



Original Article

# Adherence to Adjuvant Endocrine Therapy and Associated Factors Among Patients with Breast Cancer

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Received 18<sup>th</sup> October 2024

Revised 18<sup>th</sup> December 2024; Accepted 6<sup>th</sup> March 2025

**Abstract:** Adherence to adjuvant endocrine therapy plays an important role in the treatment of breast cancer. The study's objective was to assess the current status of adherence to adjuvant endocrine therapy in breast cancer patients and analyze some related factors. A cross-sectional study was conducted at K and Hanoi Oncology Hospital using the ARMS toolkit to assess adherence. Patient and treatment drug factors were included in regression analysis to determine the association. 863 patients agreed to participate in the study, with an average age of 53.6 years. According to the toolkit assessment, 49.2% of patients did not adhere to treatment. 9 out of 12 questions had a response rate of over 90%, indicating good adherence. Common nonadherence problems include “forgetting to take medication” and “carelessly missing medication,” as well as some cases of intentional stopping of medication or changing treatment at varying levels of frequency. Younger patients, residents outside Hanoi, or short treatment duration were factors that reduced adherence ( $p < 0.05$ ). In conclusion, compliance with adjuvant endocrine therapy in the study sample was not high. Some interventions could consider factors such as age, residence, and duration of medication to improve compliance with adjuvant endocrine therapy.

**Keywords:** Adherence, adjuvant endocrine therapy, breast cancer, ARMS.

## 1. Introduction

Oral adjuvant endocrine therapy is one of the important regimens for breast cancer. Treatment

guidelines recommend the regimen to help reduce the risk of recurrence and death in patients. To maximize the effectiveness, patients

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<https://doi.org/10.25073/2588-1132/vnumps.4713>

need to take adjuvant endocrine therapy regularly for many years. However, studies have shown that nonadherence to adjuvant endocrine therapy is a significant clinical problem among breast cancer patients. Up to 10–50% of breast cancer patients in clinical trials and real life do not take the prescribed dose or regimen or discontinue treatment [1]. Poor treatment adherence increases the risk of disease recurrence and complications, increases treatment costs, and increases patient mortality [2]. Most patients are prescribed oral adjuvant endocrine therapies. However, there have been few large-scale studies on breast cancer patients' compliance with adjuvant endocrine regimens. Therefore, this study was conducted with the following objectives: i) to evaluate adherence with oral adjuvant endocrine therapy; and ii) to analyze some factors affecting compliance with the treatment of breast cancer patients at K and Hanoi Oncology hospitals.

## 2. Methods

### 2.1. Participants

The study included patients with health insurance, re-examination, and medication at Hanoi Oncology Hospital and K Hospital (first quarter of 2020). Included criteria were female, 18 years of age or older, diagnosed with stage I-III breast cancer, currently being treated with tamoxifen or aromatase inhibitors (letrozole, anastrozole, exemestane) for at least 3 months at the time of interview. The study excluded patients with other cancers who refused to participate in the study or who did not have the capacity or behavior to answer the questions.

### 2.2. Methods

Research design: A cross-sectional study

#### 2.2.1. Data collection

Patients who agreed to participate in the study were invited to sign a consent form to

participate in the study. Patients were then interviewed by the researcher, and information was collected from the medical records. The information collected included administrative information, general patient characteristics, disease and treatment characteristics, and patient adherence to medication refilling and medication use (using the Adherence to Refills and Medication Scale (ARMS) [3]).

**ARMS Adherence Assessment Tool:** Patients were assessed for adherence by answering the ARMS questionnaire consisting of 12 questions, 8 questions about medication use, and 4 questions about medication refilling, each answer on a scale of 1 to 4. Each patient's total score ranged from 12 to 48 points. Patients were assessed as adherent to treatment if their total score was 12 points. A total score above 12 points were assessed as non-adherent. The higher the score, the higher the level of nonadherence. The questionnaire was approved by the authors, translated into Vietnamese, and used in the study [3].

#### 2.2.2. Data analysis

Data were analyzed using R Studio software. Regarding factor analysis, independent variables affecting medication adherence were collected using a questionnaire, including a group of factors on patient characteristics such as age, education level, marital status, place of residence, and income; a group of factors related to disease and treatment, including disease stage, treatment duration, comorbidities, and treatment regimen [2, 4]. The binary dependent variable was compliance (12 points) and non-compliance (over 12 points).

#### 2.2.3. Research ethics

K Hospital's ethics committee endorsed the research, and Hanoi Oncology Hospital consented to its execution. All patients who were enrolled in the study were informed about the study and were required to complete a consent form to participate.

### 3. Result

#### 3.1. Patients

863 patients agreed to participate in the study, mainly from K hospital (70.5%). The average age of the patients was 53.6 years old, and most of them were married (83%). In terms of educational level, nearly three-quarters of the patients said they had less than a high school education. 67.3% of the patients currently have no income. The proportion of patients residing in Hanoi and the other provinces was almost the same (47% and 53%).

Table 1. Sociodemographic characteristics of participants

Characteristics	N (N=863)	Percentage (%)
<b>Age (year)</b>		
Mean (SD)	53.6 (10.2)	
Min-Max	25-81	
<b>Marital status</b>		
Married	716	83.0
Single, divorced, or widowed	147	17.0
<b>Highest education level</b>		
Secondary school and lower	626	72.5
High school and above	237	27.5
<b>Income status</b>		
Have income	282	32.7
No income	582	67.3
<b>Place of residence</b>		
Hanoi	406	47.0
Outside Hanoi	457	53.0

More than half of the patients in the study were mainly in phase II (57.6%). Phase III accounted for 16.4%. 56.5% of the patients' regimens were aromatase inhibitors; the rest were tamoxifen regimens. The study sample had a higher number of patients treated for 2 years or more than the number treated for less than 2 years (55.7% vs. 44.3%). The majority of patients had no comorbidities other than breast

cancer; however, more than 60% of patients were taking other drugs concurrently with adjuvant endocrine drugs.

Table 1. Clinical- and medication-related characteristics

Characteristics	n (N=863)	Percentage (%)
<b>Cancer stage at diagnosis</b>		
I	224	26.0
II	497	57.6
III	141	16.4
<b>Type of OAET* taken for the past cycle</b>		
Tamoxifen	375	43.5
Anastrozole	77	8.8
Letrozole	230	26.7
Exemestan	181	21.0
<b>Years since the first OAET</b>		
< 2	382	44.3
≥ 2	481	55.7
<b>Comorbidities</b>		
None	521	60.4
Yes	342	39.6
<b>Taking other medications</b>		
None	338	39.2
Yes	525	60.8

\*OAET: Oral adjuvant endocrine therapy.

#### 3.2. Adherence status

Figure 1 and Table 3 present the results of the medication adherence assessment in 863 patients. The proportion of adherent patients was almost equal to the number of non-adherent patients (50.8% vs. 49.2%). Figure 1 depicts the proportion of different ARMS scores, with the lowest being 12 points (adherent to treatment) and gradually increasing to higher scores representing different levels of nonadherence. Accordingly, the 13-point level accounted for 23.6%, followed by 14 points (13%), and the number of patients with higher scores gradually decreased.

Table 3 shows the detailed responses of patients to each question in the ARMS toolkit. 9 out of 12 questions with a rate of over 90% of

patients responding showed good adherence: “never” (questions 1-11) and “always” (12<sup>th</sup> question). For the 1<sup>st</sup> question, 30.1% of patients answered “several times” and 1.8% of patients answered “many times” forgetting to take their medication. 13.7% of patients answered “several times” to running out of medication during treatment. An equal proportion of patients (14.7%) answered “several times” not taking their medication due to carelessness. Notably, 2.5% (22/863) of patients answered that they deliberately did not take their medication to varying degrees (the 2<sup>nd</sup> question), and nearly 90 patients (9.6%) intentionally skipped a dose of medication on the day of their visit (the 5<sup>th</sup> question).

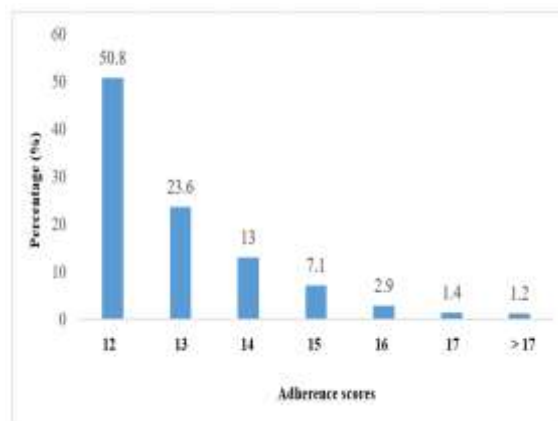


Figure 1. Percentage of participants with different adherence scores.

Table 3. Adherence status of participants with ARMS

Question	Content of question	Frequency*, (N=863)			
		1	2	3	4
1	How often do you forget to take your medicine?	68.1	30.1	1.8	0
2	How often do you decide not to take your medicine?	97.5	2.2	0.3	0
3	How often do you forget to get prescriptions filled?	98.4	1.6	0	0
4	How often do you run out of medicine?	85.7	13.7	0.6	0
5	How often do you skip a dose of your medicine before you go to the doctor?	90.4	8.1	0.6	0.9
6	How often do you miss taking your medicine when you feel better?	99.7	0.3	0	0
7	How often do you miss taking your medicine when you feel sick?	95.8	3.9	0.3	0
8	How often do you miss taking your medicine when you are careless?	84.8	14.7	0.5	0
9	How often do you miss taking your medicine when you are careless?	99.5	0.5	0	0
10	How often do you forget to take your medicine when you are supposed to take it more than once a day?	93.6	5.7	0.7	0
11	How often do you forget to take your medicine when you are supposed to take it more than once a day?	99.7	0.3	0	0
12	How often do you forget to take your medicine when you are supposed to take it more than once a day?	94.9	4.9	0.1	0.1

Note \*: 1<sup>st</sup>-11<sup>th</sup> Question: 1= never, 2= sometime, 3= many times, 4= always. 12<sup>th</sup> question: 1= always; 2= many times; 3= sometime; 4= never. Percentage in the table for each question (N=863)

### 3.3. Factors Associated with Treatment Adherence

Factors that were significantly associated with treatment adherence in multivariate

analyses were patient age, place of residence, and duration of endocrine therapy (p<0.05). Specifically, older patients had better adherence. Patients in Hanoi had better adherence than those in other provinces. Patients treated for less than

2 years had higher adherence than those who had been taking the medication for 2 years or more. Factors such as educational level, marital status, income, comorbidities, and using other

medications had significant effects on adherence in the univariate model but did not show statistical effects when included in the multivariate model.

Table 4. Multiple logistic regression analysis of factors associated with adherence

Factors	OR (95%CI)	p
Age	0.724 (0.535-0.980)	0.036
Marital status (married)	1.158 (0.788-1.701)	0.455
Income status (no income)	0.974 (0.669-1.417)	0.890
Educational level (high school and above)	1.171 (0.805-1.705)	0.409
Place of residence (outside Hanoi)	0.724 (0.535-0.980)	0.036
Years since the first OAET ( $\geq 2$ years)	1.579 (1.178-2.116)	0.002
Comorbidities (yes)	1.297 (0.943-1.784)	0.110
Taken other medications (yes)	0.899 (0.659-1.225)	0.499

#### 4. Discussion

According to the 2022 GLOBOCAN report on cancer in Vietnam, breast cancer not only accounts for the highest rate of cancer in women but also in all cancers in both sexes [5]. In 2020, the Ministry of Health developed guidelines for the diagnosis and treatment of breast cancer, updating the guidelines of prestigious organizations in the world. In the guidelines, the Ministry of Health also emphasized the important role of adjuvant endocrine drugs in the treatment of patients with hormone receptor-positive breast cancer. Tamoxifen and aromatase inhibitor regimens are recommended for use for 5 to 10 years for optimal effectiveness in reducing recurrence and complications of breast cancer [6]. However, long-term adjuvant endocrine treatment is a difficult problem for patients [7]. The current status of adherence to adjuvant endocrine therapy in Vietnamese patients is an issue that needs attention; however, there have not been many large-scale studies summarizing this status in treatment in Vietnam. Therefore, the results from our study on 863 patients at 2 large oncology hospitals help reflect the real-life treatment adherence of breast cancer patients and initially analyze some factors related to medication adherence in patients.

Our study found that patient adherence to medication was 50.8%. This result is within the range of rates reported in reports on adherence to adjuvant endocrine therapy, which range from 46% to 100% [1]. Compared to studies using self-report methods, the adherence results in our study (50.8%) were higher than those using the MMAS-4 on Singapore patients (40.8%) [2] and the interview method in Atkin's study (45%) [8]. However, Murphy et al., [1] also recorded an adherence rate of up to 88% using the MARS-5 questionnaire on breast cancer patients. The results from the analysis of each question on the level of adherence (Table 3) showed that "forgetting to take medication", "carelessly missing medication", and "running out of medication" were unintentional factors of the patients leading to low adherence scores. With long-term medication use, "forgetting to take medication" or "having difficulty remembering to take medication" was a common cause and barrier to adherence reported in breast cancer patients [2, 7]. Additionally, the study revealed intriguing findings regarding the intention to change treatments. About 10% intentionally skipped a dose of medication on the examination day with doctors, and some patients actively stopped taking medication during treatment.

The rate of adherence in different studies depends on the assessment method and assessment criteria applied by the study. Two methods were applied to adherence studies in breast cancer patients using adjuvant endocrine drugs: assessment of drug possession rate (MPR  $\geq 80\%$  is assessed as adherence) and patient self-report [1, 9]. Our study applied the ARMS adherence assessment questionnaire, which was developed and widely applied to patients with chronic diseases who required long-term drug treatment. The toolkit has been translated into Vietnamese and received comments from the authors during its use in breast cancer patients [3]. Although they tended to assess higher levels of adherence than other methods, patient self-assessment questionnaires are still considered suitable tools for daily clinical assessment because they can be assessed quickly, and effectively and are labor- and cost-effective [10].

Our study also revealed some significant factors that influenced patient adherence to treatment, such as age, place of residence, and duration of endocrine therapy. These factors have also been recognized in the literature as patient and treatment factors affecting patient adherence [1, 9]. Age has been shown to influence breast cancer treatment. Similar to our results, some studies have shown that older patients have higher adherence to treatment. The older patients may be more concerned about their health than younger patients, which may lead to involuntary nonadherence [2]. However, studies have identified very old or very young patients as factors negatively affecting adherence to endocrine therapy for cancer [4]. Treatment duration also affects patient adherence. The longer the treatment duration, the lower the level of compliance, especially with drugs that require active treatment for 5–10 years and have many adverse effects when used for a long time, such as hormonal drugs. This is supported by the fact that patients who had been on endocrine therapy for two years or more were less likely to follow through with their treatment (40% vs. 48.4%), which is similar to what Ali et

al., found (34.5% vs. 47.9%) [2]. Residence far from the treatment hospitals is a factor that negatively affects patient compliance. Patients residing in provinces outside Hanoi have a lower level of compliance than those residing in Hanoi, which is closer to the treatment hospitals. Traveling a longer distance to see a doctor and obtain medication, along with being distant from hospital support services, is another factor that contributes to patients' poor treatment compliance. Although the associated factors identified in this study are either unmodifiable (age, duration of treatment) or very difficult to modify (place of residence), the results also guide the target population to be aware of during treatment to have earlier attention and intervention measures to increase patient adherence to treatment. When counseling breast cancer patients, the counselors should pay more attention to factors such as their age, duration of treatment, and where they are living. Understanding more about these significant factors that influence patient adherence is important to find effective interventions that improve the rate of adherence to treatment among breast cancer patients.

## 5. Conclusion

The research demonstrated that approximately half of breast cancer patients adhered to adjuvant endocrine therapy. The most common nonadherence issues were “forgetting to take medication”, “carelessly missing medication”, and a few instances of intentionally discontinuing or altering treatment at varying frequencies. Three factors influenced patients' adherence to their medication including elderly age, residence in Hanoi, and taking the medication for less than two years. The study's findings indicated that the issue of adherence to adjuvant endocrine therapy necessitates attention and the implementation of suitable interventions to enhance the adherence rate to the treatment regimen.

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