Patient Preference and Adherence

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Group-Based Trajectory Modeling to Identify Patterns and Predictors of Adherence to Oral Endocrine Therapies in Underserved Population of Greater Houston Area

Yashvi Patel[1,*], Hasan Alsaedi[1,*], Zahra Majd[2], Issra Altaie[1], Sama Rahimi[1], Bilqees Fatima[2], Onyebuchi Ononogbu[1], Susan Abughosh[2], Meghana V Trivedi[1]

[1]Department of Pharmacy Practice and Translational Research, University of Houston College of Pharmacy, Houston, TX, USA; [2]Department of Pharmaceutical Health Outcomes and Policy, University of Houston College of Pharmacy, Houston, TX, USA

*These authors contributed equally to this work

Correspondence: Meghana V Trivedi, University of Houston, College of Pharmacy, Health 2, 4349 Martin Luther King Blvd, Houston, TX, 77204-5000, USA, Tel +1 832 842 8335, Fax +1 832 842 8383, Email mtrivedi@uh.edu

Background: Poor adherence to oral endocrine therapy (OET) is a significant problem among patients with hormone receptor-positive breast cancer as it results in higher risk of recurrence and mortality. Non-adherence to OET is prevalent among underserved patients, often attributable to socioeconomic factors and limited healthcare access. We evaluated OET adherence patterns over time using group-based trajectory modeling (GBTM) and identified predictors of suboptimal adherence trajectory among patients seen at Harris Health System, serving underserved patients in Houston, Texas.

Methods: A single-center, retrospective study was conducted from October 2019 through December 2020. OET adherence was measured using proportion of days covered (PDC). A logistic GBTM was conducted using 2–5 adherence groups considering the Bayesian information criteria, clinical relevance, and a 5% minimum membership requirement. Multinomial logistic regression was used to assess the predictors of non-adherence trajectories.

Results: Among 496 patients, majority were Hispanic (62.50%) or African American (15.12%) and <65 years of age (82.66%). Four distinct adherence trajectories were identified: consistent high adherence (41.4%); constant PDC at ~0.6 (32.6%); rapid decline (14.6%); low adherence with gradual decline (11.5%). African Americans had higher likelihood of having low adherence with gradual decline [odds ratio (OR): 2.462 (confidence interval (CI): 1.1149–5.276), p=0.0205]. Patients with diabetes were more likely to have constant PDC at ~0.6 [OR: 1.714 (CI: 1.042–2.820), p=0.0338]. Longer time (4 or greater years) on therapy predicted low adherence with gradual decline [OR: 2.463 (CI: 1.266–4.793), p=0.008) and constant PDC at ~0.6 (OR: 1.966 (CI: 1.141–3.388), p=0.0149] trajectories.

Conclusion: The identified predictors, including comorbidities like diabetes, African American descent, and longer OET treatment are crucial considerations when developing patient-centered interventions to enhance OET adherence among underserved populations. These insights can guide the implementation of initiatives such as mobile health applications, community-based educational programs, and financial aid efforts.

Keywords: oral endocrine therapy, breast cancer, medication adherence, group-based trajectory modeling, minority, underserved

Introduction

Breast cancer (BC) is the most common cancer among women in the United States (US) excluding skin cancers.[1–3] In 2023, 297,790 women are expected to be diagnosed with invasive BC and 43,170 women are expected to have non-invasive BC.[4] Over 70% of BC cases are hormone (estrogen and/or progesterone) receptor positive (HR+).[5] Patients diagnosed with early-stage HR+ BC are treated with oral endocrine therapies (OET), which consists of tamoxifen,

Received: 7 October 2024
Accepted: 17 December 2024
Published: 1 March 2025

a selective estrogen receptor modulator (SERM) and aromatase inhibitors (AIs), like anastrozole, letrozole, and exemestane. HR+ BC has superior survival rates compared with other subtypes because of the slow growth of tumors and effectiveness of OET.[5] OET reduces the risk of recurrence, metastasis, and mortality in patients with early-stage HR + BC when given for 5–10 years.[6,7] OET also reduces the risk of new BC diagnoses when used for 5 years as a prevention strategy in women with non-invasive BC.[8–11]

Non-adherence to OET remains a significant clinical challenge in HR+ BC patients despite its documented benefits.[12–15] Up to 70% of patients who initiate OET tend to be non-adherent and discontinue OET prematurely before the end of therapy.[16–18] For the 10-year OET regimen, the adherence is even worse in HR+ BC patients.[19,20] OET adherence is especially poor in minority and underserved BC patients in the U.S.[12,21–24] Factors associated with OET non-adherence in minority patients include low perception of recurrence risk, uncertainty about medication efficacy, unsatisfactory patient-provider relationship, adverse drug reactions from OET, and lack of social support, in addition to the well-known socioeconomic factors (financial constraints, language barriers, transportation, lack of resources/health-care access, etc).[25–27] Non-adherence to OET increases the risk of recurrence and progression, and hence, increases healthcare resource utilization and overall healthcare costs.[20,28–30] For example, a study highlighted that OET-adherent patients experienced fewer healthcare visits and significant reductions in medical costs, with half of the cost reduction attributed to decreased hospitalizations, indicating potential cost offsets. This underscores the importance of OET adherence in not only reducing the risk of BC recurrence but also mitigating associated treatment costs.[31]

The increased risk of recurrence and healthcare costs from OET non-adherence highlights the need for interventions to improve adherence in underserved populations. The use of group-based trajectory modeling (GBTM) has shown promise in identifying and predicting medication adherence behavior over time. GBTM is a statistical approach that considers both the quantity and timing of medication availability to describe complex and longitudinal patterns of adherence.[32] In simpler terms, GBTM helps us understand how patients take their medication over time in a more comprehensive way. Compared to traditional methods such as Proportion of Days Covered (PDC), which only account for the medication quantity, GBTM provides a more comprehensive understanding of medication adherence over time by recognizing that people with similar PDC scores can still exhibit different patterns of medication use. Recent research involving a large cohort of statin initiators demonstrated that the 6-group trajectory model of GBTM outperformed traditional methods like PDC in summarizing long-term adherence.[33] This highlights the broad applicability of GBTM across diverse patient populations and its potential to inform clinical decision-making, particularly in underserved populations such as those affected by HR+ BC. By identifying clusters of patients with similar adherence patterns, GBTM can guide the development of tailored interventions for non-adherent individuals.[33] However, a GBTM model has not yet been developed for OET adherence in underserved patients with HR+ BC. The aim of this study was to use GBTM to evaluate longitudinal patterns of OET adherence and identify associated predictors in underserved populations. This study identifies four distinct adherence trajectories and their associated predictors, providing a framework for implementing targeted interventions to improve OET adherence within these communities.

Methods

Study Design and Data Source

The study was approved by the University of Houston and Harris Health System's institutional review board with a waiver of informed consent. This retrospective, single-center, observational study utilized data from the Epic Health Electronic Health Record (EHR) system. The study covered the period from June 1st, 2019 to December 31st, 2020. A list of medical record numbers for patients on OET who presented to the Harris Health Institutions for diagnosis and/or follow-up appointments was extracted from the EPIC Health EHR system. The dispense history from June 2019 through September 2019 was only used to determine whether the patients had OET supply on hand after October 1st, 2019.

Study Population

Inclusion criteria included patients who were seen and followed at Harris Health System, in Houston, TX, which serves the underserved and predominantly minority population of the city. Patients with stages 0-IV of HR+ BC with at least one

outpatient dispense record of OET from June 2019 through December 2020 were included. Those taking OET for prevention because of ductal carcinoma-in-situ (DCIS), lobular carcinoma-in-situ (LCIS), or ductal or lobular hyperplasia were categorized together as Stage 0/prevention. Exclusion criteria were patients who were not taking appropriate doses of OET (from medication tab); who discontinued OET for medical reasons in consultation with their clinician (due to severe side effects, completion of therapy, or disease progression – from oncology notes); or were on OET for reasons other than BC prevention or treatment (from oncology notes and pathology tab). Recommended OET therapy regimen included tamoxifen 20 mg once daily, anastrozole 1 mg daily, letrozole 2.5 mg once daily, and exemestane 25 mg once daily. Lower doses of OET are used for indications other than BC and hence were excluded.

Data Collection and Management

We collected the following data: patient demographics (date of birth, gender, race, ethnicity, religion, zip code), vitals (body weight, height, body mass index (BMI)), history of comorbid conditions (diabetes, hypertension, hyperlipidemia, depression), diagnosis date, clinical cancer stage and pathological cancer stage at diagnosis or at the start of any treatment (chemotherapy or OET), ER/PR/HER status, current endocrine therapy for the study period (name, dose, frequency), date of first prescription for current treatment, date of current treatment initiation, reason for delay in starting the current treatment, use of other cancer therapy (CDK4/6 inhibitor, fulvestrant, LHRH/GnRH agonists), refill dates and quantity throughout the study period, date and reason of discontinuation, number of months' supply filled in-person and via home delivery, date and regimen of original OET initiation, and date and reasons for any therapy changes. Age was calculated at the start of the study period. Other constant covariates such as race, ethnicities, etc. were obtained at the time of data collection. Other variable covariates such BMI and comorbidities were also documented at the time of data collection.

The patients' prescription refill data in the EPIC EHR included the combination of prescription dispensed data of Harris Health pharmacy with an integrated e-prescribing system. Thirty patients were included in piloted data collection to resolve inconsistencies in data collection and review any necessary update in the data collection form. Four investigators (SR, HA, YP, and IA) completed the final data collection using Microsoft Excel. Queries were resolved by licensed and board-certified oncology pharmacists (MVT and OO). Random audits were performed during and after data collection to ensure data integrity. The audit process consisted of a random selection of patients from the data collection sheet and entailed a thorough review of the data, ensuring that all pertinent details were accurate and consistent with each patient's EPIC EHR patient records.

In cases where data was initially absent, a team review and thorough examination of addition-al EHR sources allowed us to address any missing information. For instance, when faced with missing comorbidities, we cross-referenced the patient's medications and meticulously re-viewed historical patient charts to ensure comprehensive data collection. Similarly, for missing ER/PR/HER status, we conducted a detailed evaluation of the pathology reports to fill any gaps in the data. Our rigorous approach to addressing missing data bolstered the robustness of our findings.

Adherence Measurements and Trajectory Modeling

Monthly adherence to OET was measured using PDC from October 2019 to December 2020. Monthly PDC was defined as the total number of days covered with OET divided by the total number of days in the measurement period (30 days). A binary indicator for "adherence" (PDC $\geq$ 0.80) vs "non-adherence" (PDC $<$ 0.80) was created for each consecutive month. Centers for Medicare & Medicaid Services (CMS) use PDC and the cutoff value of 0.8 to measure adherence and this cutoff is widely accepted because of its highest predictive validity for clinically meaningful outcomes in patients.[34] In addition, research has shown that PDC $\geq$80% is strongly associated with better health outcomes in chronic disease conditions making it a reliable indicator for assessing adherence. Many studies assessed endocrine therapy among breast cancer patients using the same cut-off (PDC $\geq$ 80%).[35–37] A logistic group-based trajectory modelling was conducted using monthly adherence indicators to identify longitudinal patterns of adherence. Four trajectory models were generated using 2–5 adherence groups and the second-order polynomial function of time. The final trajectory model was selected based on the Bayesian information criteria (BIC), clinical relevance of the adherence patterns, and a 5% minimum membership requirement for each trajectory group.[32,33]

Model Validation

The model performance of the selected 4-group trajectory model was evaluated by using following Nagins model adequacy criteria[33] as follows: (1) Average posterior probability of assignment (AvePP) values more than or equal to 0.7 for all trajectory groups reflected that the posterior probabilities of assigning observations to their respective groups were high. (2) Odds of correct classification (OCC) which is estimated as the proportion of the odds of correct classification based on the maximum probability classification rule and the estimated proportion of class members the recommended OCC value was 5 or more for all groups of the trajectories which indicated that model fit the data well (Supplementary Table 1).

Statistical Analysis

Group differences in patient characteristics between adherence trajectories were evaluated using chi-square test for categorical variables and ANOVA test for continuous variables. A multinomial logistic regression model was conducted with a "full adherence" trajectory as the reference group to determine predictors of identified adherence trajectories account for various clinical and sociodemographic variables in addition to controlling for potential confounders. Covariates included in the model were age (as a continuous variable), race (African American, White/Caucasian/others, Hispanic/Latino), OET (tamoxifen, AIs), years on therapy (≤ 1 year, 2–3 years, ≥ 4 years), BMI (≤ 24.9, 25–29.9, ≥ 30), and comorbidities such as depression, diabetes, hyperlipidemia, and hypertension. A collinearity assessment was carried out prior to running the model to ensure no multicollinearity between the predictors. The G-power 3.1 statistical software[38] was used for the sample size estimation with a 0.05 α-level, 80% power. A medium effect size of 0.30 (that is, 1.40 odds ratio), with a binominal distribution, two-tail test for multiple logistic regression model would need a total of 442 subjects (our study sample size 496). The study will need larger samples for detection of smaller effect sizes. All the statistical analysis was performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute, Cary, NC). An add-on user-written procedure called "Proc Traj" was used for trajectory modelling. It's a convenient procedure introduced to the SAS which evaluates the possible different polynomial orders to fit models adequately based on BIC. In addition, the parameter estimates for each polynomial class should be statistically significant, less than 0.05.[39]

Results

Patients

We collected data from 584 patients. Over 97% of patients filled their prescriptions at the Harris Health pharmacies. Out of these, 496 patients were included in our analysis based on the inclusion/exclusion criteria (Figure 1). During the study period, 201 patients switched between AIs and tamoxifen, which was not classified as non-adherence, and therefore, included in the final analysis.

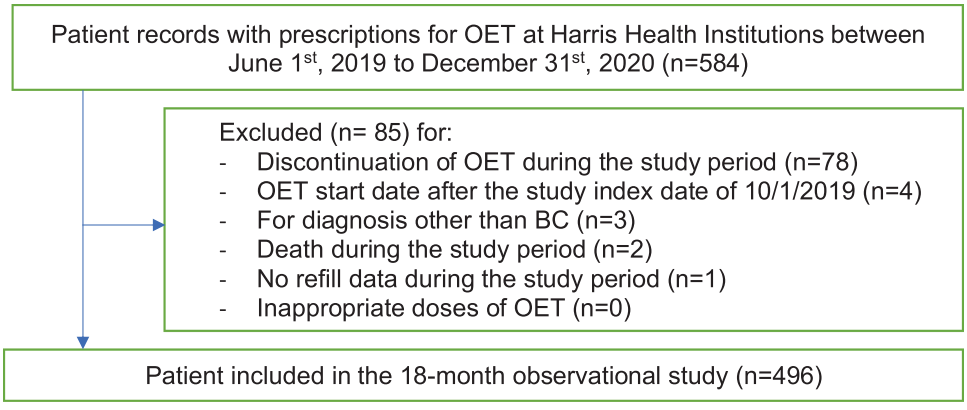

Figure 1 Selection of study subjects based on eligibility criteria. This figure illustrates the process of selecting study subjects based on specific eligibility criteria. The total number of subjects assessed for eligibility was 584, out of which 85 were excluded based on the predefined criteria. Ultimately, a total of 496 subjects were included in the study, with data collected over an 18-month period.

Baseline Characteristics

Patient demographics and tumor characteristics are detailed in Table 1. This study included 496 patients with stage 0 to IV BC. Out of the 496 patients, majority were under the age of 65 (n= 410, 82.6%) and female (n=495, 99.7%). There were 15.1% African American/non-Hispanic (n=75), 62.5% white/Hispanic (n=310), and 22.3% white/Caucasian/others (n=111) patients. The most significant comorbidities were hypertension (n=281, 56.6%) and hyperlipidemia (n=242, 48.7%), followed by diabetes (n=197, 39.7%) and depression (n=102, 20.5%). Most of our patients were classified as obese (BMI ≥ 30.0) (n=292, 58.8%) and overweight (BMI 25.0–29.9) (n=139, 28.0%). The most significant diagnosis was stage I (n=148, 29.8%) and stage II (n=142, 28.6%), followed by stage III (n=98, 19.7%), stage 0 (n=88, 17.7%) and stage IV (n=20, 4.0%). AIs were the more common OET (n=318, 64.1%,) as compared to tamoxifen (n=178, 35.8%). More patients were receiving OET for one year or less (n=205, 41.3%) or for 2–3 years (n=156, 31.4%) compared to four years or more (n=135, 27.2%).

Table 1 Baseline Characteristics of the Study Population (N (%))

Variable	Low Adherence with Gradual Decline (N=73)	Rapid Decline (N=57)	Consistent High Adherence (N=203)	Constant PDC at ~0.6 (N=163)	Total (N=496)	P-value
Age						
<65	61 (83.6)	44 (77.2)	166 (81.8)	139 (85.3)	410 (82.7)	0.5479
≥65	12 (16.4)	13 (22.8)	37 (18.2)	24 (14.7)	86 (17.3)	
Race/ethnicity						
AA	17 (23.3)	9 (15.8)	26 (12.8)	23 (14.1)	75 (15.1)	0.1799
Hispanic	39 (53.4)	32 (56.1)	128 (63.1)	111 (68.1)	310 (62.5)	
White/NH & others	17 (23.3)	16 (28.1)	49 (24.1)	29 (17.8)	111 (22.4)	
Gender						
Male	Not included in analysis				1 (0.2)	NA
Female					495 (99.8)	
Hyperlipidemia						
Yes	46 (63.0)	30 (52.6)	100 (49.3)	66 (40.5)	242 (48.8)	0.0131
No	27 (37.0)	27 (47.4)	103 (50.7)	97 (59.5)	254 (51.2)	
Hypertension						
Yes	46 (63.0)	30 (52.6)	128 (63.1)	77 (47.2)	281 (56.7)	0.0126
No	27 (37.0)	27 (47.4)	75 (36.9)	86 (57.8)	215 (43.3)	
Diabetes						
Yes	37 (50.7)	22 (38.6)	73 (36.0)	65 (39.3)	197 (39.7)	0.1796
No	36 (49.3)	35 (61.4)	130 (64.0)	98 (60.1)	299 (60.3)	
Depression						
Yes	13 (17.8)	13 (22.8)	37 (18.2)	39 (23.9)	102 (20.6)	0.5083
No	60 (82.2)	44 (77.2)	166 (81.8)	124 (76.1)	394 (79.4)	

(*Continued*)

Table 1 (Continued).

Variable	Low Adherence with Gradual Decline (N=73)	Rapid Decline (N=57)	Consistent High Adherence (N=203)	Constant PDC at ~0.6 (N=163)	Total (N=496)	P-value
Body Mass Index						
≤ 24.9	10 (13.7)	7 (12.3)	30 (14.8)	18 (11.0)	65 (13.1)	0.7803
25.0–29.9	18 (24.7)	20 (35.1)	57 (28.1)	44 (27.0)	139 (28.0)	
≥ 30.0	45 (61.6)	30 (52.6)	116 (57.1)	101 (62.0)	292 (58.9)	
Stages						
0	14 (19.2)	14 (24.6)	31 (15.3)	29 (17.8)	88 (17.7)	0.1354
I	22 (30.1)	22 (38.6)	67 (33.0)	37 (22.7)	148 (29.8)	
II	19 (26.0)	14 (24.6)	62 (30.5)	47 (28.8)	142 (28.6)	
III	13 (17.8)	6 (10.5)	38 (18.7)	41 (25.2)	98 (19.8)	
IV	5 (6.8)	1 (1.8)	5 (2.5)	9 (5.5)	20 (4.0)	
Type of Oral Endocrine Therapy						
AIs	54 (74.0)	36 (63.2)	131 (64.5)	97 (59.5)	318 (64.1)	0.2015
Tamoxifen	19 (26.0)	21 (36.8)	72 (35.5)	66 (40.5)	178 (35.9)	
Years on therapy						
≤ 1 year	27 (37.0)	24 (42.1)	93 (45.8)	61 (37.4)	205 (41.3)	0.0606
2–3 years	17 (23.3)	19 (33.3)	68 (33.5)	52 (31.9)	156 (31.5)	
≥ 4 years	29 (39.7)	14 (24.6)	42 (20.7)	50 (30.7)	135 (27.2)	

Abbreviation: AA – African American; NH – Non-Hispanic; AIs – Aromatase inhibitors.

Adherence Trajectories of OET

Four-group trajectory model was selected as the final model on the basis of Bayesian criteria, clinical relevance, and a 5% minimum membership requirement. Four adherence patterns emerged: 11.5% of patients had low adherence with gradual decline (group 1); 14.6% had rapid decline (group 2); 41.4% of patients had consistent high adherence (group 3); and 32.6% of patients had a constant PDC at ~0.6 (group 4). (Figure 2). The demographic and clinical characteristics of patients in each trajectory are presented in Table 1. The baseline characteristics were well balanced between the 4 adherence trajectories groups except for hyperlipidemia and hypertension (Table 1).

Predictors of Suboptimal Trajectories

Predictors of suboptimal trajectories are summarized in Table 2. Patients with diabetes (OR: 1.714 [1.042–2.820]) were more likely to be in the trajectory group 4 (constant PDC at ~0.6) than group 3 (consistent high adherence). The African American patients (OR: 2.462 [1.149–5.276]) had higher odds of being in the trajectory group 1 compared to Hispanic/Latinos. Patients with more than 4 years on therapy had higher likelihood of being in the trajectory group 1 (OR: 2.463 [1.266–4.793]) and trajectory group 4 (OR: 1.966 [1.141–3.388]) than the reference group (consistent high adherence).

Discussion

In this study, we described trajectories of OET adherence in underserved racial/ethnic minority patients and identified predictors of suboptimal adherence trajectories. Over a period of 18 months, four distinct adherence trajectories were followed in the selected model. These included (1) patients with slower decline over time, (2) patients with very low baseline (PDC < 0.3) and rapid decline, (3) patients with consistent high adherence (PDC > 0.8), (4) patients who had

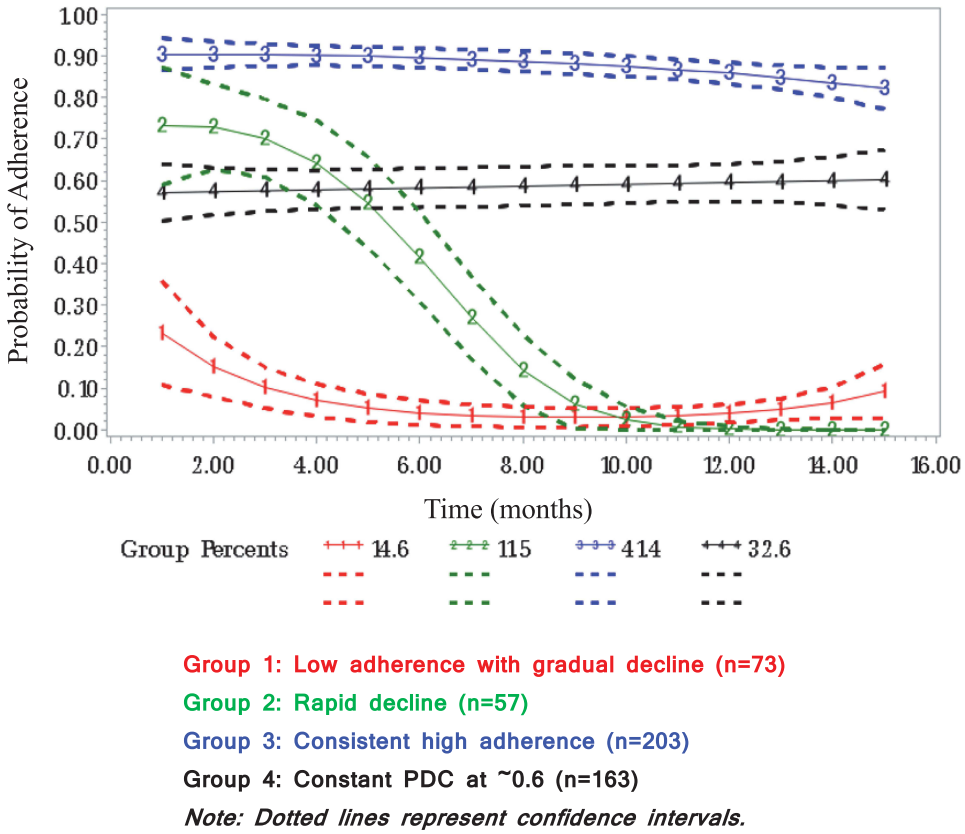

Figure 2 Group-Based Trajectory Model of OET adherence. This figure depicts the results of a Group-Based Trajectory Model analysis. The x-axis represents time in months, while the y-axis indicates the probability of adherence. The trajectories of different adherence groups are depicted as follows: The red trajectory (Group 1) shows a pattern of low adherence with a gradual decline over time. The green trajectory (Group 2) displays a rapid decline in adherence over the observed period. The blue trajectory (Group 3) demonstrates consistently high adherence throughout the study duration. The black trajectory (Group 4) represents a constant low adherence (PDC at ~0.6) throughout the study duration. This visualization provides valuable insights into the distinct adherence patterns identified within the studied population over time.

constant PDC at ~0.6. consistent high adherence was the reference group and this adherence trajectory consisted of 41.4% of our patients. Patients with diabetes and those with over four years of therapy were more likely to have constant suboptimal adherence. Additionally, African American patients and those with over four years of therapy had a higher likelihood of being in the low adherence group with gradual decline.

While our study is in overall agreement with the general trend of lower medication adherence in underserved patients,[40–45] several novel insights have emerged from our study. First, similar to our study, other GBTMs have also

Table 2 Predictors of Suboptimal Trajectories to OET Adherence by a Multinomial Logistic Regression Model

Variable	Ref	Low adherence with Gradual Decline			Rapid Decline			Constant PDC at ~0.6		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age		0.985	0.951–1.020	0.4042	1.035	0.998–1.072	0.0619	0.997	0.971–1.024	0.8482
Race/ethnicity										
AA	Hispanic	**2.462**	**1.149–5.276**	**0.0205***	1.796	0.732–4.403	0.2009	1.294	0.673–2.489	0.4393
White/NH & others	Hispanic	1.134	0.573–2.243	0.7176	1.295	0.641–2.616	0.4712	0.759	0.439–1.309	0.3212

(*Continued*)

https://doi.org/10.2147/PPA.S467892

Table 2 (Continued).

Variable	Ref	Low adherence with Gradual Decline			Rapid Decline			Constant PDC at ~0.6		
		OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
Oral Endocrine Therapy										
Tamoxifen	AIs	0.675	0.351–1.299	0.2392	1.281	0.660–2.485	0.4646	1.125	0.704–1.799	0.6214
Depression										
Yes	No	0.985	0.479–2.028	0.9682	1.34	0.645–2.783	0.4329	1.643	0.969–2.786	0.0654
Diabetes										
Yes	No	1.835	0.977–3.447	0.059	1.233	0.622–2.444	0.5479	**1.714**	**1.042–2.820**	**0.0338***
Hyperlipidemia										
Yes	No	1.634	0.844–3.164	0.1451	1.126	0.561–2.260	0.7376	0.722	0.438–1.191	0.2019
Hypertension										
Yes	No	0.645	0.325–1.281	0.2101	0.416	0.201–0.860	0.0179	0.459	0.274–0.769	0.0031
Body Mass Index										
≤ 24.9	≥ 30.0	0.871	0.373–2.031	0.7484	0.761	0.292–1.984	0.5769	0.564	0.285–1.112	0.0984
25.0–29.9	≥ 30.0	0.875	0.447–1.710	0.6954	1.303	0.660–2.573	0.4455	0.856	0.519–1.414	0.5439
Years on therapy										
2–3 years	≤ 1 year	0.888	0.440–1.795	0.7416	1.038	0.517–2.083	0.9163	1.178	0.712–1.949	0.5246
≥ 4 years	≤ 1 year	**2.463**	**1.266–4.793**	**0.008***	1.277	0.588–2.774	0.536	**1.966**	**1.141–3.388**	**0.0149***

Notes: Bolded text and * indicates statistically significant difference (P < 0.05, Multinomial logistic regression analysis). Group 1 – low adherence with gradual decline; Group 2 – rapid decline; Group 3 – consistent high adherence (PDC > 0.8); Group 4 – constant PDC at ~0.6.
Abbreviations: AA, African American; CI, confidence interval; OR, odds ratio; AIs, Aromatase inhibitors.

reported lower adherence rates among the minority patients of low socioeconomic status to other chronic medications for comorbidities such as atrial fibrillation, diabetes, hypertension, and atherosclerotic cardiovascular disease.[41–43] This pattern can be attributed to well-known socioeconomic factors (financial constraints, language barriers, transportation, lack of resources, etc.) and limitations to healthcare access, especially in this patient population. This study reported a continuous suboptimal adherence to OET as a major trajectory in an underserved population, with about a third of our patients. While this trajectory has been illustrated in other GBTM studies on OET adherence, it included only a small fraction of patients (≤ 10%).[44,45] Higher number of patients in our study in this group may indicate barriers of either cost, forgetfulness, or adverse reactions unique to underserved HR+ BC patients. Future prospective studies evaluating patient perspective on non-adherence will help us in better designing interventions to address these barriers. Other studies using GBTM for measuring OET adherence have found 5 or 6 trajectories; whereas, our study identified only four trajectories, which could be due to smaller sample size and shorter follow-up time.[46]

In comparison to another OET GBTM study, our study identified different adherence trajectories and predictors, which may be specific to the patient population.[46,47] For example, in our study, African Americans with lower SES demonstrated a trajectory marked by low adherence with a gradual decline, while a different study noted that patients with lower income were more prone to a trajectory characterized by a quick decline in adherence followed by an increase.[47] These disparities indicate potential unique predictors and trajectories associated with lower SES patients. Notably, at Harris Health, 45.9% of patients are uninsured, 21.2% are on Medicaid or Children's Health Insurance Program, 12% are on Medicare, and 19.9% are on commercial or other funding. This demographic breakdown

underscores the importance of considering the socio-economic context when interpreting adherence patterns. Furthermore, it is crucial to acknowledge that the other OET GBTM study was conducted in a country with centralized healthcare system, where cost may not pose a barrier to non-adherence. This contrasts with our U.S.-based study, particularly in underserved patients, where cost-related issues are more prominent. Understanding these differences is pivotal for tailoring interventions, education, and support programs to improve OET adherence for specific patient populations.

Our study has several strengths. This is the first study reporting GBTM of OET in the US and in underserved minority patients to our knowledge. Second, our study used prescription refill data from the EHR system to assess OET non-adherence, which provides a relatively more precise estimation of adherence compared to patient-reported data via interviews or surveys that are susceptible to overestimating adherence.[12,13,48] Discontinuation of OET due to clinical progression or life-threatening adverse effects was captured from reviewing the progress notes in the EHR and not considered as non-adherence. In addition, our study included all stages of BC including stage 0, where patients were taking OET in prevention setting, which is a largely understudied area of medication adherence research in BC.

There are some limitations to our study. The study did not account for some socio-demographic variables such as education level, patients' proximity to Harris Health facilities, or the transportation availability which could contribute to low adherence rates. As predictor variables were determined at the time of data collection, there may be some differences in BMI and/or comorbidities during follow up that were not accounted for. The study assumed that patients with a 90-day medication refill were using their medication continuously, which might result in an overestimation of their actual adherence. We also could not include patients who were prescribed OET but did not fill their prescription or used an external pharmacy that is not integrated with the Epic EHR system. This exclusion could also have contributed to an overestimation of adherence., The study assessed adherence over an 18-month period at any time during patients' OET therapy. A more effective approach would involve monitoring adherence from the initiation of therapy for at least five years. However, based on clinical practice and literature, the initial year of treatment is critical for establishing the medication adherence pattern as patients mainly experience variations during this time frame. Previous studies reported that nearly 30% of breast cancer survivors were non-adherent during the first year of therapy.[49] Future studies may benefit from considering a longer prospective cohort design, as well as integrating pharmacy data from external sources to provide a more comprehensive assessment of medication adherence over an extended period. Lastly, the study findings may not generalize to countries with universal healthcare systems where financial barriers were minimized. Despite these limitations, the study has found poor OET adherence rates among underserved minority patients, emphasizing the need of tailored interventions to address the specific barriers and enhance OET adherence in this population.

Conclusion

In summary, this study found that GBTM was valuable for understanding the longitudinal adherence patterns of OET among HR+ BC patients. We observed a significant non-adherence rate of approximately 60% within the low socio-economic minority cohort, with factors such as comorbidities like diabetes, being of African American descent, and undergoing OET for more than 4 years predicting suboptimal adherence trajectories. Our study is the first to report GBTM of OET in the US and in underserved minority patients, utilizing precise prescription refill data from the EHR system, enabling a more accurate estimation of adherence compared to patient-reported data. These conclusions should be considered in light of the limitations such as not accounting for certain socio-demographic variables and assuming continuous medication use based on refill data, which may potentially overestimate adherence rates. Nonetheless, these insights underscore the potential for developing culturally appropriate, patient-centered interventions, including mobile health applications, community-based educational initiatives, and financial aid programs tailored to address healthcare distrust, language barriers, and differing medication perspectives within these communities. Integrating these insights into tailored interventions can substantially enhance OET adherence and, consequently, improve the overall well-being of minority patient populations. Additionally, future studies focusing on investigating interventions to improve OET adherence among underserved patients with African American race, diabetes, and extended therapy durations are warranted.

Ethical Considerations

The study was performed in line with the principles of the Declaration of Helinski and approved by the institutional review boards of the University of Houston and the Harris Health System. Informed consent was waived for this retrospective analysis of the chart reviews, and patient data confidentiality was maintained.

Acknowledgments

The data in this paper have been presented at the 9th Annual Quality Improvement and Patient Safety Conference at Baylor College of Medicine in Houston, TX as a poster presentation. The poster's abstract was not published in a journal.

Funding

Research reported in this publication was supported in part by the National Institute on Minority Health and Health Disparities (NIMHD) (to Drs. Ononogbu, Abughosh, and Trivedi) and the National Cancer Institute (NCI) (to Dr. Trivedi) under Award Numbers U54MD015946 and 1P20CA221729-01A1, respectively.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Kolak A, Kaminska M, Sygit K, et al. Primary and secondary prevention of breast cancer. *Ann Agric Environ Med*. 2017;24(4):549–553. doi:10.26444/aaem/75943
2. Radecka B, Litwiniuk M. Breast cancer in young women. *Ginekol Pol*. 2016;87(9):659–663. doi:10.5603/GP.2016.0062
3. Anastasiadi Z, Lianos GD, Ignatiadou E, Harissis HV, Mitsis M. Breast cancer in young women: an overview. *Updates Surg*. 2017;69(3):313–317. doi:10.1007/s13304-017-0424-1
4. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 2023;73(1):17–48. doi:10.3322/caac.21763
5. Lopez-Tarruella S, Echavarria I, Jerez Y, Herrero B, Gamez S, Martin M. How we treat HR-positive, HER2-negative early breast cancer. *Future Oncol*. 2022;18(8):1003–1022. doi:10.2217/fon-2021-0668
6. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2019;37(5):423–438. doi:10.1200/JCO.18.01160
7. Milata JL, Otte JL, Carpenter JS. Oral endocrine therapy nonadherence, adverse effects, decisional support, and decisional needs in women with breast cancer. *Cancer Nurs*. 2018;41(1):E9–E18. doi:10.1097/NCC.0000000000000430
8. Goss PE, Ingle JN, Ales-Martinez JE, et al. Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med*. 2011;364(25):2381–2391. doi:10.1056/NEJMoa1103507
9. Cuzick J, Sestak I, Forbes JF, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. *Lancet*. 2020;395(10218):117–122. doi:10.1016/S0140-6736(19)32955-1
10. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 2005;97(22):1652–1662. doi:10.1093/jnci/dji372
11. Vogel VG, Costantino JP, Wickerham DL, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 trial: preventing breast cancer. *Cancer Prev Res*. 2010;3(6):696–706. doi:10.1158/1940-6207.CAPR-10-0076
12. Wheeler SB, Spencer J, Pinheiro LC, et al. Endocrine therapy nonadherence and discontinuation in black and white women. *J Natl Cancer Inst*. 2019;111(5):498–508. doi:10.1093/jnci/djy136
13. Atkins L, Fallowfield L. Intentional and non-intentional non-adherence to medication amongst breast cancer patients. *Eur J Cancer*. 2006;42(14):2271–2276. doi:10.1016/j.ejca.2006.03.004
14. Hwang GS, Paranjpe R, Opsomer C, et al. Oral endocrine therapy agent, race/ethnicity, and time on therapy predict adherence in breast cancer patients in a large academic institution. *Clin Breast Cancer*. 2020;20(6):520–526. doi:10.1016/j.clbc.2020.06.004
15. Ekinci E, Nathoo S, Korattyil T, et al. Interventions to improve endocrine therapy adherence in breast cancer survivors: what is the evidence? *J Cancer Surviv*. 2018;12(3):348–356. doi:10.1007/s11764-017-0674-4
16. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol*. 2008;26(4):556–562. doi:10.1200/JCO.2007.11.5451
17. Sedjo RL, Devine S. Predictors of non-adherence to aromatase inhibitors among commercially insured women with breast cancer. *Breast Cancer Res Treat*. 2011;125(1):191–200. doi:10.1007/s10549-010-0952-6
18. Hershman DL, Kushi LH, Shao T, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. *J Clin Oncol*. 2010;28(27):4120–4128. doi:10.1200/JCO.2009.25.9655
19. Nekhlyudov L, Li L, Ross-Degnan D, Wagner AK. Five-year patterns of adjuvant hormonal therapy use, persistence, and adherence among insured women with early-stage breast cancer. *Breast Cancer Res Treat*. 2011;130(2):681–689. doi:10.1007/s10549-011-1703-z
20. McCowan C, Shearer J, Donnan PT, et al. Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer*. 2008;99(11):1763–1768. doi:10.1038/sj.bjc.6604758
21. Hershman DL, Tsui J, Wright JD, Coromilas EJ, Tsai WY, Neugut AI. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. *J Clin Oncol*. 2015;33(9):1053–1059. doi:10.1200/JCO.2014.58.3062

22. Hjorth CF, Damkier P, Ejlertsen B, Lash T, Sorensen HT, Cronin-Fenton D. Socioeconomic position and prognosis in premenopausal breast cancer: a population-based cohort study in Denmark. *BMC Med*. 2021;19(1):235. doi:10.1186/s12916-021-02108-z
23. Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *J Clin Oncol*. 2009;27(21):3445–3451. doi:10.1200/JCO.2008.19.2419
24. Wheeler SB, Kohler RE, Reeder-Hayes KE, et al. Endocrine therapy initiation among Medicaid-insured breast cancer survivors with hormone receptor-positive tumors. *J Cancer Surviv*. 2014;8(4):603–610. doi:10.1007/s11764-014-0365-3
25. Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. *Cancer Prev Res (Phila)*. 2014;7(4):378–387. doi:10.1158/1940-6207.CAPR-13-0389
26. Farias AJ, Du XL. Association between out-of-pocket costs, race/ethnicity, and adjuvant endocrine therapy adherence among medicare patients with breast cancer. *J Clin Oncol*. 2017;35(1):86–95. doi:10.1200/JCO.2016.68.2807
27. Paranjpe R, John G, Trivedi M, Abughosh S. Identifying adherence barriers to oral endocrine therapy among breast cancer survivors. *Breast Cancer Res Treat*. 2019;174(2):297–305. doi:10.1007/s10549-018-05073-z
28. Font R, Espinas JA, Barnadas A, et al. Influence of adherence to adjuvant endocrine therapy on disease-free and overall survival: a population-based study in Catalonia, Spain. *Breast Cancer Res Treat*. 2019;175(3):733–740. doi:10.1007/s10549-019-05201-3
29. Hershman DL, Shao T, Kushi LH, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat*. 2011;126(2):529–537. doi:10.1007/s10549-010-1132-4
30. McCowan C, Wang S, Thompson AM, Makubate B, Petrie DJ. The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study. *Br J Cancer*. 2013;109(5):1172–1180. doi:10.1038/bjc.2013.464
31. Ma S, Shepard DS, Ritter GA, Martell RE, Thomas C. Association between medication adherence and non-drug healthcare utilisation and costs: a retrospective longitudinal cohort study among US women age 65 and older. *BMJ Open*. 2021;11(12):e052146. doi:10.1136/bmjopen-2021-052146
32. Franklin JM, Shrank WH, Pakes J, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789–796. doi:10.1097/MLR.0b013e3182984c1f
33. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab*. 2014;65(2–3):205–210. doi:10.1159/000360229
34. Nau DP. *Proportion of days Covered (PDC) as a Preferred Method of Measuring Medication Adherence*. Vol. 6. Springfield, VA: Pharmacy Quality Alliance; 2012:25.
35. Meneveau MO, Keim-Malpass J, Camacho TF, Anderson RT, Showalter SL. Predicting adjuvant endocrine therapy initiation and adherence among older women with early-stage breast cancer. *Breast Cancer Research and Treatment*. 2020;184:805–816. doi:10.1007/s10549-020-05908-8
36. Showalter SL, Meneveau MO, Keim-Malpass J, Camacho TF, Squeo G, Anderson RT. Effects of adjuvant endocrine therapy adherence and radiation on recurrence and survival among older women with early-stage breast cancer. *Annals of Surgical Oncology*. 2021;28(12):7395–7403. doi:10.1245/s10434-021-10064-4
37. Qian J, Truong B. Initiation of oral endocrine therapy and survival benefit among women with early-stage breast cancer. *Journal of Women's Health*. 2024;33:1509–1517. doi:10.1089/jwh.2023.0971
38. Faul F, Erdfelder E, Lang A-G, Buchner A. G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007;39(2):175–191. doi:10.3758/BF03193146
39. De Rubeis V, Andreacchi AT, Sharpe I, Griffith LE, Keown-Stoneman CD, Anderson LN. *Group-based Trajectory Modeling of Body Mass Index and Body Size Over the Life Course: A Scoping Review*. Wiley Online Library; 2021.
40. Nagin D. *Group-Based Modeling of Development*. Harvard University Press; 2005.
41. Mohan A, Majd Z, Trinh T, Paranjpe R, Abughosh SM. Group based trajectory modeling to assess adherence to oral anticoagulants among atrial fibrillation patients with comorbidities: a retrospective study. *Int J Clin Pharm*. 2022;44(4):966–974. doi:10.1007/s11096-022-01417-4
42. Paranjpe R, Johnson ML, Essien EJ, et al. Group-based trajectory modeling to identify patterns of adherence and its predictors Among Older Adults on Angiotensin-Converting Enzyme Inhibitors (ACEIs)/Angiotensin Receptor Blockers (ARBs). *Patient Prefer Adherence*. 2020;14:1935–1947. doi:10.2147/PPA.S270809
43. Vadhariya A, Fleming ML, Johnson ML, et al. Group-based trajectory models to identify sociodemographic and clinical predictors of adherence patterns to statin therapy among older adults. *Am Health Drug Benefits*. 2019;12(4):202–211.
44. Lailler G, Memoli V, Le Bihan Benjamin C, et al. Five-year adjuvant endocrine therapy adherence trajectories among women with breast cancer: a Nationwide French study using administrative data. *Clin Breast Cancer*. 2021;21(4):e415–e426. doi:10.1016/j.clbc.2021.01.007
45. Tervonen HE, Daniels B, Tang M, Preen DB, Pearson SA. Patterns of endocrine therapy in a national cohort of early stage HER2-positive breast cancer patients. *Pharmacoepidemiol Drug Saf*. 2019;28(6):812–820. doi:10.1002/pds.4751
46. Lambert-Cote L, Bouhnik AD, Bendiane MK, et al. Adherence trajectories of adjuvant endocrine therapy in the five years after its initiation among women with non-metastatic breast cancer: a cohort study using administrative databases. *Breast Cancer Res Treat*. 2020;180(3):777–790. doi:10.1007/s10549-020-05549-x
47. Winn AN, Dusetzina SB. The association between trajectories of endocrine therapy adherence and mortality among women with breast cancer. *Pharmacoepidemiol Drug Saf*. 2016;25(8):953–959. doi:10.1002/pds.4012
48. Wells KJ, Pan TM, Vazquez-Otero C, et al. Barriers and facilitators to endocrine therapy adherence among underserved hormone-receptor-positive breast cancer survivors: a qualitative study. *Support Care Cancer*. 2016;24(10):4123–4130. doi:10.1007/s00520-016-3229-8
49. Chang C-Y, Jones BL, Hincapie-Castillo JM, et al. Association between trajectories of adherence to endocrine therapy and risk of treated breast cancer recurrence among US nonmetastatic breast cancer survivors. *British Journal of Cancer*. 2024;1–8.