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## Unique Profile of Post Mastectomy Pain Syndrome in Breast Cancer Patients in an Oncologic Center Surabaya, Indonesia

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## ABSTRACT

**Background:** Post Mastectomy Pain Syndrome (PMPS) is a chronic neurophatic pain that is localized around the surgical site and can occur immediately or some time after surgery and lasts up to more than three months. Breast cancer is the most common malignancy in women worldwide. Mastectomy is one of the treatment options for breast cancer that is often performed. This research aimed to provide an overview of the profile of breast cancer patients who experienced PMPS at the Oncology Clinic at RSUD dr. Soetomo Surabaya in December 2023.

**Methods:** This research used a cross sectional to all breast cancer patients who experienced PMPS. Samples were taken by consecutive sampling based on inclusion and exclusion criteria. We present our data descriptively in the tabulation of diagrams and tables.

**Results:** Based on the quality of pain, most patients complained of radiating pain (52.7%), followed by stinging (33.33%), and dullness (14%). Pain was mainly felt at the surgical area (94%) with the remaining 6% feeling pain in ipsilateral arm. A total of 108 samples (60%) felt pain continuously, and most of the samples (86.7%) had a history of taking anti-pain medication to reduce complaints. Only about 36% of the samples said that pain was relieved over time.

**Conclusion:** At the Tertiary Oncologic Centre in Surabaya, most post-mastectomy pain syndrome patients were older, with luminal A type, and at higher TNM stages. The majority reported pain radiating from the surgery site, typically manifesting more than six months after the surgery.

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### INTRODUCTION

Globally, breast cancer is the most prevalent cancer among women. Global breast cancer incidence was 47.8 cases per 100,000 women in 2018, as reported by the International Agency for Research on Cancer (IARC). Approximately 15% of

all cancer patients globally lost their lives to breast cancer in 2020, with 684,996 females succumbing to the disease.<sup>1</sup> Breast cancer is a disease that causes a relatively high number of fatalities in Indonesia.

Mastectomy is one of the most frequently performed breast cancer therapy options.<sup>2</sup> Numerous complications may arise subsequent to a mastectomy, encompassing post-mastectomy pain syndrome (PMPS), which is characterized by persistent pain following the operation, seroma, infection, fat necrosis, wound dehiscence, venous

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thromboembolism, diminished tactile sensation, and wound necrosis. Post-mastectomy pain syndrome (PMPS) is a persistent neuropathic pain that is confined to the area surrounding the surgical scar. It may manifest either immediately or at some point after the procedure and persist for a duration exceeding three months. Patients may experience a decline in their quality of life as a result of the pain associated with this syndrome. Furthermore, its management is challenging due to the lack of sufficient research and the absence of a consensus regarding PMPS treatment.<sup>3</sup> Currently in Indonesia there is still not enough data regarding PMPS. Therefore, the research aims to conduct descriptive research to obtain an overview of the characteristic of patients who experience PMPS.

## METHODS

### *Design and population of the study*

This study has been accepted and ethically approved by Dr. Soetomo General Hospital Ethics Committee with reference number: 1595/LOE/301.4.2/II/2024 in accordance with The Office for Human Research Protection (OHRP) under the statement of U.S. Department of Health and Human Services (HHS). This research used a cross-sectional method without any follow up from patients to provide an overview of the profile of breast cancer outpatients who experienced post-mastectomy pain syndrome (PMPS) at the Oncology Polyclinic at RSUD Dr. Soetomo Surabaya in 2023. Samples were taken by consecutive sampling based on inclusion and exclusion criteria in the period from January 2023 until December 2023.

Research inclusion criteria were (1) Female patients with breast cancer proven by triple diagnostic results, (2) Patients who underwent mastectomy at RSUD Dr. Soetomo Surabaya, (3) Patients with post-mastectomy pain syndrome (PMPS) confirmed by history. The exclusion criteria of this research were patients with incomplete medical record data.

### *Data collection*

Data collection in this study used a structured form which included the following information: name, age at the time of mastectomy, weight, height and BMI at the time of mastectomy, occupation, education, income, history of previous breast surgery, time interval between previous breast surgery with last mastectomy, adjuvant chemotherapy, history of previous chronic diseases, history of pregnancy, use of birth control, age of first menstruation, history of breastfeeding, history of menopause, lifestyle such as exercise, smoking more than 100 cigarettes in her life, alcohol consumption

for more than 1 glass for each day, data on last mastectomy surgery at RSUD Dr. Soetomo Surabaya, which includes the type of mastectomy incision, stage and TNM of pre and post-operative breast cancer, subtypes of immunohistochemistry results, routine control, and the presence of other post-operative complications in the form of ipsilateral arm edema. The data above was taken directly from the patient's medical record by the researcher and through interviews if the data was not available in the medical record. The form also includes a detailed assessment of the nature of the PMPS pain felt including the characteristics of the pain from the patient's description of how the pain feel, the degree of severity assessed using a visual analog scale (VAS), location of the pain, the time that triggered or worsened the pain, consumption of anti-pain medication, improvement in pain, time interval between operations to the onset of pain, and the Karnofsky score. Generally, VAS is a tool with a line of 0 to 10 cm, 0 indicating no pain and 10 indicating severe pain. Patients were instructed to mark the point that corresponded to the level of pain intensity they felt on a scale of 1-10. Beside VAS, we used Karnofsky score. According to their functional impairment, patients were classified using the Karnofsky score from 0 to 100.

### *Statistical analysis*

The data was collected using Excel as the main platform. After data collection, the information was presented in the form of tabulated tables and diagrams to provide clear visualization and was also explained descriptively. The data we take has been normalized and randomized to be processed and presented in the results of this research.

## RESULTS

### *Demographic and clinicopathological characteristics*

Of the total 180 sample patients with PMPS, it was found that the majority were aged 40-49 years (36.1%) and 50-59 years (38.3%). A lower frequency was actually found in younger patients, with age <30 years at only 1.1% and age 30-39 years amounting to 7.7%. Most patients' body weight was found to be in the range of 50-59 kg, with a percentage of 51.8%. Based on BMI calculations, it was found that 36.1% of patients were overweight with a BMI of 25-29.9, 34.4% of patients had a normal BMI, and the rest were underweight and obese. As many as 93.3% of patients worked as housewives, and 3.8% worked outdoors which increased their exposure to sunlight, such as online motorbike taxi drivers and farmers. Income in most patient households was around <5 million (97.2%) (Table 1).

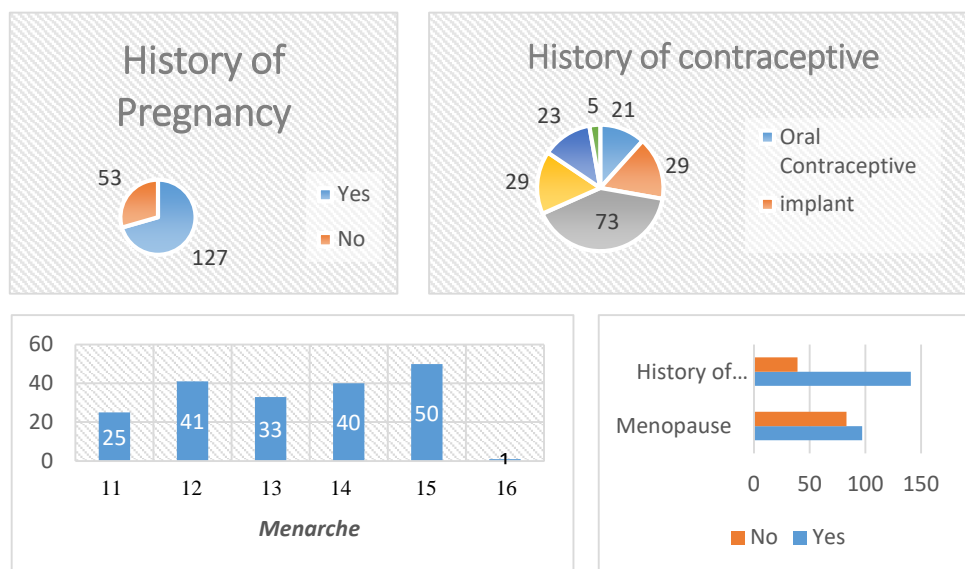


**Table 1. Demographic Characteristic**

Variables	Category	Frequency (n=180)	Percentage
Age (years old)	<30	2	1,1%
	30-39	14	7,7%
	40-49	65	36,1%
	50-59	69	38,3%
	≥60	30	16,7%
Weight (kg)	<40	26	14,4%
	40-49	31	17,2%
	50-59	93	51,8%
	60-69	29	16,1%
	≥70	1	0,5%
Height (cm)	140-149	49	27,2%
	150-159	124	68,8%
	160-169	6	3,3%
	≥170	1	0,5%
BMI (kg/m <sup>2</sup> )	<18,5 (underweight)	31	17,2%
	18,5-24,9 (normal)	62	34,4%
	25-29,9 (overweight)	65	36,1%
	≥30 (obese)	22	12,2%
	Occupation	Housewives	168
	Self-employed	5	2,7%
	Farmer/Driver	7	3,8%
Education	-	131	72,7%
	Elementary school	15	8,3%
	Junior high school	11	6,1%
	Senior high school	22	12,2%
	Bachelor	1	0,5%
Income	<5 million	175	97,2%
	5-10 million	5	2,7%

In this study, it was found that 56.7% did not exercise regularly. The criteria for regular exercise in this interview are exercise with a frequency of 3-5 times a week, with a minimum duration of 30 minutes per day. Most patients (99.5%) did not smoke or consume alcohol (Table 2). 100% of the participants in this study were female, and 78% had previously breastfed, and 70% had previously been pregnant. The use of contraceptives was documented by every patient. Among these, the sterile method of contraception was utilized the least (3%), whereas the 3-month injection contraceptive was the most commonly employed (41%). The age group at which the onset of menstruation was observed to transpire upon most frequently (27 percent) was 15 years old, with 16 years at 16 percent, 14 years at 22.2 percent, 13 years at 18 percent, and 11 years at 14 percent of the total. When this research was undertaken, up to 54% of the patients had undergone the menopausal transition (Figure 1).

In this study, it was found that 72.7% of the sample had a history of previous breast surgery, with the time interval between the previous operation and the last mastectomy being the highest in the 1-5 year group (44%), followed by the <1 year group (36%), with the lowest interval being in the 5-10 year group (2%) (Figure 1). For mastectomy operations performed, Modified Radical Mastectomy (MRM) was the type of operation most frequently performed in the sample (92.7%)(Figure 2.). In this study, the largest group of samples underwent surgery with the Stewart incision (52.2%), followed by the Orr incision (47.7%). (Figure 3).



**Figure 1. History of Maternity**

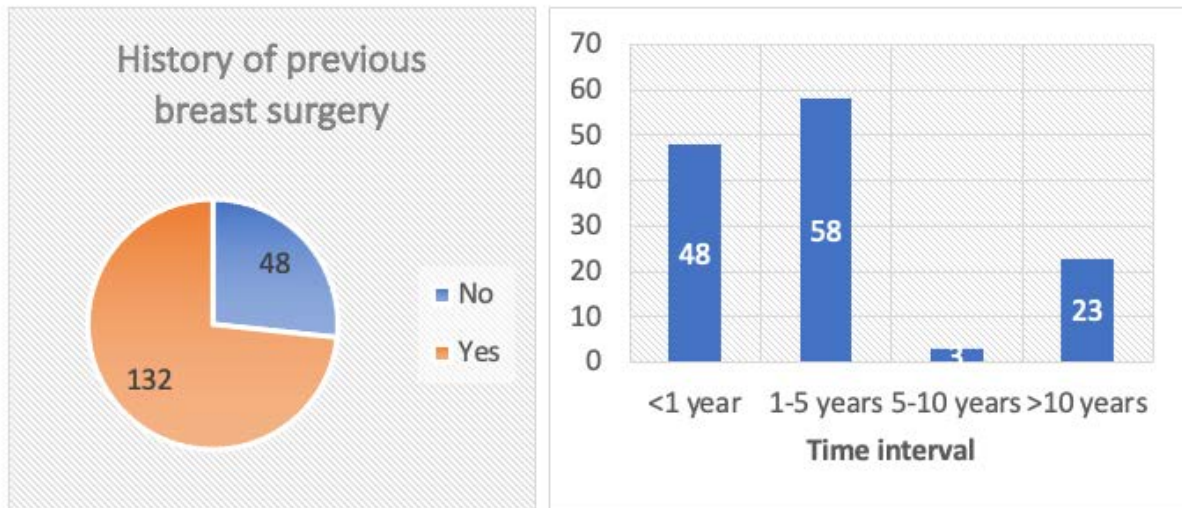


Figure 2. History of Previous Breast Surgery

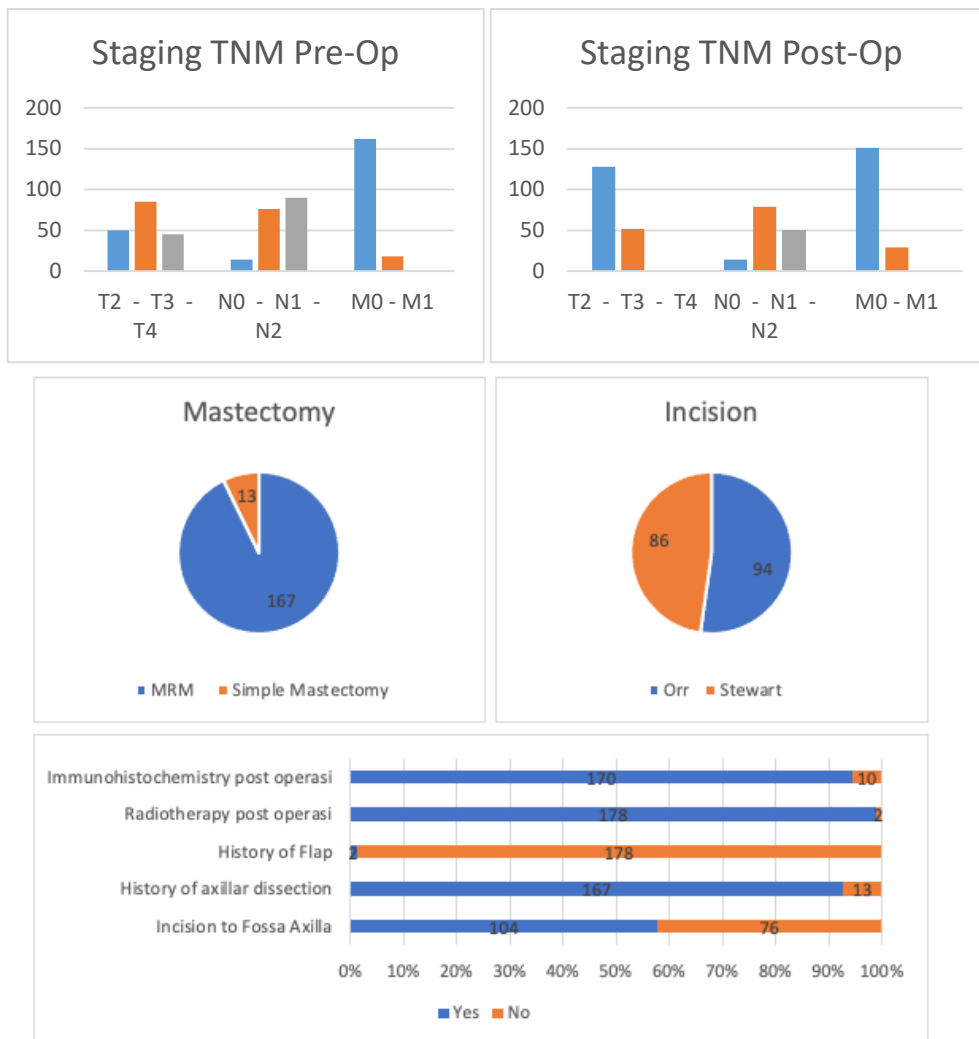


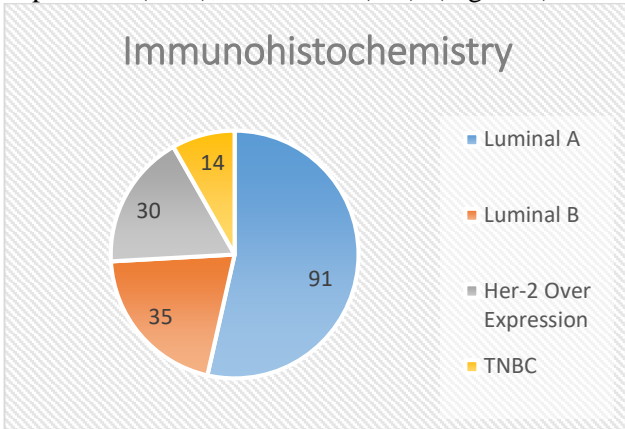
Figure 3. Mastectomy, Incision, and Postoperative Therapy

Based on pre- and post-operative TNM stages in the sample, the majority of patients had pre-operative stage T3 (47.2%), followed by T2 (27.7%) and T4

(25%); N2 (50%), followed by N1 (42%), and N0 (8%); M0 (90%) and M1 (10%). Meanwhile, the most common post-operative stage was T2 (71%)



followed by T3 (28.8%); N1 (43.8%) followed by N0 (28%); and M0 (84%) followed by M1 (16%). In this study, 170 samples underwent immunohistochemical examination, with luminal A (53.5%) being the most frequent immunohistochemical examination result, followed by luminal B (20%), HER-2 over expression (17%), and TNBC (8%). (Figure 4)

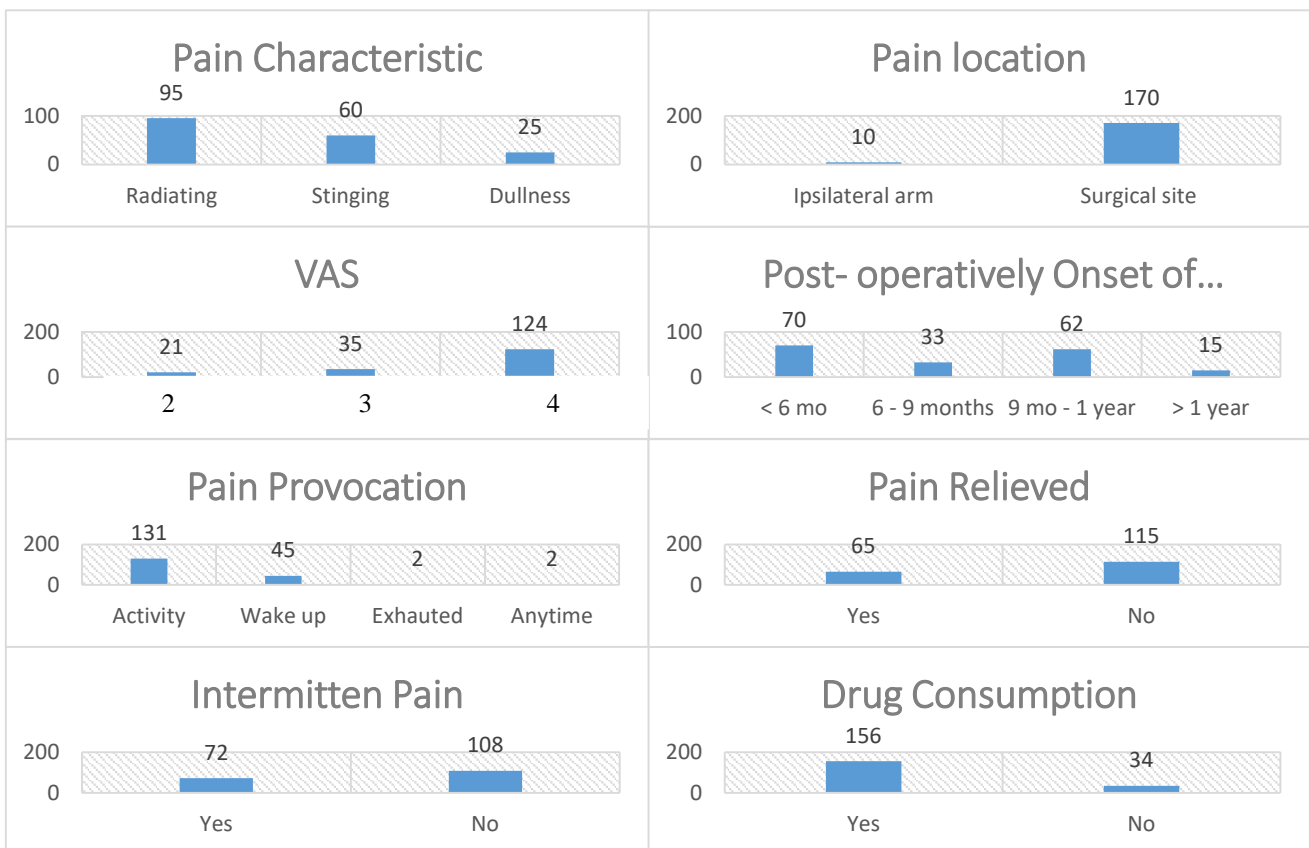


**Figure 4.** TNM Stadium Pre and Post-operation and Immunohistochemistry Results

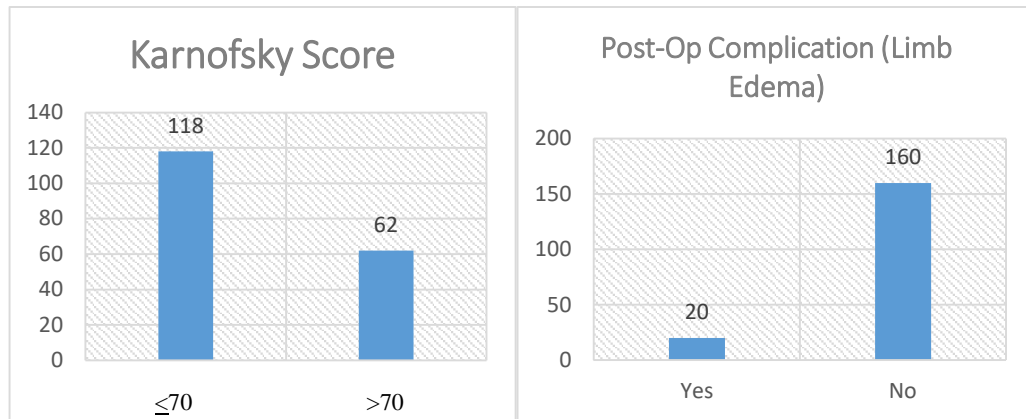
Based on the quality of pain, most patients complained of radiating pain (52.7%), followed by stinging (33.3%), and dullness (14%). Pain was mainly felt in the surgical area (94%), with the remaining 6% feeling pain in the ipsilateral arm. The

severity of pain was assessed using the Visual Analog Score (VAS), with the majority reporting pain with a VAS score of 4 (69%), with the remainder having a VAS score of 3 (19%) and a VAS2 score (11.7%). Most of the pain reported occurred during activities (72.7%). Calculating from the operation until the onset of pain, most patients reported pain occurring within 9 months to 1 year after surgery (68.8%), and only 8.3% of the patients reported pain appearing more than 1 year after surgery. A total of 108 samples (60%) felt pain continuously (60%), and most of the samples (86.7%) had a history of taking anti-pain medication to reduce complaints. Only about 36% of the sample said that pain was relieved over time. (Figure 5)

In this research, 118 samples had a Karnofsky score below 70 (65.5%), while the remaining 34.5% had a score of >70 and were able to carry out their normal activities. Reviewing other post-operative complications that may be related to the perceived PMPS pain, it was found that only 11% of the sample reported ipsilateral arm edema located in the right breast. The median size of the tumor was 5.5 cm and the majority were larger than 3 cm (84%). Lymph node infiltration was found in 73% of cases and distant metastasis at diagnosis was discovered in 16% of cases (Figure 6).



**Figure 5.** Characteristic of Pain



**Figure 6.** Karnofsky score and Post-Op Complication

In total, 36% of cases were early stage-, 47.9% were locally advanced-, and 16% were metastatic breast cancers. More than 80% of YBC cases were histologically infiltrative ductal carcinomas. Positivity of hormonal receptors and HER2 expression were reported in 39.6 and 30.6%, respectively. Molecular classification using IHC-staining revealed 43% patients as luminal- and 38% as TNBC (Table 2). Ki67 IHC staining was documented in 34 patients in which 19 patients (55.8%) were above 14%, indicating a high mitotic index.

**Table 2.** Habits Profile

Habits	Category	Frequency (n=180)	Percentage
Regular Exercise	Yes	78	43.3%
	No	102	56.7%
Smoking	Yes	1	0.5%
	No	179	99.5%
Alcohol consumption	Yes	1	0.5%
	No	179	99.5%

**DISCUSSION**

The results of this study show that the age group most frequently diagnosed with breast cancer is the 50-59 year age group, followed by the 40-49 year age group. Gong *et al.* (2020) also stated that age ≤35 years was significantly associated with PMPS in univariate analysis ( $P < 0.05$ ), and multivariate analysis showed that age ≤35 years was an independent risk factor for PMPS. It is suggested that the mechanism for increasing the risk of PMPS at a younger age is due to the possibility of a higher histopathological tumor grade, the need for adjuvant chemotherapy, and increased recurrence rates, especially in breast cancer in younger women. Another possible factor is the difference in estrogen

receptor status in young and old patients, with decreased pain receptor sensitivity in older patients.<sup>4-6</sup>

The BMI profile shows that the highest incidence of breast cancer is found in the overweight group (25-29.9 kg/m<sup>2</sup>). There was a trend of increasing frequency of PMPS as BMI increased from underweight to overweight; however, the number of PMPS patients who were obese was found to be the least with a percentage of 12.2%. In research conducted by Gong *et al.* (2020) who conducted a study on the incidence of PMPS, the incidence of PMPS was greater in the BMI <30 kg/m<sup>2</sup> group (96.8%) compared to the BMI ≥30 kg/m<sup>2</sup> group (3.2%). These results are in line with the results of this study where the incidence of PMPS was more common in the group with a BMI <30 kg/m<sup>2</sup> (87.8%) compared to the group with a BMI ≥30 kg/m<sup>2</sup> (12.2%).

Based on their occupation, most of the patients with PMPS in this study were housewives, and only 6.5% worked. This result is in contrast to the results of a study by Gong *et al.* (2020) which showed that PMPS is more common among women who have jobs (85.4%). However, the percentage of patients without PMPS who work has a similar value, namely 84.9%, which shows that there is no relationship between work and the occurrence of PMPS ( $p = 0.88$ ).<sup>7</sup>

A higher prevalence of PMPS was observed in the group (56.7%) that did not engage in regular exercise. The correlation between inflammation and pain in female patients diagnosed with breast cancer is supported by the findings of Calapai *et al.* (2023), showing that there is an elevation in pro-inflammatory cytokines, specifically C-reactive protein, within the body. Evidence shows that regular exercise has benefits for cancer patients, namely due to increased defense against endogenous antioxidants, resistance to oxidative stress, and resistance to cancer cell growth. Physical activity has



been found to be correlated with a decrease in both the intensity of pain and the inflammatory response of the patient.<sup>8</sup>

It was observed that all participants in this research had a prior utilization of contraception, with the highest proportion (73%) having employed injectable contraceptives for a duration of three months. Patients who had previously used hormonal contraception had a significantly higher risk of developing breast cancer than those who have never used hormonal contraception (RR = 1.20; 95% CI = 1.14-1.26). Morch *et al.* (2017) found that the likelihood of developing breast cancer escalated in correlation with extended contraceptive use. Additionally, Beaber *et al.* (2014) observed that an increased risk of developing breast cancer was associated with the use of combined oral contraceptives within the previous 12 months (OR = 1.5; 95% CI = 1.3-1.9).

Half of the sample experienced their first menstruation at the age of  $\geq 14$  years. Based on previous research, the risk of breast cancer increases significantly in patients with earlier onset of menarche ( $\leq 13$  years) (OR = 1.60; 95% CI = 1.08-2.38).<sup>9</sup> These results are consistent with other studies that found similar results.<sup>11,12</sup>

More than half of the sample (54%) had experienced menopause. Studies show an increase in the risk of breast cancer every 1 year of age at the time of menopause, but other studies have found no relationship between age at menopause and the incidence of breast cancer.<sup>9,12</sup>

In this study, it was found that 22% of the sample had a previous history of chronic pain, followed by a history of hypertension (11%), diabetes mellitus (10%), and autoimmune disease (4%). In research conducted by Gong *et al.* (2020), it was found that 15.9% of PMPS patients had a previous chronic history, while 15.4% had a history of comorbid diseases. Analysis in this study showed that a history of chronic pain was associated with the incidence of PMPS ( $P = 0.00$ ) but not with a history of comorbid diseases ( $P = 0.186$ ).<sup>7</sup> Bivariate analysis in other studies showed that any previous history of pain was associated with PMPS (PR = 1.39; 95% CI = 1.12-1.74), and multivariate analysis showed that previous history of headache was significantly associated with PMPS (OR = 1.92; 95% CI = 1.10-3.34).<sup>6</sup>

Upon examining the prior breast surgical procedures, it is evident that the Modified Radical Mastectomy (MRM) is the most frequently performed procedure (92.7%) among the participants in this research sample. Only 7.2% underwent simple mastectomy. Previous research by Gong *et al.* (2020) provides support for the findings of this study, indicating that 87.1% of patients who presented with

PMPS had a prior history of mastectomy. In the interim, BCS had been performed on a mere 12.9% of patients diagnosed with PMPS. The incidence of PMPS was found to be significantly associated with total mastectomy, as determined by univariate and multivariate analyses in this study.<sup>7</sup>

In this study, the sample that underwent surgery with the Stewart incision was the largest group (52.2%), followed by 47.7% with the Orr incision type. The study by Couceiro *et al.* (2013) reported that the incidence of PMPS was greater in quadrantectomy in both bivariate (PR = 1.59; 95% CI = 1.18-2.1) and multivariate analysis (OR = 2.83; 95% CI = 1.60 -5.02). It is suspected that this is related to the axillary lymphadenectomy rather than the surgical technique itself, because in this study, all quadrantectomy procedures were always accompanied by an axillary lymphadenectomy procedure.<sup>6</sup>

TNM staging in this study sample showed that most PMPS patients had stages T3 (47.2%), N2 (50%), M0 (90%) before surgery with post-operative stages T2 (71%), N1 (43.8%), M0 (84%). These results are slightly different from those of the previous research conducted by Gong *et al.* (2020) which shows that the majority of PMPS are found at advanced stages (58.4%) compared to early stages (41.6%).

This study demonstrates that chemotherapy, radiotherapy, and hormonal therapy have no bearing on the incidence of PMPS. For these three variables, the same findings ( $P > 0.05$ ) are seen in both univariate and multivariate analyses.<sup>7</sup> These findings contrast with those of the Beyaz *et al.* (2016) study, which found a significant correlation ( $P=0.028$ ) between postoperative radiation and the incidence of PMPS. According to Beyaz *et al.* (2016), 98.89% of the samples with PMPS had previously received postoperative radiation. Radiation to the axillary region and supraclavicular glands was found to produce more pain in the arms, shoulders, and breasts.<sup>4,13,14</sup> Numerous studies have also reported radiation as a risk factor for chronic pain.

In this study, the quality of pain that elicited the highest number of complaints regarding PMPS pain characteristics was radiating pain (52.7%), followed by stinging (33.3%) and dullness (14%). Numbness was the most prevalent pain symptom in prior research (77.3%), followed by stabbing pain (50.9%), swelling pain (32.1%), and electric overstress pain (22.5%).<sup>7</sup> According to Bruce *et al.* (2004), the pain was described by patients as stabbing, shooting, aching, and nagging. Comparable pain characteristics were also documented by Beyaz *et al.* (2016): stabbing (15%), shooting (12.8%), aching (12.8%), gnawing (10.5%), nagging (10.5%),



annoying (9.8%), numb (9.8%), tiring (9.8%), and tight (9%).

This study showed that 94% of patients with PMPS complained of pain in the surgical area, while the remaining 6% felt pain in the ipsilateral arm. Previous studies on PMPS showed that pain often occurred in the ipsilateral axilla (63.6%), followed by the ipsilateral chest wall (43.4%), ipsilateral arm (28.2%), and other sites (4.1%) (Gong *et al.*, 2020). Another study reported that the majority of pain was felt in the arm/axilla (39%), followed by scar tissue from surgery (29.9%), chest wall (12.3%), shoulder (11%), and a small percentage experienced phantom pain. (7.8%).<sup>15</sup> Meanwhile, Stevens *et al.* (1995) reported that 84% of pain was felt in the axilla, followed by the medial upper arm (74%), anterior chest wall (58%), and shoulder (32%).

The VAS assessment in this study obtained the highest VAS score of 4 (69%), followed by score 3 (19%), and score 2 (11.7%). Research on 1983 patients conducted by Gong *et al.* (2020) showed that 28 cases (5.0%) experienced severe pain (numerical rating scale score  $\geq 4$ ).<sup>7</sup> Another study by Couceiro *et al.* (2013) reported a median VAS of 5 (4-7) in patients with PMPS. Meanwhile, another study by Beza *et al.* (2016) reported that the majority of patients (78.6%) experienced pain with a VAS score of 0-3, and only the remaining 21.4% experienced moderate pain with a VAS score of 4-7.

This study shows that the majority of PMPS appear 9 months to 1 year after surgery, followed by <6 months after surgery. The results of this study differ from previous research by Stevens *et al.* (1995) who found that pain generally occurs within days to weeks after breast cancer surgery. Other studies also show that the onset of pain in PMPS varies from 2 weeks to 3 months after surgery. However, this study showed the same results as those found in this research, that most of the pain was felt to come and go.<sup>7</sup> Meanwhile, a study by Stevens *et al.* (1995) reported a number that was not much different between intermittent pain (52%) and continuous pain (48%) in patients with PMPS. This study found that 86.7% of patients had a history of taking anti-pain medication to treat their PMPS. The study by Bezal *et al.* (2016) also reported that 89.9% of patients had tried one or more pain medications, most of which were over-the-counter medications or medications prescribed by general practitioners. Other patients try non-pharmacological therapies or a combination of both, such as physiotherapy, homeopathy, reflexology, acupuncture, massage and counseling. Only 72.9% of PMPS patients said their pain had improved.<sup>15</sup> These results contradict the results of this study where the majority of patients (63.9%) did not feel any improvement in pain.

This study found that most patients with PMPS had a Karnofsky score <70 (65.6%). Prior research has indicated that post-mastectomy patients who experience severe pain have Karnofsky scores that are lower than those who do not experience pain (Miaskowski *et al.*, 2012). An additional investigation conducted by Langford *et al.* (2014) corroborates these findings, revealing that individuals experiencing mild PMPS pain exhibited higher Karnofsky scores than those with moderate to severe PMPS pain.

Arm edema, which is frequently observed in patients following mastectomy surgery, is a complication induced by lymphedema in the upper limbs.<sup>14</sup> Overall, 11.1% of PMPS patients exhibited arm edema, according to the findings of this study. Patients with PMPS and lymphedema who underwent lymphedema surgery reported a reduction in pain, according to a study by Becker *et al.* (2008). Following surgery, it was observed that neuropathic pain resolved entirely, and all patients ceased the use of analgesic medications. According to Becker *et al.* (2008), the findings suggest that lymphedema in the upper extremities subsequent to mastectomy may be a contributing factor to PMP in affected individuals. In this study, the majority of patients complained of pain, especially with activity. These results are in line with the study by Beyaz *et al.* (2016) who reported pain that was aggravated by activity (54.5%), lying down (14.3%), cold weather (10.3%), rubbing of scars on clothes (10.3%), and waking up from sleep (10.3%). Activities such as lifting, carrying and housework are generally found to aggravate pain. Some even complain of pain when walking, driving, and working.<sup>15</sup> Another study also reported that all sample patients with PMPS said the pain was especially worse with movement and when tired.<sup>21</sup>

#### Limitation

The use of a cross-sectional study design using monocentric data collected prospectively is the primary source of limitations in this study. It is necessary to understand our observations as both descriptive and exploratory. Caution must be exercised when extrapolating to another institution. This study did not identify all of the causes or contributing variables to PMPS in certain areas. It is necessary to conduct more research.

#### CONCLUSION

At the Tertiary Oncologic Centre in Surabaya, the majority of patients with post-mastectomy pain syndrome were older, had luminal A type, and were at higher TNM stages. Most people with a VAS score of 4 report having pain that radiates from the surgery site. Most patients with PMPS had a Karnofsky score





of at least 70, and the pain usually manifests 9 months to a year after the surgery. Our research reveals no characteristics that PMPS patients share with previous studies in terms of their pain profile or demographics. These results might be specific to our neighborhood because PMPS is impacted by a wide range of internal and external variables. In the management of breast cancer, all stakeholders, particularly oncologic experts, ought to promote a more patient- and community-focused approach to PMPS research, prevention, and treatment in their local communities.

### ETHICAL CONSIDERATIONS

The ethics committee has approved this study with the code 1595/LOE/301.4.2/II/2024.

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