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ORIGINAL RESEARCH

Management Strategies for Aromatase Inhibitor-Associated Musculoskeletal Symptoms and Their Impact on Treatment Persistence in Postmenopausal Breast Cancer: A Single-Center Retrospective Cohort Study

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Background: Aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) frequently lead to discontinuation of adjuvant endocrine therapy in postmenopausal breast cancer (BC) patients. This retrospective study assessed the impact of initial combined versus monotherapy management on aromatase inhibitor (AI) treatment persistence and explored whether baseline pain interference moderates this effect.

Methods: In this single-center, retrospective cohort study of 253 postmenopausal hormone receptor-positive BC patients with AIMSS, Patients were categorized into the monotherapy group (n = 182) or the combined therapy group (n = 71) based on initial management. Combined therapy was defined as the simultaneous use of ≥2 different categories of management interventions initiated at the time of AIMSS diagnosis (eg, analgesics, physical therapy, or AI regimen adjustment). The primary outcome was treatment interruption-free survival. Kaplan-Meier and Cox regression analyses were conducted to test for an interaction between management strategy and baseline Brief Pain Inventory (BPI) interference score (high: ≥ 7; low: < 7).

Results: Treatment interruptions occurred in 68 (26.9%) patients. Combined therapy was associated with superior interruption-free survival (Log-rank $P = 0.037$). A significant interaction was found between management strategy and baseline pain interference (interaction $HR = 0.192$, *95% CI*: 0.051–0.722, $P = 0.015$). Subgroup analysis revealed combination therapy significantly reduced interruption risk only in the high interference group ($HR = 0.125$, *95% CI*: 0.042–0.378, $P < 0.001$), not in the low interference group ($HR = 0.731$, $P = 0.454$). Combination therapy also yielded greater pain reduction at 3 months ($P < 0.001$).

Conclusion: Initiating multimodal combination management for AIMSS patients with severe baseline pain interference significantly improves AI treatment persistence and provides greater short-term symptom relief, supporting stratified management based on symptom severity.

Keywords: breast cancer, aromatase inhibitor, musculoskeletal symptoms, pain management

Introduction

Breast cancer (BC) is the most common malignancy among women worldwide, with its incidence strongly associated with increasing age, making postmenopausal women the primary group of new cases.[1] Aromatase inhibitors (AIs) are the mainstay of postoperative adjuvant endocrine therapy for these patients, significantly reducing recurrence risk and

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improving survival.[2] However, adverse events associated with long-term AI use, particularly AI-associated musculoskeletal symptoms (AIMSS),[3] pose a major challenge in clinical practice.

AIMSS primarily manifest as joint pain, morning stiffness, bone aches and limited mobility, with reported incidence of 20%-50%, often leading to reduced quality of life.[4,5] Symptoms typically begin within months of treatment initiation. Their pathogenesis is not fully understood, with current research suggesting possible links to inflammation triggered by a sharp decline in estrogen, alterations in the local joint microenvironment, individual genetic susceptibility, history of chemotherapy, and more recent menopause.[6–9] AIMSS has a substantial negative impact on quality of life and also pose a serious threat to treatment adherence. A considerable proportion of patients discontinue or become non-adherent to AI therapy due to intolerable musculoskeletal symptoms, which may be associated with increased mortality.[4,10] Consequently, improving AI treatment persistence—often evaluated as treatment interruption-free survival in clinical studies—represents a critical objective in AIMSS management. Therefore, effective interventions are of paramount clinical value for maintaining treatment continuity and ensuring optimal outcomes.

Current management strategies for AIMSS are diverse, including analgesic medication,[11] non-pharmacological interventions (eg, exercise therapy),[12,13] and AI dosing adjustments.[14] However, existing studies have largely focused on evaluating single interventions in isolation, and direct evidence comparing monotherapy with multimodal combination strategies in real-world settings remains scarce.[15] A recent scoping review of prospective AIMSS studies noted that many positive findings originated from uncontrolled trials awaiting replication, and most intervention durations were brief relative to the expected 5–10 year course of AI therapy.[11] Furthermore, current clinical guidelines from the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) provide general recommendations for AIMSS management but do not yet incorporate stratified approaches based on baseline symptom severity.[16] Furthermore, existing evidence primarily focuses on short-term symptom relief, while evaluation based on real-world data regarding whether different management strategies can improve long-term treatment adherence is lacking. Notably, it remains unclear which patient characteristics might modify the efficacy of different management strategies, thus hindering the development of personalized treatment approaches.

The Brief Pain Inventory (BPI) interference score grades pain severity by its impact on daily function. Using pooled data from Phase III cancer trials, Shi et al identified a score of ≥7 as the cutpoint for severe interference, which correlates with worse performance status.[17] We therefore selected baseline pain interference as a potential effect modifier, hypothesizing that patients with severe interference may benefit more from multimodal than monotherapy. Therefore, this study aims to investigate the association between initial management strategy for AIMSS (monotherapy vs. combined therapy) and treatment persistence in real-world clinical practice, and to examine the moderating effect of baseline pain interference on this association. We hope to provide real-world evidence for clinical AIMSS management and a reference for future individualized intervention.

Materials and Methods

Study Design and Population

This was a single-center retrospective cohort study. The study protocol was approved by the Ethics Committee of The Third Affiliated Hospital of Wenzhou Medical University (No. 2025-029), and the requirement for informed consent was waived due to the retrospective nature of the study, which involved the use of existing medical records and posed minimal risk to participants. All patient data were anonymized and de-identified prior to analysis, and strict confidentiality of personal information was maintained throughout the study in accordance with institutional guidelines and the Declaration of Helsinki. Postmenopausal women with hormone receptor (HR)-positive invasive BC newly initiating adjuvant AI therapy between November 1, 2021 and November 1, 2023, were consecutively screened via the hospital's electronic medical record (EMR) system. All clinical, pathological and treatment data were extracted from EMRs and outpatient follow-up records.

Inclusion criteria: (1) Postmenopausal women aged ≥ 18 years (menopause defined as natural amenorrhea for ≥ 1 year or status post bilateral oophorectomy); (2) Histopathologically confirmed HR-positive invasive BC; (3) Initiation of standard-dose adjuvant AI therapy postoperatively; (4) Development of new or worsening AIMSS clearly diagnosed and

documented during treatment; (5) Receipt of at least one clearly documented management intervention for these symptoms; (6) Complete medical records and a follow-up of ≥ 18 months from AIMSS diagnosis.

Exclusion criteria: (1) Initial diagnosis of stage IV BC; (2) Recurrence/metastasis after starting AI therapy but before the onset of musculoskeletal symptoms; (3) Pre-existing active rheumatic disease or musculoskeletal conditions causing chronic pain or functional impairment prior to AI initiation; (4) Long-term use (≥ 1 month) of glucocorticoids or immunosuppressants; (5) Discontinuation/change of AI therapy during the study period due to reasons other than musculoskeletal symptoms, such as tumor progression or severe hepatic/renal dysfunction; (6) Missing key data exceeding 20%; (7) Concurrent participation in other clinical trials that might interfere with AIMSS management.

Grouping

Patients were grouped based on the initial clinical management plan implemented after AIMSS diagnosis. Group assignment was determined by two independent researchers reviewing medical records, with discrepancies resolved through discussion or adjudication by a third senior researcher.

Monotherapy group: Patients received, at initiation and persistently thereafter following AIMSS diagnosis, only one core management measure. Core intervention categories included: (1) Analgesic medication (eg, Celebrex capsules and Loxoprofen tablets); (2) Physical therapy (eg, exercise guidance, physiotherapy); (3) Adjustment of AI dosing regimen (eg, dose reduction or intermittent dosing); (4) Complementary/alternative therapies (eg, vitamin D supplementation).

Combined therapy group: Patients received, from the initial phase after AIMSS diagnosis, simultaneous application of ≥ 2 different categories of core management measures. Typical combinations included: analgesic medication combined with physical therapy, analgesic medication combined with AI regimen adjustment, physical therapy combined with complementary therapy, or combinations of three or more modalities.

Data Collection

(1) Baseline data: Age, body mass index (BMI), TNM stage, type of surgery, receipt of chemotherapy/radiotherapy, initial AI drug type, and time from AI initiation to AIMSS onset were collected.

(2) Symptom assessment: Symptoms were assessed using the BPI. Two core metrics were collected at baseline and during follow-up: ① Average pain score (average pain intensity in the past 24 hours, 0–10, where 0 = no pain, 10 = worst pain imaginable); ② Pain interference score (degree of interference with daily activities, mood, sleep, etc., across 6 domains, 0–10, higher scores indicating greater interference).

(3) Management measures: All documented measures for managing AIMSS were extracted from medical records, including their type (eg, specific drug name, physical therapy, AI regimen adjustment, etc.), and documented start time and usage.

(4) Outcome events: The primary outcome was treatment interruption-free survival, defined as the time from AIMSS diagnosis to the earliest occurrence of: ① Permanent AI discontinuation due to AIMSS (based on the treating physician's clear documentation of discontinuation reason; defined as discontinuation lasting ≥ 3 months or explicit record of AI termination due to AIMSS intolerance); ② Radiologically or pathologically confirmed BC recurrence/metastasis; ③ Death from any cause.

Statistical Analysis

Analyses were conducted using SPSS 26.0 and GraphPad Prism 10.1.2. Continuous and categorical variables were presented as mean ± standard deviation and frequency (%), compared via independent samples *t*-tests and chi-square /Fisher's exact tests, respectively. Survival curves were plotted using the Kaplan-Meier method and compared via the Log rank test. Univariate Cox regression analysis was performed first, followed by multivariate Cox proportional hazards modeling adjusting for variables with $P < 0.05$ in univariate analysis and those of clinical importance. Based on prior literature,[18] a BPI pain interference score ≥ 7 was defined as severe interference, categorizing patients into high and low interference groups to assess effect modification. To assess model stability and minimize overfitting, we confirmed that the final multivariate Cox model maintained an events-per-variable (EPV) ratio exceeding the recommended threshold of 10. An interaction term between management strategy and baseline pain interference group was introduced into the

multivariate model to test for interaction. Stratified Cox regression was performed within each pain interference group. Repeated-measures analysis of variance (ANOVA) was used to compare changes in BPI scores from baseline to month 3, focusing on the time-by-group interaction. All tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

Patient Baseline Characteristics

The study ultimately included 253 postmenopausal BC patients who developed AIMSS, with 182 (71.9%) assigned to the monotherapy group and 71 (28.1%) to the combined therapy group. The two groups showed no statistically significant differences in baseline characteristics such as age, BMI, receipt of radiotherapy, initial AI type, or type of surgery (all $P > 0.05$) (Table 1). At AIMSS diagnosis, the combined therapy group had significantly higher baseline BPI average pain score (6.23 ± 1.30 vs. 5.52 ± 1.42, $P < 0.001$) and pain interference score (6.93 ± 1.36 vs. 6.09 ± 1.32, $P < 0.001$) compared to the monotherapy group. Additionally, the proportion of stage III patients was higher in the combined therapy group (16.9% vs. 7.7%, $P = 0.038$).

Treatment Interruption-Free Survival Analysis

A total of 68 (26.9%) treatment interruption events due to AIMSS occurred. Kaplan-Meier analysis (Figure 1) showed that the treatment interruption-free survival rate was significantly higher in the combined therapy group compared to the monotherapy group (Log rank test, $P = 0.037$).

Interaction and Subgroup Analysis Based on Baseline Pain Interference

Univariate Cox regression analysis showed that the combined therapy strategy (*HR* = 0.528, *95% CI*: 0.283–0.986, $P = 0.045$) was a protective factor reducing the risk of treatment failure (Table 2). Higher baseline BPI average pain score (*HR* = 1.367, $P < 0.001$) and pain interference score (*HR* = 1.203, $P = 0.041$) were associated with increased risk.

Given that in clinical decision-making, patients with more severe symptoms are more likely to receive combined therapy, we further investigated whether baseline symptom burden modified the effect of management strategy. The multivariate Cox regression model (Table 3) revealed a significant interaction between management strategy and baseline

Table 1 Comparison of Patient Baseline Characteristics

Baseline Characteristic	Monotherapy (n = 182)	Combined Therapy (n = 71)	t/χ^2	*p*
Age (years)	62.93 ± 4.01	63.31 ± 3.95	−0.682	0.496
BMI (kg/m^2)	24.29 ± 2.74	23.89 ± 2.49	1.079	0.282
TNM stage			6.522	0.038
0/I	100 (54.9%)	29 (40.8%)		
II	68 (37.4%)	30 (42.3%)		
III	14 (7.7%)	12 (16.9%)		
Chemotherapy	76 (41.8%)	39 (54.9%)	3.574	0.059
Radiotherapy	123 (67.6%)	51 (71.8%)	0.429	0.512
Initial AI type			1.475	0.478
Anastrozole	161 (88.5%)	59 (83.1%)		
Exemestane	9 (4.9%)	6 (8.5%)		
Letrozole	12 (6.6%)	6 (8.5%)		
Type of surgery			0.307	0.579
Lumpectomy	112 (61.5%)	41 (57.7%)		
Mastectomy	70 (38.5%)	30 (42.3%)		
Time to AIMSS onset (months)	4.11 ± 1.45	3.80 ± 1.57	1.478	0.141
BPI average pain score	5.52 ± 1.42	6.23 ± 1.30	−3.656	< 0.001
BPI pain interference score	6.09 ± 1.32	6.93 ± 1.36	−4.516	< 0.001

Abbreviations: BMI, Body mass index; AI, Aromatase inhibitor; AIMSS, Aromatase inhibitor-associated musculoskeletal symptoms; BPI, Brief Pain Inventory.

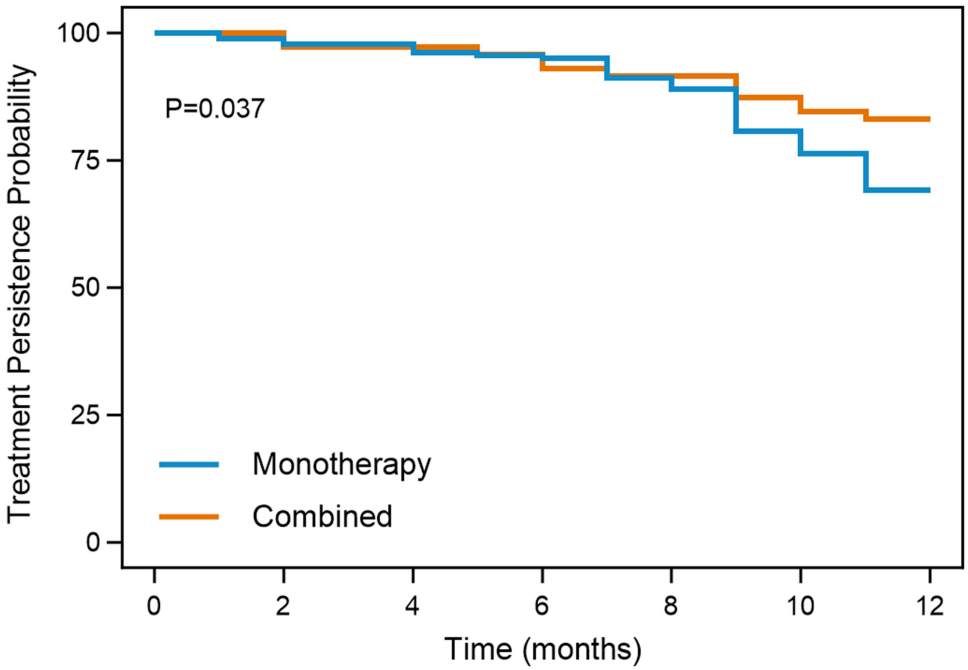

Figure 1 Kaplan-Meier curves for treatment interruption-free survival by AIMSS management strategy.
Abbreviation: AIMSS, Aromatase inhibitor-associated musculoskeletal symptoms.

pain interference group (high interference ≥ 7 vs. low interference < 7) (interaction term *HR* = 0.192, *95% CI*: 0.051–0.722, *P* = 0.015). This indicates that the effect of management strategy on treatment interruption risk differs depending on the baseline level of pain interference.

Table 2 Univariate Cox Regression Analysis

Variable	HR (95% CI)	*P*
Management strategy (combined vs. monotherapy)	0.528 (0.283–0.986)	0.045
Baseline pain interference group [high (≥7) vs. Low (<7)]	1.215 (0.754–1.959)	0.423
BPI average pain score	1.367 (1.151–1.624)	< 0.001
BPI pain interference score	1.203 (1.007–1.436)	0.041
Age	1.056 (0.995–1.121)	0.071
BMI	0.956 (0.875–1.045)	0.321
TNM stage (II/III vs. 0/I)	0.625 (0.386–1.013)	0.057
Chemotherapy	1.530 (0.949–2.465)	0.081
Radiotherapy	1.042 (0.623–1.742)	0.877
Initial AI type (letrozole vs. others)	0.825 (0.421–1.613)	0.573
Type of surgery	0.996 (0.613–1.619)	0.987
Time to AIMSS onset	1.096 (0.935–1.285)	0.258

Abbreviations: BPI, Brief Pain Inventory; BMI, Body mass index; AI, Aromatase inhibitor; AIMSS, Aromatase inhibitor-associated musculoskeletal symptoms; *HR (95% CI)*, Hazard ratio (95% confidence interval).

Table 3 Multivariate Cox Regression Model Testing Interaction Between Management Strategy and Baseline Pain Interference

Variable	*HR (95% CI)*	*P*
Interaction term (strategy × interference group)	0.192 (0.051–0.722)	0.015
BPI average pain score	1.438 (1.200–1.725)	< 0.001
Age	1.064 (0.999–1.133)	0.055
TNM stage (II/III vs. 0/I)	0.568 (0.346–0.931)	0.025

Abbreviations: BPI, Brief Pain Inventory; *HR (95% CI)*, Hazard ratio (95% confidence interval).

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Table 4 Effect of Management Strategy Based on Baseline Pain Interference Strata: Adjusted Subgroup Analysis

Subgroup	*HR (95% CI)*	*P*
High interference group (≥7)	0.125 (0.042–0.378)	< 0.001
Low interference group (<7)	0.731 (0.322–1.659)	0.454

Therefore, stratified analyses were conducted. The results (Table 4) showed that in the patient subgroup with severe baseline pain interference (≥ 7), where 31 treatment interruption events occurred, the combined therapy strategy demonstrated a strong protective effect, significantly reducing the risk of treatment interruption (*HR* = 0.125, *95% CI*: 0.042–0.378, $P < 0.001$). In the patient subgroup with mild-to-moderate baseline pain interference (< 7), in which 37 events occurred, no difference in risk was observed between combined and monotherapy strategies (*HR* = 0.731, *95% CI*: 0.322–1.659, $P = 0.454$).

Short-Term Symptom Improvement Trajectory

The trajectories of pain score changes within 3 months after AIMSS diagnosis are shown in Figure 2. Repeated-measures ANOVA revealed a significant interaction effect between time and management strategy for both average pain score (Figure 2A) and pain interference score (Figure 2B) (both $P < 0.001$). This indicates differing symptom improvement trajectories between the groups. Despite having more severe baseline symptoms, the combined therapy group showed faster and greater symptom improvement. By month 3, the combined therapy group had significantly lower average pain score (2.75 ± 0.77 vs. 3.63 ± 0.98, $P < 0.001$) and pain interference score (2.51 ± 0.89 vs. 3.30 ± 1.19, $P < 0.001$) compared to the monotherapy group. These results suggest that the combined strategy led to greater symptom relief in the short term.

Discussion

AIs are the standard adjuvant endocrine therapy for postmenopausal HR-positive BC, but associated AIMSS is a leading cause of treatment interruption and non-adherence.[19] Although various management strategies exist, the impact of different strategies on long-term treatment persistence in real-world clinical settings, particularly whether their effectiveness varies by initial patient characteristics, lacks sufficient evidence. This study explored the association between the initial management strategy for AIMSS and the risk of treatment interruption, and analyzed the potential moderating effect of baseline symptom burden on this association.

The findings indicate that the effect of the initial management strategy on treatment interruption risk is significantly moderated by baseline pain interference. Specifically, the benefit of combined therapy was confined primarily to the patient subgroup with greater baseline symptom burden. This suggests that AIMSS management may require stratification based on initial symptom severity rather than a uniform initial strategy. It is noteworthy that patients with more severe symptoms in this study were more likely to receive combined therapy at baseline, reflecting real-world clinical practice where physicians tend to offer more aggressive management to those with greater symptom burden. This non-random treatment allocation indeed introduces selection

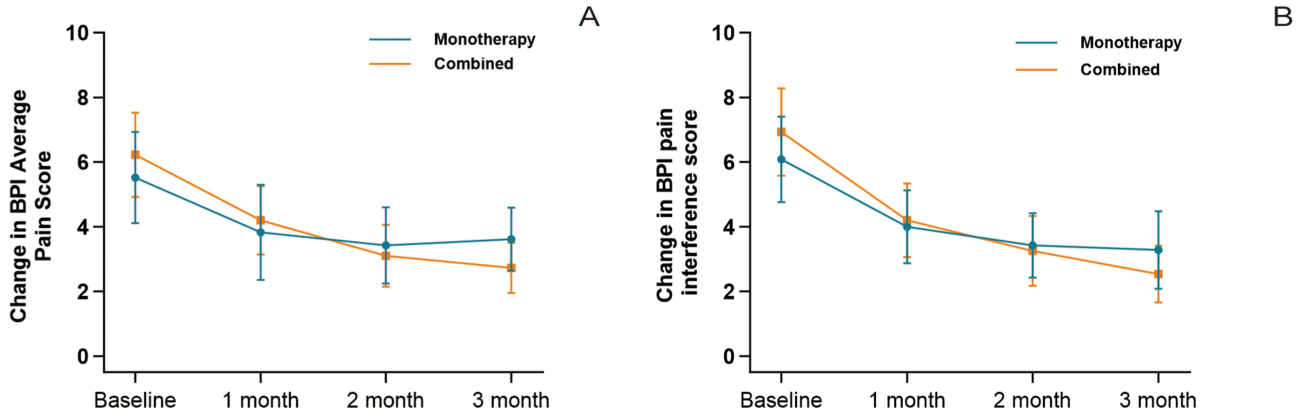

Figure 2 Trajectories of pain score changes within 3 months after AIMSS diagnosis: (**A**) Average pain score; (**B**) Pain interference score.
Abbreviation: AIMSS, Aromatase inhibitor-associated musculoskeletal symptoms.

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bias. To disentangle this bias and investigate true effect modification, our study incorporated an interaction term between management strategy and baseline pain interference group in the multivariate Cox model and conducted stratified analyses to assess the true effect of management strategy on patients with different symptom burdens. The significant interaction indicates effect modification, suggesting that baseline pain interference alters the association between management strategy and treatment interruption risk. It more likely reveals that the efficacy of management strategies fundamentally depends on initial symptom state. Methodologically, this enhances the credibility of our findings.

Differences in symptom burden may reflect heterogeneity in the underlying pathophysiology of AIMSS. Research indicates that AIMSS involves multiple interconnected aspects, including estrogen deprivation-induced chronic low-grade inflammation, alterations in the biomechanical properties of joints and tendons, and functional remodeling of central nervous system pain processing pathways.[6,20] For patients with severe symptoms and significant functional impairment, the pathophysiological state may be more complex or active. Interventions targeting a single pathway may be insufficient for comprehensive symptom control. Combined strategies, by integrating interventions with different mechanisms of action, may more effectively address multiple pathological processes simultaneously, leading to superior symptom control. Effective symptom relief is widely recognized as a key mediator for improving patients' treatment experience, enhancing self-efficacy, and ultimately maintaining long-term treatment adherence.

It is important to note that the primary endpoint in this study was a composite outcome, including treatment interruption due to AIMSS, as well as recurrence and all-cause mortality. While this composite endpoint reflects clinically meaningful events that may lead to treatment discontinuation in real-world settings, it may also introduce complexity in interpreting adherence-related effects, as recurrence or death could act as competing events rather than direct consequences of AIMSS. Therefore, the observed associations should be interpreted with caution when specifically attributing effects to treatment adherence. Future studies may benefit from applying competing-risk models or focusing on AIMSS-specific treatment interruption as a primary endpoint to further clarify these relationships.

These findings align with the prevailing concept in chronic pain management that multimodal combined interventions are often superior to monotherapy for moderate-to-severe or complex pain syndromes.[21] Although previous randomized controlled trials have demonstrated the efficacy of specific single interventions in improving AIMSS pain scores,[11,22] they have less frequently focused on treatment persistence. This study provides observational evidence from real-world practice, highlighting the importance of stratified management based on baseline symptom severity and offering preliminary support for applying individualized pain management in AIMSS. However, caution is warranted when generalizing these findings to other populations, as this was a single-center study conducted in an Asian population, and local clinical practices, healthcare systems, and patient preferences regarding AIMSS management may differ across regions. From a practical perspective, these findings support the implementation of an operationalized clinical decision-making pathway based on routine symptom assessment. Using standardized tools such as the BPI interference scale at the time of AIMSS diagnosis can triage patients into distinct management tracks. Consistent with established oncology pain frameworks that designate a BPI score of ≥7 as indicating severe functional impairment, this tool may help guide initial management decisions.[23] Specifically, patients reporting mild-to-moderate interference (BPI < 7) could follow a standard stepwise approach, initiating with monotherapy (eg, targeted physical therapy or oral NSAIDs) and escalating only if symptoms persist. Conversely, identifying patients with severe interference (BPI ≥ 7) triggers immediate referral for an upfront multimodal combined regimen, thereby optimizing symptom control and preventing premature treatment discontinuation.

Limitations

This study has several limitations. First, the retrospective observational design means treatment allocation was not randomized, potentially leading to selection bias. Although multivariate models were used to adjust for measured baseline differences and interaction was tested, residual confounding from unmeasured factors such as patients' motivation for adherence, physician prescribing preferences, socioeconomic status, or prior pain history cannot be entirely excluded. Second, the definition of combined therapy encompassed various combinations of different interventions, and the inherent heterogeneity means the effects of different combined regimens may vary. This study did not further subdivide and compare them due to limited subgroup sample sizes. Third, although the total sample size was generally adequate for a retrospective study, the sample size of the combined therapy subgroup within the high interference group was relatively limited, potentially affecting the precision of the effect size

estimate. Moreover, no a priori sample size or power calculation was performed, which is a limitation inherent to the retrospective design. Nevertheless, the risk of model overfitting was effectively controlled, as our primary multivariate Cox model maintained an acceptable EPV ratio of approximately 11 (68 events for 6 terms), exceeding the standard threshold of 10. Additionally, the minimum follow-up of 18 months, while sufficient to capture early treatment interruption events and short-term symptom changes, remains inadequate to assess long-term adherence patterns. Consequently, this study lacks an evaluation of long-term symptom trajectories, patient-reported quality of life, and definitive survival outcomes. Finally, single-center data may limit the generalizability of the findings, requiring validation through multicenter, large-sample retrospective or prospective studies.

Conclusion

These real-world data suggest that for postmenopausal BC patients suffering from severe pain interference due to AIMSS, initiating a multimodal combination management strategy at diagnosis is associated with a lower risk of AI treatment termination and greater short-term symptom relief. Given the retrospective design and single-center setting, these findings are practice-informing rather than practice-changing, providing evidence that supports considering early initiation of an aggressive multimodal intervention for AIMSS patients with severe pain interference. For patients with mild-to-moderate symptoms, combined therapy showed no additional benefit, suggesting that a stepwise management approach starting with monotherapy may be appropriate. This study underscores the importance of stratified management of AIMSS based on baseline symptom severity, providing a reference for clinical decision-making to optimize adjuvant endocrine therapy adherence. However, future prospective studies are required to validate the effectiveness of specific combined regimens before this stratified approach can be recommended for routine clinical implementation.

Data Sharing Statement

The datasets generated and/or analyzed during the current study can be obtained upon reasonable request from the corresponding author.

Ethics Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of The Third Affiliated Hospital of Wenzhou Medical University (No. 2025-029), and the requirement for informed consent was waived due to the retrospective nature of the study, which involved the use of existing medical records and posed minimal risk to participants. All patient data were anonymized and de-identified prior to analysis, and strict confidentiality of personal information was maintained throughout the study in accordance with institutional guidelines and the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Meizhen Liang and Shaofei Yuan are co-first authors for this study. The authors declare that they have no competing interests in this work.

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