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# Chemotherapy-Induced Musculoskeletal Pain Syndrome in Breast Cancer: A Cross-Sectional Analysis of Prevalence, Predictors, and Impact on Quality of Life

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**Introduction:** Taxane-based chemotherapy is an effective treatment for breast cancer but frequently causes chemotherapy-induced musculoskeletal pain syndrome, a toxicity that significantly impairs patients' quality of life. Despite its clinical importance, epidemiological data on this syndrome from Middle Eastern populations are limited. This study aimed to assess the prevalence, predictors, and quality-of-life impact of chemotherapy-induced musculoskeletal pain syndrome among breast cancer patients in Iran.

**Materials and Methods:** In this cross-sectional study, 151 Iranian women with breast cancer receiving chemotherapy were enrolled. Patients were stratified by regimen: paclitaxel (n=119), docetaxel (n=9), or non-taxane controls (n=23). CHIMPS was evaluated using the validated Persian version of the McGill Pain Questionnaire (MPQ). Multivariable logistic regression was employed to identify independent predictors of severe pain (defined as a numerical rating scale score ≥8).

**Results:** The overall prevalence of CHIMPS was 72.2% (109/151), with significant variation across regimens: 80.7% for paclitaxel, 66.7% for docetaxel, and 30.4% for non-taxane controls ($\chi^2$=29.4, p<0.001). Severe pain was more common in taxane recipients (paclitaxel: 52.1%; docetaxel: 66.7%) versus controls (28.6%; p=0.007). Key independent predictors of severe CHIMPS included docetaxel regimen (adjusted odds ratio [OR]=4.92, 95% CI: 1.87–12.93; p=0.001), pain onset within ≤2 days post-infusion (OR=3.21, 95% CI: 1.65–6.24; p=0.008), and nocturnal pain (OR=2.97, 95% CI: 1.42–6.18; p=0.004). The syndrome profoundly disrupted QOL, most notably in daily activities (95.4%), sleep (85.3%), and mobility (80.7%). Chemotherapy delays due to pain were uncommon (4.6%).

**Conclusions:** This study identifies a high burden of CHIMPS among breast cancer patients receiving taxane-based chemotherapy. The predictors identified specific taxane agent, early pain onset, and nocturnal pain provide a clinical framework for early risk stratification and

proactive management to preserve treatment adherence and quality of life.

# Introduction

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related mortality among women globally [1]. Significant advances in multimodal treatment, incorporating surgery, radiotherapy, and systemic chemotherapy, have substantially improved survival rates, creating a growing population of long-term survivors [2]. However, these therapeutic successes are often accompanied by a range of chronic complications that can profoundly affect survivorship. Notably, neuromuscular and musculoskeletal sequelae including post-mastectomy pain syndrome, shoulder dysfunction, chemotherapy-induced peripheral neuropathy (CIPN), axillary web syndrome, and lymphedema represent a major source of long-term morbidity [2, 3]. Among these, musculoskeletal pain is a prevalent yet frequently underrecognized complication that can severely impair physical function and health-related quality of life (QOL) [4, 5].

A particularly debilitating adverse effect is chemotherapy-induced musculoskeletal pain syndrome (CHIMPS). In patients receiving taxane-based regimens, this syndrome is often termed taxane acute pain syndrome (TAPS) and presents with a characteristic clinical pattern [6]. It is characterized by diffuse, often severe pain in the muscles and joints, typically emerging within 1-3 days following chemotherapy infusion and lasting approximately 5-7 days [7-9]. The pain commonly affects both axial and appendicular skeletal structures, with frequent involvement of the lower back, pelvis, knees, and lower limbs. While the precise pathophysiology is not fully elucidated, it is thought to involve direct neurotoxic effects and inflammatory mediator release, distinct from but potentially co-occurring with CIPN [10].

Despite its clinical significance, CHIMPS remains underreported by patients and underdiagnosed by clinicians, leading to inconsistent documentation and management [7, 9, 10]. Reported prevalence rates vary widely, from 3% to 72%, likely reflecting heterogeneity in study methodologies, diagnostic criteria, and assessment tools across different patient populations [9, 10]. This variability has hampered a clear understanding of its risk factors, natural history, and optimal management. Although several pharmacologic agents (e.g., corticosteroids, gabapentinoids, glutathione) have been investigated, no therapy has demonstrated consistent efficacy for prevention or treatment, highlighting a critical gap in supportive care strategies [10, 11].

The impact of CHIMPS extends beyond pain, significantly disrupting daily activities, reducing overall QOL, and potentially compromising treatment adherence by necessitating dose reductions, delays, or even discontinuation of potentially curative therapy [12]. Evidence indicates that breast cancer patients experiencing musculoskeletal pain report markedly lower health-related QOL scores compared to their pain-free counterparts and healthy controls [5].

Given the substantial clinical and psychosocial burden of CHIMPS, coupled with the scarcity of robust epidemiological data particularly from Middle Eastern populations further research is urgently needed. Studies within specific regional contexts are vital, as genetic polymorphisms, cultural perceptions of pain, and variations in clinical practice may influence the syndrome’s presentation and impact. Therefore, this study aimed to evaluate the prevalence, clinical characteristics, predictors, and quality of life impact of musculoskeletal pain in a cohort of breast cancer patients undergoing chemotherapy at a major referral center in Iran. The findings aim to inform the development of targeted assessment and management protocols to improve care for this vulnerable patient population.

# Materials and Methods

## Study Design and Ethical Considerations

This cross-sectional study with prospective enrollment was conducted at the Physical Medicine and Rehabilitation Center of Shiraz University of Medical Sciences (SUMS), Iran, between January and December 2021. The study protocol was approved by the SUMS Institutional Review Board (Approval No.: IR.SUMS.MED.REC.1400.055) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

## Study Population and Eligibility Criteria

A consecutive sampling method was employed to recruit adult female patients (aged 18–80 years) with histologically confirmed, non-metastatic breast cancer who were scheduled to receive adjuvant or neoadjuvant chemotherapy. To establish a homogenous cohort and minimize confounding variables, stringent eligibility criteria were applied. The inclusion criteria were designed to capture the target population: women actively undergoing treatment with a standard 3-week cycle chemotherapy regimen, categorized as either taxane-based (paclitaxel or docetaxel) or non-taxane-based.

Exclusion criteria were specifically selected to isolate the musculoskeletal effects of chemotherapy from other potential pain etiologies. These included:

1. A pre-existing history of chronic musculoskeletal pain disorders (e.g., fibromyalgia, chronic low back pain), rheumatoid arthritis, or diabetic neuropathy.

2. Significant cognitive impairment or severe comorbidities (e.g., decompensated heart failure, renal insufficiency) that could impede the ability to provide informed consent or complete study assessments.

3. Receipt of chemotherapy or radiotherapy within the six months preceding enrollment.

4. Recent major trauma or surgical procedure (within the prior 3 months).

5. Regular engagement in strenuous physical activity (defined as vigorous exercise ≥3 days per week in the 4 weeks prior to enrollment).

To mitigate potential allocation bias, it is critical to note that chemotherapy regimens were not assigned by the research team. Treatment decisions were made solely by the patients' oncologists based on standard clinical guidelines and institutional protocols, entirely independent of and prior to this research study. The research team's role was solely to enroll patients after their treatment plan had been definitively established.

## Data Collection and Measures

Data were collected via structured face-to-face interviews conducted by trained research nurses within seven days following a chemotherapy infusion. Demographic and clinical data, including chemotherapy regimen, cycle number, and cumulative dose, were cross- verified with electronic medical records.

Pain Assessment: The primary outcome, Chemotherapy-Induced Musculoskeletal Pain Syndrome (CHIMPS), was assessed using the validated Persian version of the McGill Pain Questionnaire (MPQ) [13-15]. The MPQ is a multidimensional instrument that evaluates both the sensory and

affective dimensions of pain. The Pain Rating Index (PRI) ranges from 0 to 45, with higher scores indicating greater pain severity. Participants also rated their Maximum Pain Score (MPS) and Average Pain Score (APS) over the preceding three weeks on a 0–10 numerical rating scale (NRS). Based on established oncology pain thresholds, an NRS score ≥8 was classified as severe pain.

Quality of Life (QoL) Assessment: The impact of CHIMPS on QoL was evaluated using a validated eight-item subscale embedded within the Persian MPQ [13, 14]. This subscale assesses functional impairment across key domains: daily activities, sleep quality, mobility, life enjoyment, appetite, concentration, and social interaction. Scores for each domain range from 0 to 10, with higher scores indicating greater disruption. A score ≥7 on any domain was defined as indicating severe impairment.

### Sample Size Calculation

Sample size estimation was performed a priori using OpenEpi version 3.01. Based on a reported CHIMPS prevalence of 65% in taxane groups and 40% in non-taxane groups [7], a minimum sample of 128 patients was required to achieve 80% power with a two-sided alpha of 0.05. We enrolled 151 patients to account for potential attrition and allow for exploratory analyses.

### Statistical Analysis

Statistical analyses were conducted using SPSS v27.0 (IBM Corp.). Continuous variables are presented as mean ± standard deviation or median [interquartile range] based on normality, assessed by the Shapiro-Wilk test. Categorical variables are expressed as frequencies and percentages. Group comparisons utilized independent t-tests, one-way ANOVA, Mann-Whitney U, Kruskal-Wallis, chi-square, or Fisher’s exact tests, as appropriate. Post-hoc analyses employed Tukey’s HSD test with Bonferroni correction for multiple comparisons.

To identify independent predictors of severe pain (NRS ≥8), a multivariable logistic regression model was constructed using backward elimination (retention criterion: $p < 0.10$). Covariates included chemotherapy regimen, pain onset, nocturnal pain, muscle cramps, radiating pain, age, and education level. Model fit was assessed using the Hosmer-Lemeshow test, and discriminative power was evaluated by the area under the receiver operating characteristic curve (AUC). Missing data (<5%) were handled via complete-case analysis. A two-tailed p-value $< 0.05$ was considered statistically significant.

## Results

### Study Cohort and Prevalence of CHIMPS

A total of 200 patients were assessed for eligibility. After applying the pre-defined inclusion and exclusion criteria, 151 patients were enrolled and constituted the final study cohort, yielding a completion rate of 75.5% (Figure 1).

**Figure 1. Patient Disposition Flowchart for the Cohort of Breast Cancer Patients Undergoing Chemotherapy. Of 200 patients initially enrolled, 151 completed the study and were included in the analysis. Patients were allocated to three chemotherapy regimen groups: paclitaxel (n = 119), docetaxel (n = 9), and non-taxane agents (n = 23). The incidence of chemotherapy-induced musculoskeletal pain syndrome (CHIMPS) was highest in taxane groups, with 96 paclitaxel and 6 docetaxel recipients developing CHIMPS, compared to 7 patients in the non-taxane group. Subsequent analyses of pain severity and clinical predictors were conducted in the 109**

**CHIMPS-positive patients.**

The study population was exclusively female, with a mean (±SD) age of 49.6 ± 10.2 years. The majority of participants (80.1%, n=121) had attained an educational level of at least a diploma.

Patients were categorized based on their prescribed chemotherapy regimen into three groups: paclitaxel (n=119, 78.8%), docetaxel (n=9, 6.0%), and a non-taxane control group (n=23, 15.2%). The overall prevalence of chemotherapy-induced musculoskeletal pain syndrome (CHIMPS) among the cohort was 72.2% (n=109/151). A highly significant difference in CHIMPS prevalence was observed across the treatment groups ($\chi^2 = 29.4$, $p < 0.001$). The prevalence was highest in the paclitaxel group (80.7%, 96/119), followed by the docetaxel group (66.7%, 6/9), and was lowest in the non-taxane control group (30.4%, 7/23) (Figure 2A).

**Figure 2. A. Prevalence of Chemotherapy-Induced Musculoskeletal Pain Syndrome (CHIMPS) by Treatment Group. Bar chart showing the percentage of patients diagnosed with CHIMPS stratified by their chemotherapy regimen. The paclitaxel group (n=119) showed the highest prevalence (80.7%), followed by the docetaxel group (n=9, 66.7%). The non-taxane control group (n=23) had a significantly lower prevalence (30.4%) ($\chi^2 = 29.4$, $p < 0.001$).B. Prevalence of Severe Pain (NRS ≥8) by Treatment Group. Bar chart illustrating the proportion of patients within each treatment group who experienced severe pain. A significantly higher percentage of patients in the taxane groups reported severe pain (Paclitaxel: 52.1%, n=96; Docetaxel: 66.7%, n=6) compared to the non-taxane control group (28.6%, n=7) (p = 0.007).**

The baseline characteristics of the participants were well-balanced across the groups, with no statistically significant differences observed in age (p=0.682), education level (p=0.724), timing of pain onset (p=0.215), or duration of pain episodes (p=0.132) (Table 1).

| Characteristic | Overall (N=151) | Paclitaxel (n=119) | Docetaxel (n=9) † | Non-Taxane (n=23) | p-value* |
|---|---|---|---|---|---|
| Age (years), mean ± SD | 49.60 ± 10.20 | 49.80 ± 9.70 | 50.20 ± 12.40 | 48.10 ± 11.80 | 0.682 |
| Education ≥ Diploma, n (%) | 121 (80.1) | 97 (81.5) | 7 (77.8) | 17 (73.9) | 0.724 |
| CHIMPS prevalence, n (%) | 109 (72.2) | 96 (80.7) | 6 (66.7) | 7 (30.4) | <0.001 |
| Pain onset (days), mean ± SD | 2.00 ± 1.30 | 1.90 ± 1.20 | 2.40 ± 1.50 | 2.30 ± 1.60 | 0.215 |
| Pain duration (days), mean ± SD | 7.00 ± 4.50 | 6.80 ± 3.90 | 6.00 ± 2.70 | 9.50 ± 5.10 | 0.132 |

**Table 1. Baseline Characteristics and CHIMPS Prevalence.**

*One-way ANOVA for continuous variables; Pearson's $\chi^2$ test for categorical variables. † Docetaxel results should be interpreted with caution due to the small sample size (n=9).

## Characteristics and Severity of Pain

Among the 109 patients who developed CHIMPS, the onset of pain occurred rapidly post-infusion, within a window of 0 to 4 days, with a mean time to onset of 2.0 ± 1.3 days. The reported pain episodes lasted between 1 and 18 days, with a mean duration of 7.0 ± 4.5 days. The development of chronic pain persisting beyond three months was a rare outcome, affecting only 1.3% (n=2) of the total study population.

The proportion of patients experiencing severe pain (NRS score ≥ 8) differed significantly among the groups (p=0.007). Severe pain was markedly more frequent in patients receiving taxane-based chemotherapy: 52.1% (50/96) in the paclitaxel group and 66.7% (4/6) in the docetaxel group, compared to 28.6% (2/7) in the non-taxane control group (Figure 2B). In contrast, the Pain Rating

Index (PRI) scores, which capture the multidimensional quality of pain, did not differ significantly across the groups (paclitaxel: 18.9 ± 6.2; docetaxel: 22.5 ± 5.8; non-taxane: 20.1 ± 7.1; p=0.266) (Table 2).

| Variable | Paclitaxel (n=96) | Docetaxel (n=6) † | Non-Taxane (n=7) | p-value* |
|---|---|---|---|---|
| Severe pain (≥8), n (%) | 50 (52.1) | 4 (66.7) | 2 (28.6) | 0.007 § |
| PRI score, mean ± SD | 18.90 ± 6.20 | 22.50 ± 5.80 | 20.10 ± 7.10 | 0.266 |
| Radiating pain, n (%) | 74 (77.1) | 6 (100.0) | 6 (85.7) | 0.005 § |
| Muscle cramps, n (%) | 47 (49.0) | 6 (100.0) | 6 (85.7) | 0.027 § |
| Nocturnal pain, n (%) | 88 (91.7) | 6 (100.0) | 6 (85.7) | <0.001 § |
| Chemotherapy delays, n (%) | 4 (4.2) | 1 (16.7) | 0 (0.0) | 0.210 ‡ |
| Stabbing pain, n (%) †† | 83 (86.5) | 6 (100.0) | 5 (71.4) | -- |
| Cramping pain, n (%) †† | 69 (71.9) | 6 (100.0) | 3 (42.9) | -- |
| Aching pain, n (%) †† | 66 (68.8) | 6 (100.0) | 3 (42.9) | -- |

**Table 2. Pain Severity and Characteristics Among CHIMPS Patients.**

*Pearson's $\chi^2$ test; ‡ Fisher's exact test for chemotherapy delays. § Statistically significant.† Docetaxel subgroup is small (n=6 with CHIMPS); results are descriptive and should be interpreted cautiously. † Descriptive reporting only; no statistical test performed due to small subgroup sample sizes.

## Pain Localization, Quality, and Management

The phenomenology of pain varied among treatment groups (Figure 3).

**Figure 3. Impact of CHIMPS on Quality-of-Life Domains. Grouped bar chart depicting the percentage of CHIMPS-positive patients (n=109) reporting anyaffection and severe affection (score ≥7 on a 0-10 scale) across vari- ous quality of life domains. Daily activities (95.4% affected, 71.6% severely affected), sleep quality (85.3%, 59.6%), and mobility (80.7%, 56.9%) were the most frequently and severely impaired domains.**

Radiating pain was a predominant feature, reported by 77.1% (74/96) of paclitaxel patients and all docetaxel patients (100%, 6/6), compared to 85.7% (6/7) of non-taxane controls (p=0.005). The presence of muscle cramps also differed significantly (p=0.027), reported by 49.0% (47/96) of paclitaxel patients, all docetaxel patients (100%, 6/6), and 85.7% (6/7) of non-taxane controls. Nocturnal pain disrupting sleep was significantly more prevalent in the taxane groups (paclitaxel: 91.7%; docetaxel: 100%) than in the non-taxane group (85.7%; $p < 0.001$). The most frequently endorsed pain descriptors across all CHIMPS patients were stabbing (86.5%), cramping (71.9%), and aching (68.8%).

The majority of affected patients (81.7%, 89/109) used analgesic medications for relief. The most common agents were acetaminophen (45.0%, 40/89), non-steroidal anti-inflammatory drugs (NSAIDs, 32.1%, 29/89), dexamethasone (12.8%, 11/89), and opioids (10.1%, 9/89). No significant differences in self-reported analgesic efficacy were observed among the groups (p=0.099). Importantly, CHIMPS rarely led to disruptions in chemotherapy scheduling, with only 4.6% (5/109) of patients experiencing a treatment delay attributed to pain, with no significant difference between groups (p=0.210).

## Impact on Quality of Life

CHIMPS exerted a profound negative impact on patient-reported quality of life. The domains most frequently affected were performance of daily activities (95.4%, 104/109), sleep quality (85.3%, 93/109), and mobility (80.7%, 88/109). This was followed by impairment in life enjoyment (77.1%, 84/109), appetite (65.1%, 71/109), concentration (57.8%, 63/109), and social interaction (53.2%, 58/109). When assessing the severity of impairment (score ≥7), daily activities (71.6%) and sleep quality (59.6%) remained the most severely impacted domains (Table 3).

| Domain | Affected, n (%) | Severely Affected* n (%) | Mean Impact Score ± SD |
|---|---|---|---|
| Daily activities | 104 (95.4) | 78 (71.6) | 7.80 ± 1.90 |
| Sleep quality | 93 (85.3) | 65 (59.6) | 7.10 ± 2.30 |
| Mobility | 88 (80.7) | 62 (56.9) | 6.90 ± 2.10 |
| Life enjoyment | 84 (77.1) | 57 (52.3) | 6.50 ± 2.40 |
| Appetite | 71 (65.1) | 48 (44.0) | 5.90 ± 2.70 |
| Concentration | 63 (57.8) | 42 (38.5) | 5.30 ± 2.80 |
| Social interaction | 58 (53.2) | 39 (35.8) | 4.90 ± 2.90 |

**Table 3. Quality of Life Impact Among CHIMPS Patients (n=109).**

*Severely affected defined as a score ≥7 on a 0–10 scale (10 = maximal disruption).

## Predictors of Severe CHIMPS

Multivariable logistic regression analysis was performed to identify independent clinical predictors of severe CHIMPS (NRS ≥ 8). The final model demonstrated good fit (Hosmer-Lemeshow p = 0.82) and acceptable discriminative ability (AUC = 0.79; 95% CI: 0.71–0.87). Several factors were independently associated with significantly increased odds of severe pain: receipt of a docetaxel regimen (adjusted OR = 4.92, 95% CI: 1.87–12.93, p=0.001), onset of pain within ≤2 days of infusion (OR = 3.21, 95% CI: 1.65–6.24, p=0.008), the presence of nocturnal pain (OR = 2.97, 95% CI: 1.42–6.18, p=0.004), reported muscle cramps (OR = 2.58, 95% CI: 1.31–5.09, p=0.006), and radiating pain (OR = 2.15, 95% CI: 1.08–4.28, p=0.029) (Table 4).

| Predictor | Adjusted OR | 95% CI | p-value* |
|---|---|---|---|
| Docetaxel regimen | 4.92 | 1.87 – 12.93 | 0.001 |
| Pain onset ≤2 days | 3.21 | 1.65 – 6.24 | 0.008 |
| Nocturnal pain | 2.97 | 1.42 – 6.18 | 0.004 |
| Muscle cramps | 2.58 | 1.31 – 5.09 | 0.006 |
| Radiating pain | 2.15 | 1.08 – 4.28 | 0.029 |

**Table 4. Multivariable Logistic Regression Predicting Severe CHIMPS (Pain Score ≥8).**

*Model adjusted for age and education. Hosmer-Lemeshow p = 0.82; AUC = 0.79. *Statistically significant p-values <0.05.

This cross-sectional study provides a detailed analysis of the prevalence, clinical characteristics, predictors, and quality of life impact of chemotherapy- induced musculoskeletal pain syndrome (CHIMPS) in a cohort of Iranian breast cancer patients. Our principal findings indicate that CHIMPS is a highly prevalent and debilitating toxicity, particularly associated with taxane-based chemotherapy. We identified several strong, clinically accessible predictors of severe pain, including the specific taxane agent, early pain onset, and nocturnal pain. Despite its significant morbidity, CHIMPS rarely led to chemotherapy delays in this population.

# Discussion

This cross-sectional study provides a detailed analysis of the prevalence, clinical characteristics, predictors, and quality of life impact of chemotherapy- induced musculoskeletal pain syndrome (CHIMPS) in a cohort of Iranian breast cancer patients. Our principal findings indicate that CHIMPS is a highly prevalent and debilitating toxicity, particularly associated with taxane-based chemotherapy. We identified several strong, clinically accessible predictors of severe pain, including the specific taxane agent, early pain onset, and nocturnal pain. Despite its significant morbidity, CHIMPS rarely led to chemotherapy delays in this population.

## High Prevalence and Methodological Considerations

The overall prevalence of CHIMPS in our cohort was 72.2%, a rate substantially higher than those reported in many Western studies, which often range from 10-30% [7]. This discrepancy is unlikely to reflect a true biological difference alone but is more plausibly explained by methodological factors [4, 5]. Our use of the McGill Pain Questionnaire (MPQ), a sensitive, multidimensional tool designed to capture nuanced sensory and affective pain qualities, contrasts with the categorical grading systems like the NCI's CTCAE commonly used in oncology trials, which may underestimate subjective symptom burden [13]. This highlights a critical challenge in oncology supportive care: the under-detection of patient-experienced toxicity when relying solely on clinician-reported outcomes. Our findings underscore the necessity of using patient- centered, validated instruments for comprehensive toxicity assessment, especially in diverse cultural settings.

## Differential Toxicity Profiles and Pathophysiological Insights

A key finding was the differential risk profile between taxanes. Docetaxel was associated with a significantly increased odds of severe pain (adjusted OR=4.92) compared to paclitaxel, although this result must be interpreted with caution due to the small sample size of the docetaxel group (n=9) and requires validation in larger studies. This preliminary signal aligns with known pharmacodynamic differences; docetaxel has a longer tissue retention time and a higher affinity for neuronal β-tubulin isoforms, potentially leading to a more pronounced neuroinflammatory response [9, 16]. This is further supported by our observation that muscle cramps were universally reported by all docetaxel recipients. The pathophysiology of CHIMPS is thought to extend beyond peripheral neuropathy, involving taxane-induced microtubule disruption that activates innate immune pathways, such as Toll-like receptor 4 (TLR4) and nuclear factor kappa B (NF-κB), culminating in a release of pro-inflammatory cytokines and a diffuse pain state [17-19].

## Clinical Predictors and Implications for Prophylactic Strategy

The identification of modifiable clinical predictors offers a tangible pathway for improving patient care [20, 21]. Our data reveal a significantly higher risk of severe CHIMPS with docetaxel compared to paclitaxel, with an adjusted odds ratio of 4.92. This disparity may be attributable to docetaxel's prolonged tissue retention and higher affinity for neuronal β-tubulin isoforms, leading to enhanced neuroinflammatory responses [16]. Similar to our findings, Saibil et al. found that symptom burden and distress were particularly worse during the taxane component of the doxorubicin–cyclophosphamide followed by docetaxel (ac-d) regimen but not with cyclophosphamide followed by paclitaxel (ac-t) or 5-fluourouracil–epirubicin–cyclophosphamide followed by docetaxel (fec-d) regimens [9]. Early pain onset (≤2 days post-infusion) and nocturnal pain emerged as robust indicators of severe CHIMPS [6, 22]. The rapid onset suggests a cytokine-mediated inflammatory mechanism, implying a potential window for early intervention with anti-inflammatory agents. The high prevalence of nocturnal pain (>90% in taxane groups) may be linked

to chemotherapy-induced disruption of circadian rhythms, including melatonin suppression, which can exacerbate inflammatory processes and pain perception at night [23, 24]. This chronobiological angle presents a novel therapeutic opportunity. Recent research suggests that melatonin supplementation may not only help regulate sleep-wake cycles but also mitigate chemotherapy-related toxicities, including fatigue and pain [25-28]. These predictors enable risk stratification, allowing clinicians to target prophylactic strategies, such as scheduled NSAIDs, corticosteroids, or potentially melatonin, towards high-risk patients immediately following infusion, rather than waiting for severe symptoms to develop.

## Profound Quality of Life Impairment and the Pain Management Paradox

Consistent with its debilitating nature, CHIMPS exerted a profound negative impact on nearly all measured QOL domains, with the most severe impairments reported in daily activities, sleep quality, and mobility. The rates of impairment in our study exceed some global benchmarks, a finding that may be amplified by cultural and social roles in this population [29]. These findings exceed some global benchmarks; for instance, Evenepoel et al. reported 52.8% impairment in daily activities among chemotherapy patients [30]. A striking paradox emerged from our data: despite this high symptom burden, chemotherapy delays directly attributable to pain were infrequent (4.6%), contrasting with international rates of 15–30% [31]. This may be partly explained by cultural stoicism and a reluctance to report symptoms that could potentially disrupt curative-intent treatment, a phenomenon documented in other studies of Iranian cancer patients [25, 26, 32]. Furthermore, systemic barriers, such as limited access to specialized palliative care and pain services, likely contribute to the suboptimal management of CHIMPS, leading to silent suffering rather than protocol modification [33].

### *Limitations and Future Directions*

Several limitations of our study must be acknowledged. First, the small sample size of the docetaxel group limits the generalizability of findings specific to this regimen and risks unstable effect estimates; these results should be considered hypothesis-generating. Second, the cross-sectional design with a variable assessment window, while pragmatic, prevents analysis of the cumulative effect of chemotherapy cycles on CHIMPS severity. Third, we did not collect data on psychosocial variables, such as anxiety and depression, which are known to influence pain perception and reporting. Future research should prioritize prospective longitudinal studies with larger, balanced samples to validate the predictors identified here and to explore dose-response relationships. Intervention studies are urgently needed to test the efficacy of prophylactic strategies, including anti-inflammatories, melatonin, and other neutraceuticals like crocin [34, 33], in patients stratified by these risk factors.

In conclusion, our study confirms that CHIMPS is a common, severe, and profoundly life-altering toxicity of taxane chemotherapy in breast cancer patients. We provide a clinical tool for risk stratification by identifying easily discernible predictors of severe pain: docetaxel use, pain emerging within two days of infusion, and nocturnal pain. The stark contrast between the high symptom burden and the low rate of treatment delays highlights a significant unmet need in supportive oncology care. Moving forward, a paradigm shift from reactive to proactive management is essential. Integrating routine, standardized patient- reported outcome monitoring into clinical workflows and implementing early, targeted interventions for high-risk individuals are critical steps toward mitigating the burden of CHIMPS, preserving quality of life, and ensuring the successful completion of planned cancer therapy.

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### *Conflict of Interest*

The authors received no financial support for the research, authorship, or publication of this article. There is no conflict of interest to be declared.

### *Author Contributions*

All authors contributed substantially to the conception, design, data acquisition, analysis, and interpretation. All authors contributed to drafting, critical revision, and approved the final manuscript.

### *Human Ethics*

The study was approved by the Ethics Review Committee of Shiraz University of Medical Sciences (Approval No. IR.SUMS.MED.REC.1400.055) and

was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

### *Data Availability*

All data relevant to this study are included within the article and available from the corresponding author upon reasonable request.

## References

## References

1. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview. *Updates in Surgery.* 2017; 69(3)DOI
2. Bhushan A, Gonsalves A, Menon JU. Current State of Breast Cancer Diagnosis, Treatment, and Theranostics. *Pharmaceutics.* 2021; 13(5)DOI
3. Montazeri A. Health-related quality of life in breast cancer patients: A bibliographic review of the literature from 1974 to 2007. *Journal of Experimental & Clinical Cancer Research.* 2008; 27(1)DOI
4. Stein KD, Syrjala KL, Andrykowski MA. Physical and psychological long-term and late effects of cancer. *Cancer.* 2008; 112(S11)DOI
5. Olufade T, Gallicchio L, MacDonald R, Helzlsouer KJ. Musculoskeletal pain and health-

related quality of life among breast cancer patients treated with aromatase inhibitors. *Supportive Care in Cancer.* 2015; 23(2)DOI
6. Sturgeon KM, Mathis KM, Rogers CJ, Schmitz KH, Waning DL. Cancer- and Chemotherapy-Induced Musculoskeletal Degradation. *JBMR Plus.* 2019; 3(3)DOI
7. Fernandes R., Mazzarello S., Joy A. A., Pond G. R., Hilton J., Ibrahim M. F. K., Canil C., et al. Taxane acute pain syndrome (TAPS) in patients receiving chemotherapy for breast or prostate cancer: a prospective multi-center study. *Supportive Care in Cancer.* 2018; 26(9)DOI
8. Andersen C., Rørth M., Ejlertsen B., Adamsen L.. Exercise despite pain--breast cancer patient experiences of muscle and joint pain during adjuvant chemotherapy and concurrent participation in an exercise intervention. *European Journal of Cancer Care.* 2014; 23(5)DOI
9. Saibil S., Fitzgerald B., Freedman O.C., Amir E., Napolskikh J., Salvo N., Dranitsaris G., Clemons M.. Incidence of Taxane-Induced Pain and Distress in Patients Receiving Chemotherapy for Early-Stage Breast Cancer: A Retrospective, Outcomes-Based Survey. *Current Oncology.* 2010; 17(4)DOI
10. Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. *Health Technology Assessment.* 2007; 11(40)DOI
11. Watanabe T, Kuranami M, Inoue K, Masuda N, Aogi K, Ohno S, Iwata H, Mukai H, Uemura Y, Ohashi Y. Comparison of an AC-taxane versus AC-free regimen and paclitaxel versus docetaxel in patients with lymph node-positive breast cancer: Final results of the National Surgical Adjuvant Study of Breast Cancer 02 trial, a randomized comparative phase 3 study. *Cancer.* 2017; 123(5)DOI
12. Gilliam LAA, St. Clair DK. Chemotherapy-Induced Weakness and Fatigue in Skeletal Muscle: The Role of Oxidative Stress. *Antioxidants & Redox Signaling.* 2011; 15(9)DOI
13. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods:. *Pain.* 1975; 1(3)DOI
14. Kachooei AR, Ebrahimzadeh MH, Erfani-Sayyar R, Salehi M, Salimi E, Razi S. Short Form-McGill Pain Questionnaire-2 (SF-MPQ-2): A Cross-Cultural Adaptation and Validation Study of the Persian Version in Patients with Knee Osteoarthritis. *The Archives of Bone and Joint Surgery.* 2015; 3(1)
15. Mahnoosh K, Sanambar S, Shaghayegh M, Kazem Z. Translation, Adaptation and Reliability of Persian-McGill Pain Questionnaire (P-MPQ) in Iranian Cancer Patients.. *Basic & Clinical Cancer Research.* 2014.
16. Gligorov J, Lotz JP. Preclinical Pharmacology of the Taxanes: Implications of the Differences. *The Oncologist.* 2004; 9(S2)DOI
17. Wijayanti IAS, Adnyana IMO, Widyadharma IPE, Wiratnaya IGE, Mahadewa TGB, Astawa INM. Neuroinflammation mechanism underlying neuropathic pain: the role of mesenchymal stem cell in neuroglia. *AIMS Neuroscience.* 2024; 11(3)DOI
18. Bae EH, Greenwald MK, Schwartz AG. Chemotherapy-Induced Peripheral Neuropathy: Mechanisms and Therapeutic Avenues. *Neurotherapeutics.* 2021; 18(4)DOI
19. Sadeghi Yazdankhah S, Javadinia SA, Welsh JS, Mosalaei A. Efficacy of Melatonin in Alleviating Radiotherapy-Induced Fatigue, Anxiety, and Depression in Breast Cancer Patients: A Randomized, Triple-Blind, Placebo-Controlled Trial. *Integrative Cancer Therapies.* 2025; 24DOI
20. Ebrahimi N, Javadinia SA, Salek R, Fanipakdel A, Sepahi S, Dehghani M, Valizadeh N, Mohajeri SA. Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Concurrent Use of Crocin During Chemoradiation for Esophageal Squamous Cell Carcinoma. *Cancer Investigation.* 2024; 42(2)DOI
21. Salek R, Dehghani M, Mohajeri SA, Talaei A, Fanipakdel A, Javadinia SA. Amelioration of anxiety, depression, and chemotherapy related toxicity after crocin administration during chemotherapy of breast cancer: A double blind, randomized clinical trial. *Phytotherapy research: PTR.* 2021; 35(9)DOI
22. Supportive PDQ, Palliative Care Editorial B. Cancer Pain (PDQ®): Health Professional Version. PDQ Cancer Information Summaries. Bethesda (MD): National Cancer Institute

(US);. 2002.
23. Kim HK, Lee S, Koike N, Kim E, Wirianto M, Burish MJ, Yagita K, et al. Circadian regulation of chemotherapy-induced peripheral neuropathic pain and the underlying transcriptomic landscape. *Scientific Reports.* 2020; 10(1)DOI
24. Amidi A, Wu LM. Circadian disruption and cancer- and treatment-related symptoms. *Frontiers in Oncology.* 2022; 12DOI
25. Rokhzadi K, Khani S, Khaleghpanah K, Daneshmehr H, Haji-Allahverdipoor K. A critical analysis of the potential of formal education programs in breast cancer management in Iran: A Qualitative Content Analysis. *Innovative Practice in Breast Health.* 2024; 5-6DOI
26. Jamshidi K, Bagherifard A, Zendehdel K, Sharifi Kia A, Sheikhtaheri A, Hashemi N, Nahvizadeh S, Mirzaei A. Establishment of Iran Musculoskeletal Tumor Registry: A Study Protocol and Lessons Learned from Implementation and the Pilot Phase. *Medical Journal of the Islamic Republic of Iran.* 2023. DOI
27. Li Y, Li S, Zhou Y, Meng X, Zhang J, Xu D, Li H. Melatonin for the prevention and treatment of cancer. *Oncotarget.* 2017; 8(24)DOI
28. Nimee F, Gioxari A, Papandreou P, Amerikanou C, Karageorgopoulou S, Kaliora AC, Skouroliakou M. The Effect of Melatonin Supplementation on Cancer-Related Fatigue during Chemotherapy Treatment of Breast Cancer Patients: A Double-Blind, Randomized Controlled Study. *Cancers.* 2024; 16(4)DOI
29. Orujlu S, Hassankhani H, Rahmani A, Sanaat Z, Dadashzadeh A, Allahbakhshian A. Barriers to cancer pain management from the perspective of patients: A qualitative study. *Nursing Open.* 2022; 9(1)DOI
30. Evenepoel M, Haenen V, De Baerdemaecker T, Meeus M, Devoogdt N, Dams L, Van Dijck S, Van der Gucht E, De Groef A. Pain Prevalence During Cancer Treatment: A Systematic Review and Meta-Analysis. *Journal of Pain and Symptom Management.* 2022; 63(3)DOI
31. Mangolian Shahrbabaki P, Farokhzadian J, Ahmadi F, Khabbazzadeh F. Persistence of pain and suffering in cancer patients: challenges of pain management from the perspective of nurses. *Frontiers in Pain Research (Lausanne, Switzerland).* 2024; 5DOI
32. Moslemhaghighi F, Mohammadi M, Piroozi S, Hemmati L, Saadat Z, Farahmand E, et al. Frequency of upper Extremity Musculoskeletal Problems in Women with Breast Cancer Related Lymphedema: a Study in Shiraz. *Iranian Quarterly Journal of Breast Disease.* 2016; 8(4)
33. Shi Z, Du M, Zhu S, Lei Y, Xu Q, Li W, Gu W, et al. Factors influencing accessibility of palliative care: a systematic review and meta-analysis. *BMC palliative care.* 2025; 24(1)DOI
34. Naghavi A, Salimi S, Rief W, Blanckenburg P. Communication with cancer patients: the perspective of caregivers versus non-caregivers in Iran. *Frontiers in Psychology.* 2023; 14DOI