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ORIGINAL ARTICLE

State sequence analysis for a deeper understanding of treatment adherence patterns in fragility fracture patients

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Abstract

Summary We compared two methods to describe adherence to osteoporotic drugs after fragility fractures. While both similarly predicted refracture risk, a novel approach using sequence analysis provided a clearer picture of patient behavior, helping clinicians better understand and address adherence issues in osteoporosis care.

Background Fragility fractures are common among individuals with osteoporosis, causing significant morbidity, mortality, and healthcare costs. Although effective pharmacological treatments exist, underdiagnosis and poor treatment adherence remain pervasive in clinical practice.

Methods In order to select an effective methodology to describe and visually represent treatment adherence and correctly stratify patients with fragility fractures according to their adherence patterns, a conventional method using average PDC was compared to an alternative method, given by the state sequence analysis (SSA) and clustering procedure. Data on patients aged 50 or older who experienced fragility fractures between 2012 and 2017 were retrieved from healthcare utilization databases in Lombardy, Italy. Fine and Gray's model was employed to analyze the association between adherence (calculated by conventional and alternative methods) and refracture risk. Finally, the discriminatory power to predict outcomes was calculated for each approach.

Results Out of the 8976 patients included in this observational study, four different adherence groups were considered using the conventional method (very poor, poor, intermediate, and optimal), while three clusters (non-adherence, short-term adherence, and long-term adherence) were obtained from the SSA. Compared with non-adherent patients, those with long-term adherence were found to have a significantly reduced risk of combined death and refracture with both methods. Regarding discriminatory performance, the two approaches showed similar AUC, 0.646 and 0.644 for conventional and alternative methods, respectively.

Conclusions Based on the SSA and cluster analysis, the alternative method does not significantly modify the prediction of the refracture risk but enhances the description and visualization of the adherence patterns.

Keywords Adherence · Fragility fractures · Pharmacoepidemiology · State sequence analysis · Treatment

Laura Savaré and Gloria Porcu contributed equally to this work and served as co-first authors.

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Introduction

Fragility fractures, which occur due to minimal or unidentifiable trauma such as a fall from a standing height or less, have garnered great attention as a public health concern [1]. Osteoporosis, a chronic degenerative disease characterized by a decline in bone mineral density (BMD) and alterations in skeletal microarchitecture, primarily affects the elderly population, particularly women [2–7]. Globally, it is estimated that osteoporosis is responsible for approximately 9 million fractures each year, leading to significant serious consequences in terms of morbidity, mortality, quality of life, and healthcare costs [2, 3, 8].

Over the past few decades, several medicaments have been developed to treat osteoporosis, including hormonal therapies preventing bone loss, anabolic agents stimulating bone formation, and antiresorptive drugs enhancing bone strength [7, 9, 10]. Consistent evidence from randomized clinical trials suggests that these medicaments can improve patients' overall health and reduce the risk of subsequent fractures [1–3, 8, 11].

However, in real-world practice, osteoporosis remains largely underdiagnosed, and even when identified and treated by clinicians, many patients show a low propensity to follow the recommended therapies. This limited adherence is compounded by challenges in assessing treatment patterns over long-term periods, as common adherence measures often provide only point estimates of drug availability without capturing temporal changes or treatment interruptions [12]. Moreover, variability between patients is frequently simplified by assigning arbitrary adherence categories, which may obscure clinically relevant differences in behavior.

Given these challenges, undertreatment and suboptimal adherence emerge as major barriers to effective osteoporosis management [2, 11].

With the primary objectives of (i) selecting an effective methodology for describing and visually representing treatment adherence, (ii) stratifying patients with fragility fractures based on between-pattern distance, and (iii) validating stratification by assessing its association with the risk of refracture and all-cause mortality within the study population, we carried out an observational cohort study on patients suffering from fragility fractures.

Methods

Setting

Data were obtained from Lombardy's healthcare utilization databases, a region in northern Italy. In Italy, all citizens have equal access to healthcare provided by the National Health Service (NHS). An automated healthcare utilization (HCU) database system is used to manage health services in each region, including Lombardy. HCU data contain various information on residents, such as diagnosis at discharge from public or private hospitals, outpatient drug prescriptions, specialist visits, and diagnostic exams provided entirely or in part, free of charge by the NHS. Record linkage across these data sources is performed and maintained by ARIA S.p.A. (Azienda Regionale per l'Innovazione e gli Acquisti), the regional agency responsible for healthcare data management on behalf of Regione Lombardia. To preserve privacy, each identification code is automatically anonymized by ARIA; the inverse process is only allowed to the Regional Authority upon request of Judicial Authorities. Moreover, to ensure the accuracy of this record linkage, consistency checks and validation procedures are routinely performed by the regional data management infrastructure, including verification of identifier uniqueness, cross-database consistency, and comparison with previously validated linkage protocols. Further details on the HCU database in the field of osteoporosis and fractures have been reported elsewhere [13, 14]. Diagnostic and therapeutic codes used in this study can be found in Supplementary Table S1.

Cohort selection and follow-up

The target population consisted of all beneficiaries of the NHS residents in Lombardy aged 50 years or older who experienced a fracture between January 1, 2012, and June 30, 2017 [15]. The first fracture that occurred during this period was defined as the *index fracture*.

Since only fragility fractures were of interest for the current study, patients with exposed fractures were excluded, as they were likely due to major trauma [16]. Additionally, we excluded patients who, within 2 years before the index fracture, (i) had become new beneficiaries of the Regional Health Service (because information for characterizing them according to previous health journey was insufficient), (ii) had signs of Paget syndrome or neoplasms (as these conditions affect indication for antiosteoporosis medications and the risk of fracture), (iii) had already experienced fractures (because we were interested in the first fracture that occurred), and (iv) had already received at least one antiosteoporosis drug (because we were interested in the first drug therapy administered). Furthermore, we excluded patients who had experienced a second fracture before the drug prescription (to ensure that the drugs of interest were prescribed in response to the initial fragility fracture). Patients who did not initiate pharmacological therapy within 6 months following the fracture were also excluded, i.e., for those who, according to the "user-only" principle, may not indicate starting antiosteoporosis medication [17]. Finally, the cohort was restricted to patients with at least 2 years of follow-up after initiating antiosteoporosis treatment, as pharmacoutilization metrics were calculated over a predefined 2-year period. The date of the first antiosteoporosis drug dispensed within 6 months after the index fracture served as the *entry date*, and the subsequent 2 years as the *exposure period*.

Included patients accumulated person-years of follow-up from the end of the exposure period until the earliest of the following events, which define the follow-up for outcome occurrence: (i) a new fracture or death (the outcomes of interest), (ii) censorship due to emigration, transfer to a hospice or residential care facility, or the study's endpoint on December 31, 2020.

Covariates

The included patients were assessed at baseline for several covariates, including age at the index fracture, sex, fracture site (vertebral, hip, or other sites), and selected comorbidities and cotreatments. Additionally, the so-called multisource comorbidity score (MCS), a comorbidity index derived from inpatient diagnostic information and outpatient treatment data, was calculated for each individual. Patients were categorized as having good (0), milder (1–4), middle (5–14), or severe (≥ 15) clinical profiles [18]. Estimates were adjusted for covariates measured at baseline (see Table 1) and tested for trend (considering significant p-values < 0.05).

Measuring adherence

All antiosteoporosis medicaments dispensed during the exposure period were identified. The coverage for each prescription was calculated by dividing the total prescribed quantity by the defined daily dose (DDD), the estimated average maintenance dose per day for a drug when used for its primary indication in adults [19]. Adherence to drug therapy was assessed according to the proportion of days covered (PDC) metric [20]. PDC is defined as the ratio of the number of days during which one or more antiosteoporosis drugs were available to the total number of days in the considered period [20].

Two methods were adopted for assigning drug therapy exposure and grouping cohort members according to similar exposure patterns.

The first one, hereinafter referred to as the *conventional approach*, consists of assigning each member of the cohort the average PDC accumulated during the whole *exposure period* and grouping patients according to the predefined categories of PDC, labeled as indicative of very poor ($0 < \text{PDC} \leq 25\%$), poor ($25\% < \text{PDC} \leq 50\%$), intermediate ($50\% < \text{PDC} \leq 75\%$), and optimal ($75\% < \text{PDC} \leq 100\%$) adherence.

Due to the limitations of conventional approaches, the second method, hereinafter referred to as the *alternative approach*, consists of (i) assigning a monthly exposure PDC pattern through the state sequence analysis (SSA) and (ii) grouping similar exposure patterns through a clustering procedure.

State sequence analysis

Because the conventional approach assigned to each patient his/her average PDC over the exposure period, it implicitly assumes a uniform adherence level during this period, which is not necessarily true, as drug adherence may fluctuate on a monthly basis. To overcome this limitation, the SSA, allowing for a comprehensive exploration of the entire adherence pattern, provides a more realistic understanding of individual drug adherence behaviors over time [21, 22].

A sequence is an ordered list of elements characterized by the list of possible elements (i.e., the alphabet) and the temporal axis that assigns a timestamp to each state. In our application, it denotes the succession of treatments received, with each element representing a specific status (in our case, treatment coverage given by the PDC metric) [23]. For the present study, each month during the *exposure period* (the 2 years following the entry date) is considered a state, serving as the elementary building block of the sequences. These states are then assigned one of the possible states of the alphabet (i.e., one of four adherence categories based on the PDC metric: very poor [0–25]%, poor [25–50]%, intermediate [50–75]%, and optimal [75–100]%). Consequently, this results in a sequence of 24 states for each patient, as illustrated in Supplementary Figure S1. The decision to study these pathways for 2 years strikes a balance, providing a sufficiently long period to characterize the pathway without being overly extensive and thus mitigating the impact of immortal bias [24].

Clustering procedure

A clustering procedure was implemented to address the potential heterogeneity introduced by individual adherence patterns revealed through the SSA, as opposed to the oversimplified approach of assigning patients into predefined categories of PDC, as in the case of traditional methods. Clustering patients based on similar adherence patterns identified through the SSA aimed to create more homogeneous subgroups within the cohort. This method facilitated the exploration of adherence patterns by capturing underlying similarities and differences in drug adherence behaviors, offering insights into distinct subpopulations with varying adherence profiles, and identifying typologies.

With this purpose, we first adopted a dissimilarity measure based on counts of shared attributes and subsequently

Table 1 Characteristics of cohort members stratified by adherence levels

Covariates	Very poor PDC < 25 (*N* = 3894)	Poor 25 < PDC < 50 (*N* = 1150)	Intermediate 50 < PDC < 75 (*N* = 1404)	Optimal PDC > 75 (*N* = 2528)	*p*-value
Female	3309 (42.0%)	1029 (13.1)	1264 (16.0)	2282 (28.9)	< 0.0001
Age class					
50–64 years	738 (19.0)	195 (17.0)	243 (17.3)	421 (16.7)	< 0.0001
65–84 years	2456 (63.1)	778 (67.7)	939 (66.9)	1764 (69.8)	
85 +	700 (18.0)	177 (15.4)	222 (15.8)	343 (13.6)	
Type of fracture					
Hips	517 (13.3)	155 (13.5)	204 (14.5)	398 (15.7)	< 0.0001
Vertebra	910 (23.4)	337 (29.3)	450 (32.05)	844 (33.4)	
Other	2467 (63.4)	658 (57.22)	750 (53.4)	1286 (50.9)	
Type of treatment					
Strontium ranelate	665 (17.1)	113 (9.8)	97 (6.9)	92 (3.6)	< 0.0001
Anabolics	17 (0.4)	21 (1.8)	19 (1.4)	105 (4.2)	
Bisphosphonates and denosumab	3212 (82.5)	1016 (88.4)	1288 (91.7)	2331 (92.2)	
Multisource comorbidity score					
0	1497 (38.4)	406 (35.3)	502 (35.8)	972 (38.5)	0.0016
1–4	1461 (37.5)	413 (35.9)	574 (40.9)	991 (39.2)	
5–14	857 (22.0)	298 (25.9)	304 (21.7)	526 (20.8)	
15 +	79 (2.0)	33 (2.9)	24 (1.7)	39 (1.5)	
Comorbidities					
Immunity disorders	126 (3.2)	40 (3.5)	44 (3.1)	87 (3.4)	0.9316
Parkinson's, Alzheimer's, and dementia diseases	189 (4.9)	65 (5.7)	52 (3.7)	127 (5.0)	0.1227
Diabetes	508 (13.1)	137 (11.9)	156 (11.1)	255 (10.1)	0.0035
Chronic inflammatory bowel disease	124 (3.2)	44 (3.8)	37 (2.6)	68 (2.7)	0.2109
COPD	58 (1.5)	21 (1.8)	28 (2.0)	43 (1.7)	0.6028
AIDS	11 (0.3)	3 (0.3)	6 (0.4)	7 (0.3)	0.8248
Abnormal movement disorders	12 (0.3)	5 (0.4)	13 (0.9)	11 (0.4)	0.0332
Others connective tissue diseases	457 (11.7)	170 (14.8)	192 (13.7)	363 (14.4)	0.0045
Peripheral vascular disease	23 (0.6)	10 (0.9)	5 (0.4)	10 (0.4)	0.2200
Diseases of the circulatory system	564 (14.5)	167 (14.5)	200 (14.3)	320 (12.7)	0.1826
Chronic renal failure	36 (0.9)	15 (1.3)	12 (0.9)	21 (0.8)	0.5537
Adjuvant hormonal blockade	93 (2.4)	26 (2.3)	30 (2.1)	60 (2.4)	0.9536
Corticosteroids	711 (18.3)	255 (22.2)	295 (21.0)	536 (21.2)	0.0030
Disorders of lipoid metabolism	969 (24.9)	298 (25.9)	369 (26.3)	677 (26.8)	0.3691
Obesity	11 (0.3)	6 (0.5)	2 (0.1)	7 (0.3)	0.3590

grouped individuals showing similar sequences [25]. Dissimilarity was measured according to a metric based on the length of the longest common subsequence (LCS) [26]. This method measures the dissimilarity as the number of elements in one sequence that can be uniquely matched with elements appearing in the same order in the other sequence. We then performed a cluster analysis employing the hierarchical clustering method, specifically utilizing the Ward algorithm [27]. Hierarchical agglomerative clustering algorithms operate by iteratively merging pairs of clusters, and the choice of which clusters to merge varies based on the criterion employed. Ward's algorithm identifies the two clusters for merging by minimizing the increase in within-group dispersion, effectively reducing the number of partitions. After generating partitions, we used a silhouette analysis to determine the optimal number of clusters [28]. Interpreting the resulting partitions from the clustering procedure provides insights into each patient's drug utilization pattern.

Comparing the predictive potential of conventional and alternative approaches

Under the assumption that the adherence pattern to antiosteoporosis medicaments during the first 2 years after the index fracture predicts the risk of a secondary fracture occurring afterward, we evaluated whether the alternative approach improved the prediction of the considered outcomes with respect to the conventional one. This was done using a two-step procedure. The first one measured the association between the adherence category (as measured by averaging coverage with drug availability or clustering patterns) and the risk of refracture (i.e., the main outcome of interest) through a time-to-event model. Specifically, the approach proposed by Fine and Gray [29] was used, considering death as a competitive outcome. In order to account for the competing risk of death, Cumulative Incidence Functions (CIFs) for refracture were estimated and graphically presented for each adherence cluster (Supplementary Figure S2).

Subsequently, predictive performance was evaluated through discrimination by comparing how well conventional and alternative approaches distinguish between patients who experienced the outcome and those who did not. For this purpose, discriminatory powers were compared using (i) the receiver operating characteristic (ROC) curves and the corresponding area under the ROC curves (AUCs), (ii) the concordance statistic (*C*-statistic), and (iii) the net reclassification improvement (NRI) [30]. Given the time-to-event nature of the data and the use of competing risk models, time-dependent AUC and *C*-statistics were calculated at multiple time points (from 3 to 7 years of follow-up) to assess predictive performance over time [31]. The *C*-statistic measures the agreement between two variables (i.e., risk score and time until the event), while the NRI assesses the improvement in risk classification by measuring the net proportion of subjects correctly reclassified by evaluating the predicted probability between those who experienced and did not experience the outcome [32, 33].

To assess the internal validity of the predictive models and avoid optimistic bias from apparent performance, we performed a tenfold cross-validation [34]. The *C*-statistic was manually calculated using Harrell's concordance index for each test fold. The optimism, difference between apparent and cross-validated performance, quantifies the degree of overfitting.

Sensitivity analysis

Several sensitivity analyses were performed to verify the robustness of our findings. Firstly, different dichotomous adherence levels at commonly used thresholds (PDC $\geq$ 80% vs $<$ 80% and PDC $\geq$ 90% vs $<$ 90%) were considered [35]. Secondly, to more comprehensively address potential confounding, we applied inverse probability of treatment weighting (IPTW) using generalized propensity scores [36] which were estimated via multinomial logistic regression, including all baseline covariates from the primary model (age, sex, fracture site, comorbidities, cotreatments, and MCS). Stabilized weights were calculated to improve precision and reduce extreme weights, and were applied to Fine–Gray competing risk models. Thirdly, a Cox proportional hazards regression was fitted, modeling the time-dependent classification that accommodates changes in adherence during follow-up and considering death as a censoring instead of a competitive outcome, as described in Fine and Gray's methodology [37]. Lastly, since several patients discontinued drug therapy within the few months following the initial prescription, a subset of the cohort comprising individuals who renewed their original prescriptions at least once during the 2-year exposure period from the entry date was considered.

All analyses were carried out with the SAS 9.4 statistical software (SAS Institute, Cary, NC) and an R software environment, using the TraMineR package for mining and visualizing sequences of categorical data [38, 39].

Results

Cohort selection and features

From a target population of roughly 4 million residents over 50 years old in the Lombardy Region, approximately 774,000 patients experienced a fracture between January 1, 2012, and June 30, 2017. Of these, 8976 patients fulfilling the inclusion criteria were admitted in the final cohort (Fig. 1). At baseline, they were aged about 74.5 years, 87.8% were female, 28.3% were admitted for vertebral fractures, and 14.2% were admitted for hip fractures. Baseline characteristics of patients included in the cohort are detailed in Supplementary Table S2. Since the endpoint of this period, cohort members accumulated 46,915 person-years of follow-up (approximately 5.2 years per patient), during which 1555 individuals (17.3%) experienced a new fracture (the incidence being 33 patients experiencing refracture every 1000 person-years). According to the conventional approach, 3894 (43.4%), 1150 (12.8%), 1404 (15.6%), and 2528 (28.2%) cohort members, respectively, exhibited very poor, poor, intermediate, and optimal adherence during the exposure period (i.e., the first 2 years after starting antiosteoporosis drug therapy). Patients with low adherence tend to be younger and have experienced hip or vertebral fractures less frequently. This group also shows a higher proportion of strontium ranelate users compared with patients with high adherence. Conversely, the proportion of users of anabolic agents and of bisphosphonates or denosumab is lower. Moreover, patients with low adherence more often exhibit critical MCS levels and show a higher prevalence of diabetes (Table 1).

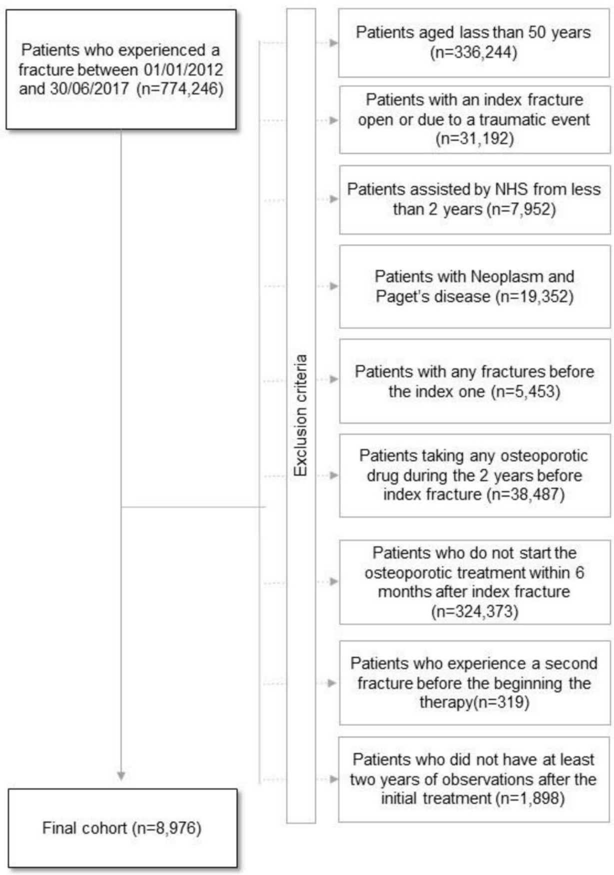

Fig. 1 Flowchart of the cohort selection

State sequence analysis

The monthly state frequency distribution over 2 years of exposure period is shown in Fig. 2. Adherence quickly decreased after the second month, reaching an extremely low level. Over the course of the exposure period, the percentage of patients with very poor adherence increased rapidly, comprising 50% of the cohort after a year. Supplementary Figure S3 presents the ten most common sequences observed among included patients. The prevailing patterns predominantly depict patients undergoing drug therapy for a brief period, typically spanning 1–3 months, followed by an extended phase marked by suboptimal adherence or complete discontinuation of antiosteoporosis therapy. The resumption of drug therapy after a therapeutic holiday period does not appear in this representation, suggesting that this eventuality is infrequent in current practice.

Transition rates between adherence states are presented in Supplementary Table S3. The most long-lasting states are concerned with the lowest and the highest categories of adherence, respectively, with 93% and 74% persisting probabilities in this state for those already positioned there. Conversely, poor adherence and intermediate adherence are unstable states, as two-thirds of patients in these states transit towards improving adherence, while a quarter of them transit towards worsening adherence.

Clustering analysis

Three adherence patterns, derived from the SSA, categorize patients into distinct groups: the first with persistent *non-adherence* (3616 patients), the second with *short-term*

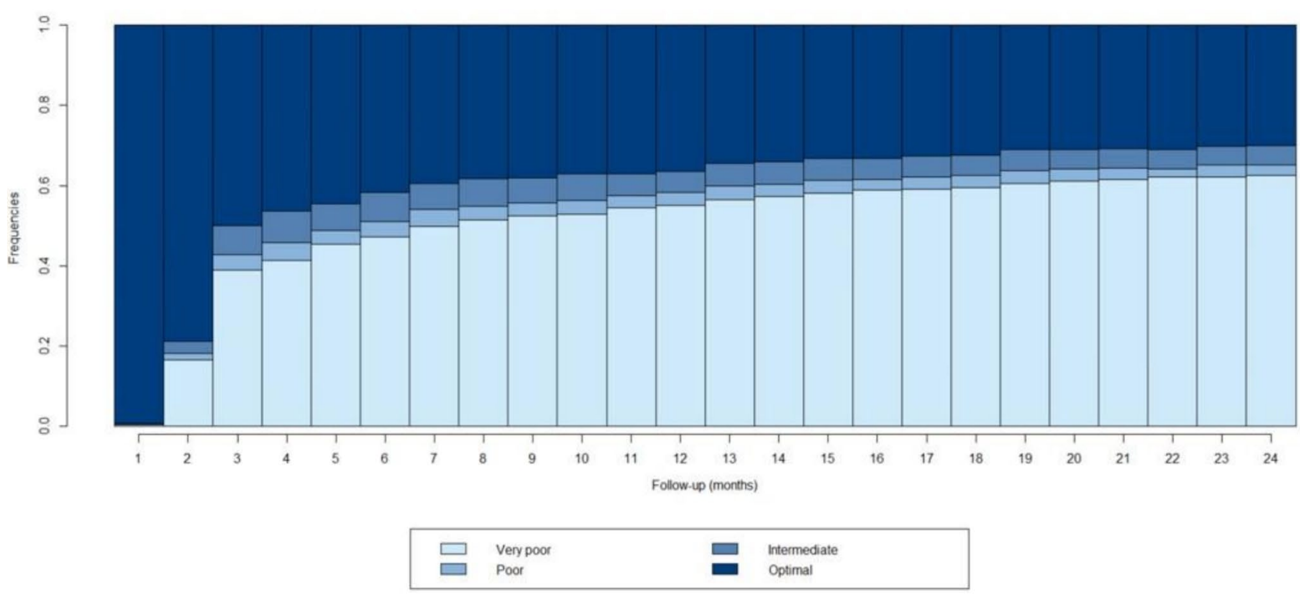

Fig. 2 Frequency distribution of adherence states

adherence followed by interruption (1553 patients), and the third with consistent optimal adherence (3807 patients) over the 2-year period, denoted as the *long-term adherence* cluster (Fig. 3). These clusters exhibit unique characteristics, with the non-adherence group being younger and clinically stable, while the short-term adherence group comprises older and medically complex patients (Table 2). The distribution of the baseline covariates across the clusters obtained by the novel approach shows no substantial differences compared with those reported for the adherence levels defined using the conventional method.

Comparing the predictive power of conventional and alternative approaches

Supplementary Table S4 provides a detailed comparison of estimates obtained from conventional and alternative methodologies. Both models indicate a protective effect associated with higher adherence to antiosteoporosis treatments, with a consistent trend observed across various adherence groups.

Figure 4 displays the time-dependent AUC values for both approaches at 7 years of follow-up, while the values for other time points are reported in Supplementary Table S5. The apparent AUC values (95% CI) were 0.6455 (0.6268–0.6642) for the conventional PDC-based approach and 0.6444 (0.6257–0.6632) for the alternative SSA-based approach, while the values of the *C*-statistic were 0.6411 and 0.6406, respectively.

Internal validation using tenfold cross-validation confirmed these findings. The mean *C*-statistics were 0.6379 (0.6279–0.6482) and 0.6381 (0.6285–0.6477), respectively. The optimism was 0.0032 for the conventional method and 0.0025 for the alternative method, which showed similar discrimination compared to the conventional method (mean difference, 0.000225; $p = 0.8017$ by paired *t*-test). These estimates were consistent with the apparent performance metrics, indicating minimal overfitting and supporting the generalizability of our findings to new patient populations.

Additionally, performance analysis using NRI showed no significant improvement in the prediction of refractures by using the alternative approach instead of the conventional one. Particularly, the SSA improved by 1% the specificity of the correct reclassification of patients who did not experience the outcome, whereas it decreased the sensitivity by 2%.

Sensitivity analyses

The sensitivity analyses confirmed the robustness of our findings, showing that the estimates remained largely unchanged across alternative specifications and assumptions. Considering the dichotomous PDC with cutoffs at 80% and 90%, the results are confirmed: patients with higher adherence show a lower risk of refracture (see

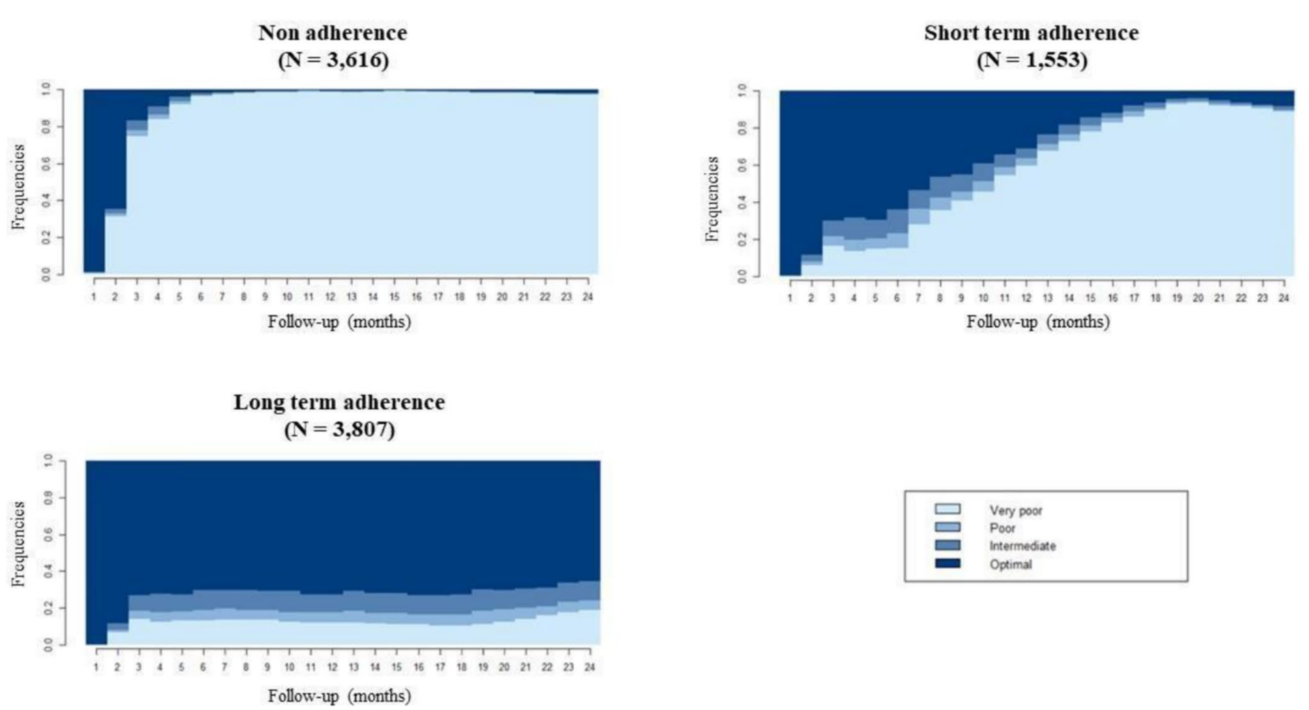

Fig. 3 Frequency distribution of adherence states among clusters

Table 2 Characteristics of cohort members stratified by clusters

Covariates	Non-adherence ($N=3616$)	Short-term adherence ($N=1553$)	Long-term adherence ($N=3807$)	*p*-value
Female	3076 (85.1%)	1375 (88.5%)	3433 (90.2%)	< 0.0001
Age class				
50–64 years	692 (19.1%)	264 (17.0%)	641 (16.8%)	< 0.0001
65–84 years	2285 (63.2%)	1010 (65.0%)	2642 (69.4%)	
85 +	639 (17.7%)	279 (18.0%)	524 (13.8%)	
Type of fracture				
Hips	475 (13.1%)	206 (13.3%)	593 (15.6%)	< 0.0001
Vertebra	829 (22.9%)	466 (30.0%)	1246 (32.7%)	
Other	2312 (63.9%)	881 (56.7%)	1968 (51.7%)	
Type of treatment				
Strontium ranelate	630 (17.4%)	153 (9.9%)	184 (4.8%)	< 0.0001
Anabolics	13 (0.4%)	26 (1.7%)	123 (3.2%)	
Bisphosphonates and denosumab	2973 (82.2%)	1374 (88.5%)	3500 (91.9%)	
Multisource comorbidity score				
0	1388 (38.4%)	570 (36.7%)	1419 (37.3%)	0.0005
1–4	1362 (37.7%)	555 (35.7%)	1522 (40.0%)	
5–14	800 (22.1%)	381 (24.5%)	804 (21.1%)	
15 +	66 (1.8%)	47 (3.0%)	62 (1.6%)	
Comorbidities				
Immunity disorders	121 (3.4%)	44 (2.8%)	132 (3.5%)	0.4935
Parkinson's, Alzheimer's, and dementia diseases	175 (4.8%)	81 (5.2%)	177 (4.7%)	0.6791
Diabetes	476 (13.2%)	175 (11.3%)	405 (10.6%)	0.0027
Chronic inflammatory bowel disease	116 (3.2%)	50 (3.2%)	107 (2.8%)	0.5502
COPD	47 (1.3%)	35 (2.6%)	68 (1.8%)	0.0378
AIDS	10 (0.3%)	6 (0.4%)	11 (0.3%)	0.7915
Abnormal movement disorders	11 (0.3%)	9 (0.6%)	21 (0.6%)	0.2102
Others connective tissue diseases	421 (11.6%)	219 (14.1%)	542 (14.2%)	0.0021
Peripheral vascular disease	23 (0.6%)	10 (0.6%)	15 (0.4%)	0.2918
Diseases of the circulatory system	515 (14.2%)	243 (15.7%)	493 (13.0%)	0.0279
Chronic renal failure	30 (0.8%)	25 (1.6%)	29 (0.8%)	0.0096
Adjuvant hormonal blockade	82 (2.3%)	36 (2.3%)	91 (2.4%)	0.9401
Corticosteroids	648 (17.9%)	340 (21.9%)	809 (21.3%)	0.0002
Disorders of lipoid metabolism	910 (25.2%)	389 (25.1%)	1014 (26.6%)	0.2722
Obesity	10 (0.3%)	7 (0.5%)	9 (0.2%)	0.4085

Supplementary Table S6). To address potential confounding more comprehensively, we applied IPTW using generalized propensity scores: the results remained consistent with the primary analysis, supporting the robustness of our findings to residual confounding (Supplementary Table S6). The relationships between the pattern of adherence and the risk of refracture did not substantially change by (i) considering death as censored data instead of competing risk and (ii) limiting the analysis to a subset of the cohort comprising individuals who renewed their original prescriptions at least once during the 2-year exposure period (Supplementary Table S6).

Discussion

Our population-based study aimed at achieving the following objectives: (i) selecting an effective methodology for describing and visually representing treatment adherence, (ii) stratifying patients with fragility fractures based on commonly observed adherence patterns, and (iii) validating this stratification approach by assessing its association with the risk of refracture and all-cause mortality within the study population. The study advanced beyond the conventional method, overcoming its limitations with the SSA methodology, which more effectively enables the exploration of the

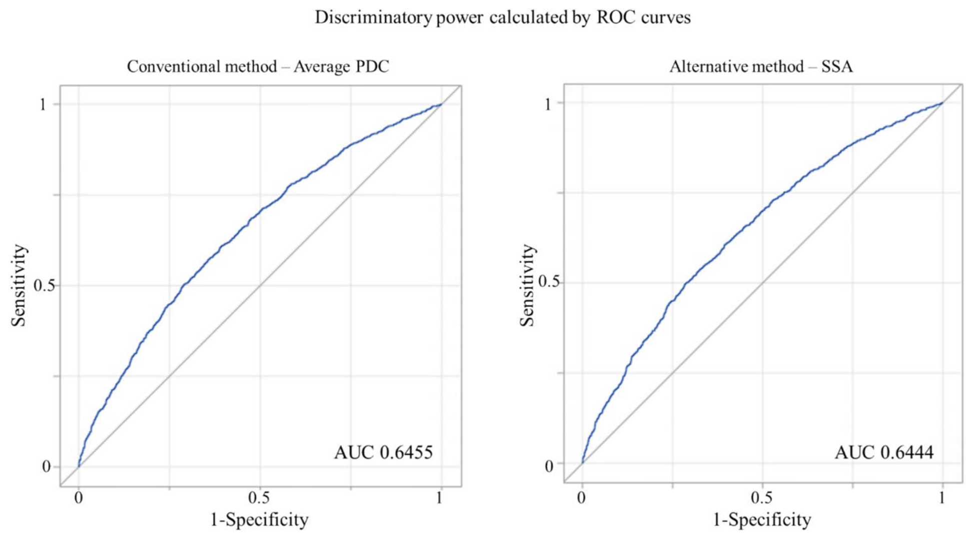

Fig. 4 Receiver operating characteristic (ROC) curves at 7 years of follow-up comparing the discriminant power of conventional and alternative approaches in predicting refractures (AUC, area under the ROC curve)

entire adherence pattern, avoiding the average estimate of adherence across the entire period. Moreover, the analysis was refined through clustering techniques to deepen our comprehension of the highly heterogeneous phenomenon of drug adherence. The findings of the study support the successful realization of these objectives. The chosen methodology effectively described and visually represented treatment adherence, enabling a comprehensive understanding. This new strategy appears to be no worse than the conventional one in terms of predicting the outcome: the discriminatory power of the two approaches is relatively similar. As a result, even if the alternative approach using the SSA with cluster analysis does not provide additional predictive information regarding the outcome of interest, it is still highly recommended, especially when analyzing adherence patterns. However, it should be acknowledged that the SSA method is less straightforward to implement compared to traditional adherence measures, which may limit its routine use in some research or clinical settings.

In practice, our population-based study on fractured patients provides compelling evidence that the proportion of patients exhibiting optimal adherence gradually diminishes over time, stabilizing at approximately 40% after approximately 6–8 months of treatment. In contrast, the cohort of patients with the lowest adherence levels experiences notable growth, particularly after the third month of treatment.

Patients with previous fragility fractures who sustained optimal adherence to therapy for nearly the entire 2-year exposure period were associated with a significantly reduced risk of refractures when compared to non-adherent patients.

The observed pattern of adherence appears to be in line with the adherence and persistence rates reported for the initial year of follow-up in most articles, just as it is confirmed in the literature that maintaining optimal adherence to antiosteoporotic therapy throughout the follow-up period is associated with a reduced risk of refracture [1, 2, 4, 5, 20, 22–24, 26, 27]. While both the conventional PDC-based and alternative SSA-based approaches demonstrated statistically significant associations between adherence and refracture risk, the modest discriminatory performance (AUC ~ 0.64) warrants careful interpretation. These values indicate that, although adherence patterns are clearly associated with outcome risk, they represent relatively weak predictors for individual patient risk stratification.

This limited discriminative ability reflects the multifactorial nature of refracture risk, which is influenced by numerous factors beyond medication adherence, including bone mineral density, fall risk, comorbidities, frailty, nutritional status, and genetic factors [40, 41]. From a clinical perspective, however, the consistent association between higher adherence and reduced refracture risk across both methodologies reinforces the importance of adherence as a modifiable risk factor at the population level, even if its predictive utility for individual patients remains limited. Given these findings, it is imperative for general practitioners to closely monitor and support patients in managing their treatment adherence.

The present study has five main strengths. Firstly, it leverages Italy's free healthcare system, which ensures comprehensive coverage for all residents irrespective of their ethnicity or socioeconomic status, and allows us to base our study on a large and unselected population. Secondly, the administrative database generates highly accurate data because all services claimed by health providers are checked to allow reimbursement by the Regional Health Authority, and incorrect reports may have legal consequences. Thirdly, real-world analysis enables the inclusion of long-term effects that may be challenging to observe through a randomized controlled trial (RCT) design. Moreover, RCTs may not be feasible or ethical in certain settings (e.g., when a therapy has already demonstrated effectiveness, it may not be ethical to request patients to discontinue it), whereas real-world analyses are. Fourthly, our application of the SSA represents an emerging epidemiological methodology that holds promise in providing profound insights into the sequence of care received, the frequency and timing of treatments administered in clinical practice, and the impact of various drug-based pathways on specific outcomes of interest [11]. Specifically, this technique yields more realistic and informative results when compared to commonly used baseline measures, such as adherence with the intention-to-treat approach [8]. This is because it considers the entire evolution of each patient's clinical pathway, retaining the valuable heterogeneity and variability inherent in longitudinal data. Moreover, our study employed a dual-method approach, combining sequence analysis with a more conventional one. Despite our intention to conduct a direct comparative analysis, we encountered challenges as the obtained classes differed. The lack of a priori knowledge regarding these divergent outcomes complicates our ability to perform meaningful tests for homogeneity. This unforeseen variability highlights the heterogeneity and variability inherent in real-world data and underscores the importance of exploring alternative avenues for understanding the observed patterns. Finally, multiple sensitivity analyses supported the robustness of our findings. Using alternative PDC thresholds (≥ 80% and ≥ 90%), applying IPTW with generalized propensity scores, treating death as censored rather than a competing event, and restricting the cohort to patients who renewed their initial prescription all yielded results consistent with the primary analysis, reinforcing the stability of our conclusions across analytical specifications.

We acknowledge some other limitations in this study. First, the generalizability of our findings to patients treated in other healthcare systems may be limited. Second, although administrative databases provide robust information on drug purchases, they have inherent limitations: reasons for treatment discontinuation are not captured; information on potentially relevant patient characteristics, such as genetic factors, bone mineral density, lifestyle behaviors (e.g., smoking, diet), and other clinical details, is lacking; drug exposure may be misclassified due to variations between prescribed dosages and actual intake; services provided in private healthcare settings are not recorded; additionally, some conditions may not require hospital admission, potentially leading to outcome misclassification. However, it is noteworthy that pharmacological therapies are predominantly reimbursed through the healthcare service, and fractures typically necessitate access to emergency rooms, reducing the risk of privatization. The exception might be vertebral fractures, which may not always result in hospital admission, potentially leading to outcome misclassification. Third, the simplification of complex 24-month adherence sequences into three interpretable clusters, while enhancing clinical applicability, may reduce some predictive granularity. This represents a trade-off between model complexity and practical utility. Lastly, although categorization inevitably entails some loss of information relative to a continuous measure, our approach relied on predefined monthly PDC thresholds (0–25%, 25–50%, 50–75%, ≥ 75%) commonly used in the literature [42] and aligned with our previous work, where these levels showed distinct associations with severe outcomes and mortality [43, 44]. Maintaining these thresholds ensured methodological consistency and facilitated comparability with existing pharmacoepidemiological research. Moreover, when applying alternative adherence thresholds (PDC ≥ 80% and ≥ 90%), the association between higher adherence and lower refracture risk was consistently confirmed. Nevertheless, future studies could investigate data-driven approaches, such as latent class analysis, to identify adherence patterns without a priori categorization, potentially uncovering more nuanced and clinically meaningful trajectories, and could integrate adherence patterns with clinical and biological markers to enhance individual risk prediction.

Conclusions

This study compared conventional and alternative methods to explore adherence patterns and predict the risk of refractures in patients with previous fragility fractures. Based on the SSA and cluster analysis, the alternative method does not significantly modify the prediction of the outcome of interest but enhances the description and visualization of the adherence patterns.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07834-1.

Declarations

Conflicts of interest GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part in a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN, and BMS). He also received honoraria as a member of the Advisory Board from Roche. No other potential conflicts of interest relevant to this article were disclosed.

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