% of the patients. In all patients suffering from pain, the pain site was dominated by ipsilateral chest wall, followed by ipsilateral armpit, ipsilateral upper arm, and other sites. Additionally, the nature of pain was mainly numbness, which had accounted for 77.3%. All patients reported that the pain was intermittent, with the attack time ranging from few days to few weeks.

The etiology of PMPS is complex and poorly understood, but it is mainly suggested that intraoperative nerve injury is the main cause of the symptom,^[8] associated risk factors include the presence and intensity of postoperative pain,^[14] the type of surgery,^[15] young age,^[15–19] body mass index,^[20] education level,^[21] marital status,^[3] adjuvant chemotherapy and radiotherapy, and psychological factors such as preoperative anxiety.^[16] Similar to published studies in the Western world, we observed that age, NSR score, ALND, and total mastectomy were the risk factors of PMPS. With respect to age, most scientific evidence suggests that the younger the woman, the more likely she is to develop PMPS. Cairns et al reported that the incidence of PMPS was 65% among the age group of 30 to 49 years, 40% among the age group of 50 to 59 years, and 26% among the age group of 70 and above.^[26] In addition, Couceiro et al^[9] suggested in a cross-sectional cohort study involving 250 women that, the morbidity of PMPS among the female samples aged 18 to 75 years was about 44.4%, and the age of < 50 years was related to the incidence of PMPS. Our results were consistent with above reports, a younger age was associated with higher incidence of PMPS, the average age of PMPS patients was (47.0 ± 11.5) years, while that of non-PMPS patients was (53.4 ± 12.0) years, and the difference was statistically significant ($P < .05$). Age is closely correlated with the incidence of PMPS, which may be attributed to the following causes^[27]: young patients are more sensitive to nerve injury and have a wider range of ALND, the morbidity of breast cancer in premenstrual women is higher, and young patients are more susceptible to anxiety. Therefore, they have reduced thresholds to a variety of adverse feelings. However, a

Table 1
Characteristics of the study population.

Characteristics	Patients with PMPS (n=560) N (%)	Patients without PMPS (n=1423) N (%)	Total (n=1983) N (%)	P value
Age (y)				
≤35	88 (15.7)	102 (7.2)	190 (9.6)	.000
>35	472 (84.3)	1321 (92.8)	1793 (90.4)	
BMI				
<30	542 (96.8)	1367 (96.1)	1909 (96.3)	.512
≥30	18 (3.2)	56 (3.9)	74 (3.7)	
Tumor stage				
Early stage	233 (41.6)	665 (46.7)	898 (45.3)	.041
Advanced stage	327 (58.4)	758 (52.3)	1085 (54.7)	
History of chronic pain				
Yes	89 (15.9)	133 (9.3)	222 (11.2)	.000
No	471 (84.1)	1290 (90.7)	1761 (88.8)	
Depression				
Yes	17 (3.0)	35 (2.5)	52 (2.6)	.532
No	543 (97.0)	1388 (97.5)	1931 (97.4)	
Breast surgery type				
Breast-conserving	72 (12.9)	378 (26.6)	450 (22.7)	.000
Total mastectomy	488 (87.1)	1045 (73.4)	1533 (77.3)	
Axillary surgery type				
SLNB	84 (15.0)	709 (49.8)	793 (40.0)	.000
ALND	476 (85.0)	714 (50.2)	1190 (60.0)	
Chemotherapy				
Yes	356 (63.6)	850 (59.7)	1206 (60.8)	.125
No	204 (36.4)	573 (40.3)	777 (39.2)	
Radiotherapy				
Yes	319 (56.9)	830 (58.3)	1149 (57.9)	.579
No	241 (43.1)	593 (41.7)	834 (42.1)	
Endocrinotherapy				
Yes	325 (58.0)	882 (62.0)	1207 (60.9)	.113
No	235 (42.0)	541 (38.0)	776 (39.1)	
Lymphedema				
Yes	51 (9.1)	105 (7.4)	156 (7.9)	.196
No	509 (90.9)	1318 (92.6)	1827 (92.1)	
Infection				
Yes	3 (0.5)	8 (0.6)	11 (0.6)	1.000
No	557 (99.5)	1415 (99.4)	1972 (99.4)	
Comorbidity				
Yes	86 (15.4)	255 (17.9)	341 (17.2)	.186
No	474 (84.6)	1168 (82.1)	1642 (82.8)	
Poor schooling				
Yes	406 (72.5)	980 (68.9)	1386 (69.9)	.062
No	154 (27.5)	443 (31.1)	597 (30.1)	
Marital status				
Married	482 (86.1)	1215 (85.4)	1697 (85.6)	.723
Other	78 (13.9)	208 (14.6)	286 (14.4)	
Employment status				
Employed	478 (85.4)	1208 (84.9)	1686 (85.0)	.888
Unemployed	82 (14.6)	215 (15.1)	297 (15.0)	

ALND = axillary lymph node dissection, BMI = body mass index, SLNB = sentinel lymph node biopsy, PMPS = postmastectomy pain syndrome.

case-control study suggested younger age might not be associated with increased risk of PMPS development.^[28] The different result which was observed in that study might be due to different assessment of pain and its consequences, classification of the type of pain, different types of surgery and treatment modalities, and the type of study.

The pathogenesis of PMPS is largely related to intraoperative nerve injury. Not surprisingly, the type of surgery was also a risk factor for PMPS base on our result. Recent findings have identified that the morbidity of PMPS after breast-conserving

surgery is lower than that after modified radical mastectomy.^[21] In addition, the morbidity after sentinel lymph node dissection (SLND) is much higher than that of ALND.^[29] In the present study, in agreement with data reported by above investigators, the incidence of PMPS in patients undergoing breast-conserving surgery was obviously lower than that in those receiving total mastectomy, and that in patients undergoing ALND was dramatically higher than that in those without ALND. Analysis showed that total mastectomy and ALND were the independent risk factors of the incidence of breast cancer PMPS, this may be

Table 2**Univariate and multivariate analysis of risk factors for PMPS.**

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age ≤ 35 y	2.19 (1.67–2.86)	.000	1.87 (1.49–2.98)	.000
BMI ≥ 30	1.01 (0.98–1.03)	.528	0.92 (0.75–1.16)	.562
Advanced tumor stage	1.23 (1.01–1.58)	.046	1.14 (0.93–1.65)	.103
History of chronic pain	2.23 (1.37–3.64)	.002	2.15 (1.28–3.06)	.021
Depression	1.23 (0.69–2.18)	.571	1.04 (0.65–1.64)	.825
Total mastectomy	1.99 (1.35–3.42)	.000	2.46 (1.59–3.94)	.000
ALND	2.15 (1.64–3.95)	.000	2.63 (1.58–4.52)	.000
Chemotherapy	1.06 (0.98–1.15)	.125	0.86 (0.68–1.23)	.732
Chemotherapy cycles > 4	1.22 (0.86–1.64)	.163	1.06 (0.73–1.58)	.342
Radiotherapy	1.03 (0.92–1.15)	.615	0.89 (0.62–1.21)	.581
Normal radiotherapy	1.15 (0.76–2.36)	.183	0.95 (0.64–1.96)	.328
Endocrinotherapy	1.10 (0.98–1.24)	.113	1.17 (0.92–1.32)	.214
Lymphedema	1.23 (0.89–1.70)	.232	0.93 (0.81–1.82)	.264
Comorbidity	1.03 (0.97–1.08)	.195	0.83 (0.58–1.25)	.315

ALND = axillary lymph node dissection, BMI = body mass index, HR = hazard ratio, PMPS = postmastectomy pain syndrome.

Table 3**QoL of patients according to the QLQ-C30 questionnaire.**

Functioning scales	Patients with PMPS (n = 560)		Patients without PMPS (n = 1423)		P value
	Mean	SD	Mean	SD	
Global QoL	63.3	15.8	69.5	16.8	.042
Physical function	75.7	19.2	82.6	18.0	.016
Role function	71.5	18.0	85.8	21.5	.000
Emotional function	81.6	18.6	82.5	20.3	.926
Cognitive function	83.5	21.2	85.4	19.7	.833
Social function	78.9	16.4	86.2	18.1	.022

QoL = quality-of-life, PMPS = postmastectomy pain syndrome.

related to the operation region and injury to chest wall muscle and skin of total mastectomy are greater than those of breast-conserving surgery. ALND may induce numerous complications, including nerve injury, and nerve injury will result in paresthesia in arm and armpit, thus leading to long-term paresthesia and pain. It is proposed that intercostal nerve injury is the most common during breast surgery, particularly those involving ALND. However, nerves governing breast and the deep nerves may also be damaged, including the medial pectoral nerve, lateral pectoral nerve, thoracodorsal nerve, and long thoracic nerve.^[30]

Besides, injury derived from traction or scar during the surgery may also lead to PMPS. In this study, the long thoracic nerve and thoracodorsal nerve in all patients undergoing ALND were protected. Nonetheless, the intercostal brachial nerve may also be injured during ALND, at the same time, other tiny sensory nerves in the armpit may also be damaged. In this way, SLND can markedly reduce the injury to intercostal brachial nerve, as well as the sensory nerves in chest wall and armpit. The prosthesis in patients receiving breast prosthesis implantation may be an unknown influence factor that cannot be acutely judged.

Table 4**QoL of patients according to the QLQ-BR23 questionnaire.**

Functioning scales	Patients with PMPS (n = 560)		Patients without PMPS (n = 1423)		P value
	Mean	SD	Mean	SD	
Body image	75.2	21.7	81.3	25.2	.000
Sexual functioning	23.7	16.3	25.1	15.6	.521
Sexual enjoyment	43.5	15.0	50.8	19.4	.000
Future perspective	68.1	24.8	75.5	20.3	.286
Arm symptoms	15.1	13.9	18.7	16.0	.109
Breast symptoms	22.6	15.6	12.8	13.2	.000
Systemic therapy side effects	12.5	8.2	13.4	10.3	.833

QoL = quality-of-life, PMPS = postmastectomy pain syndrome.

Therefore, patients receiving breast prosthesis implantation were excluded in this study. Currently, most studies suggested that, completely preserving the intercostal bronchial nerve during ALND can guarantee the thoroughness of surgery without increasing the risk of local tumor recurrence. As a result, the intercostal bronchial nerve should be completely preserved as far as possible during surgery, which may contribute to lessening the incidence of breast cancer PMPS.

Furthermore, we also found that the patients with a prior history of chronic pain had a higher risk of developing PMPS. It is believed that this could be explained by central sensitization. Frequent chronic pain can produce a state of central hypersensitivity that initially is merely functional but which may consolidate by perpetuating the pain process due to neuronal plasticity. Consistent with our results, Cui et al^[10] reported that history of chronic pain was an independent risk factor related to the PMPS occurrence, and Couceiro et al^[9] reported that prior history of headache was a risk factor for PMPS.

PMPS may affect the patient's quality of life. This study uses the simple healthy life quality scale to assess the quality of life, higher scores stand for better health status and functioning. Our results showed that the global QoL score, physical function score, role function score, and social function score were reduced in PMPS group. Patients with PMPS also had worse body image, sexual enjoyment, and breast symptoms. The results suggested that PMPS has a considerable negative influence on the quality of life of the affected women, in agreement with data reported by other investigators.^[31] Therefore, PMPS needs our attention to carry out effective intervention and prevention, which is of positive significance to improve the postoperative quality of life of breast cancer patients. However, the amount of research on the treatment of PMPS is very limited and no consensus of the treatment of PMPS has yet been made. Therefore, we should pay attention to the prevention of PMPS. According to the results of the analysis on risk factor for PMPS in the present study, preservation of the intercostal nerve during surgery could decrease chronic pain, the use of sentinel lymph node biopsy could reduce the need for axillary dissection and thereby reduce intercostal nerve damage. Besides, it is of high clinical relevance to find a safe, reliable, and tolerated treatment with a substantial effect on PMPS.

Our study has a few limitations. It was a retrospective study, although the sample size was not small, but they were from a single center. It is also important to point out that other important variables including socioeconomic conditions and religiousness were not investigated. Further high-quality, prospective, multicenter studies are needed to investigate the prevalence of PMPS and its related risk factors as well as the influence on quality of life.

In conclusions, PMPS is linked with a high incidence among postmastectomy patients, and has a considerable negative influence on the quality of life. In addition, age, total mastectomy, ALND, and history of chronic pain are the independent risk factors of PMPS.

Author contributions

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Funding acquisition: Changyuan Wei.

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Methodology: Qinghong Qin, Changyuan Wei.

Project administration: Changyuan Wei.

Software: Qinghong Qin.

Writing – original draft: Qixing Tan.

Writing – review & editing: Qinghong Qin.

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