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# Osteoporosis treatment gap and risk of refracture: a pilot retrospective study on a cohort of patients referred to a Fracture Liaison Service in Italy

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**Introduction:** The timely administration of anti-osteoporotic medications (AOM) to patients with fragility fractures (FF) reduces the imminent refracture risk. European studies found a wide osteoporosis treatment gap, but Italian cohort-based data are lacking.

**Materials and methods:** We aimed to assess the entity of the osteoporosis treatment gap in an Italian cohort, i.e., the percentage of patients not treated within 2 months from the index fragility fractures (FF) and the time delay in anti-osteoporotic medications (AOM) administration, and its impact on refracture risk. We retrospectively collected the clinical histories of 500 randomly selected osteoporotic patients with FFs referred to our Fracture Liaison Service. We identified those who had AOM prescribed within 2 months from the index FF ("early treatment" group) and those who had not ("untreated" group). Refracture occurrence was retrospectively assessed in both groups, followed by a survival and risk analysis.

**Results:** Forty-one patients were excluded for missing data. Out of 459 patients, 374 (81.5%) received AOM therapy more than 2 months after the index FF, with a median delay of 24 months (IQR 52) (range 3–312; mean 47 months). The log-rank test showed that the "untreated" group was significantly more prone to refracture than "early treatment" (78% vs. 48%, respectively;  $p = 0.0001$ ). Cox regression revealed a 44% lower probability of refracture in the "early treatment" group.

**Discussion:** In this study, 81.5% of individuals had their first AOM prescription after a median time of 24 months after the index FF, resulting in higher refracture risk. Preventive strategies to reduce the osteoporosis treatment gap should be implemented.

## KEYWORDS

osteoporosis, treatment gap, fragility fracture, Fracture Liaison Service/FLS, refracture risk, Italy, Europe, prevention

## 1 Introduction

Osteoporosis (OP) is a progressive skeletal disease characterized by reduced bone mass and deterioration of bone architecture. It is prevalent especially among postmenopausal women and the elderly population. OP is the most frequent cause of atraumatic or low-energy fractures, also called fragility fractures (FFs), and therefore is often associated with disability and low quality of life, along with increased premature mortality rates (1). Comprehensive data showed that in 2019, more than 23 million people were at high risk of FFs in the European Union (EU), with a lifetime risk of 33% for women and at least 15% for men. Moreover, an increase of 24.8% in the number of FFs was estimated to occur in the EU between 2019 and 2034, mirroring the expected increase in the elderly population by 11.4% in the same timeframe. OP is a major and increasingly relevant economic burden for healthcare systems across Europe; the total direct cost of incident FFs in the EU amounted to €56.9 billion in 2019, after an increase of 64% from 2010 despite the lack of increment in pharmacological costs (2).

Medical management of FFs is aimed at secondary prevention of subsequent fractures and includes pain control, surgical intervention, physical therapy, and nowadays numerous anti-osteoporotic medications (AOM) comprising both antiresorptive (oral or intravenous bisphosphonates, denosumab, and selective estrogen receptor modulators) and anabolic agents (parathyroid hormone receptor agonists and romosozumab) (3). It is undisputed that a patient with a prior FF has an increased risk for subsequent FFs and that such risk is highest immediately after an FF (4). Thus, timely AOM prescription after an FF is vital to limit refracture occurrence (5, 6). However, the gap between patients eligible for AOM treatment and the number of patients treated with AOMs, which is referred to as the OP treatment gap, is still very high in recent reports from several countries (6–12) and in some cases has even increased over the past decades (13). Recent estimates suggested that untreated women with FFs increased from 10.6 million to 14 million between 2010 and 2019 in the EU (14).

As for Italy, the scorecard for osteoporosis in Europe (SCOPE) showed that it was the country with the highest prevalence of OP (6.3% of the population) in the EU and had a crude incidence of FFs amounting to 20.6/1,000 individuals aged 50 or more. Notably, Italy is projected to have the second-largest number of FFs—approximately 666,000—in the EU in 2034. The estimated OP treatment gap for postmenopausal women in Italy was approximately 71% in 2019 (2). In 2019, the total direct cost for FFs amounted to €9.45 billion and accounted for approximately 6% of the national healthcare expenditure, the second highest proportion across the EU. The number of FF-related deaths exceeded that for diseases such as lung cancer (14).

A survey carried out by the Italian Region of Tuscany showed that in 2018, out of 2,964 patients with a recent vertebral FF and out of 6,972 cases of femoral FF, only 10.8% and 4.6% were prescribed AOM therapy within 90 days after the FF, respectively; the proportion of patients who performed a dual-energy X-ray absorptiometry (DXA) scan and went to a OP consultation within 90 days from the FF was even lower, at approximately 1% (15).

To our knowledge, no Italian cohort-based data concerning the OP treatment gap have ever been published in the scientific literature, nor the time delay in AOM prescription for fractured patients has ever been quantified. Therefore, we carried out a pilot retrospective study aimed at measuring the OP treatment gap using local data collected in the Fracture Liaison Service (FLS) of the Pisa University Hospital in Tuscany, Italy. We also investigated whether the OP treatment gap affected the risk of refracture in the population herein described.

## 2 Materials and methods

### 2.1 Study design and data collection

We conducted a monocentric, retrospective, observational, and longitudinal study using data from a cohort of 500 adult patients of both sexes followed at the FLS of the Pisa University Hospital and with a history of primary OP- or secondary OP-related major FFs, i.e., fractures at the vertebrae, hip, proximal humerus, wrist, and pelvis, which occurred spontaneously or were caused by a fall from standing height or by low-intensity trauma. Our FLS is a multidisciplinary outpatient clinic specializing in the diagnosis, treatment, and rehabilitation of patients with vertebral FFs and is made up of rheumatologists, orthopedic surgeons, and physiatrists of the Pisa University Hospital. All patients followed at our FLS have a history of at least one vertebral FF, either as first FF or as refracture—or both.

We gathered data based on the information collected during visits that took place between January 2014, coinciding with the beginning of the FLS activity, and December 2023. For each patient, an accurate medical history is performed at the time of the first visit. Firstly, at the time of retrospective analysis, we collected patient demographics, weight, height, body mass index (BMI), smoking status, medications including glucocorticoids and psychotropic drugs (a risk factor for falls), comorbidities [expressed with the Charlson Comorbidity Index (16)], family history of FFs (considered positive if a patient's parent ever had vertebral or femoral FFs), and previously performed DXA scans. Due to the focus of our FLS on patients with vertebral FFs, we considered *T*-scores only at the total hip on DXA scans in consideration of the known artifacts caused by vertebral FFs on *T*-scores at L1–L4.

Secondly, we retrieved information on each patient's previous history of FF(s), specifically the month, year, and site of the first (index) FF. FFs were considered only if patients had either radiologic documentation for image review or a hospital or emergency department discharge letter demonstrating the diagnosis of FF. The patients' age and FRAX value (17) following the index FF were retrieved.

Thirdly, we assessed whether patients had ever taken AOM therapy after the index FF. Our definition of AOM included only drugs with proven anti-refracture efficacy and available in Italy in compliance with reimbursement policies established by *Nota 79* provided by the Italian Medicines Agency (AIFA) (18) during the 2014–2023 period, i.e., alendronate, ibandronate, risedronate,

zoledronate, raloxifene, bazedoxifene, denosumab, and teriparatide. AOM history was ascertained with previous medical documentation retrieved at the first visit, or, if not available, by self-report by the patient.

Incompleteness of any of the previous data resulted in patient exclusion from the definitive cohort.

Our endpoints were to assess the OP treatment gap, i.e., the percentage of patients with FF(s) who had not received AOM treatment within 2 months from the index FF, and the time delay in AOM prescription. The cutoff of 2 months was chosen with the assumption that it would be rational for a patient with OP-related FFs to receive a timely AOM treatment, considering that, as previously mentioned, the risk of subsequent FF is highest immediately after an index FF.

With regards to this endpoint, at the time in which patients came to our FLS for the first time, we assessed whether patients ever received an AOM prescription after the index FF. If AOM therapy had been prescribed elsewhere after their index FF, we measured the time elapsed between the index FF and AOM prescription. By contrast, if they had never been prescribed any AOMs, patients were prescribed the most appropriate AOM at the first visit at our FLS, and then we measured the time elapsed between the index FF and the day of the visit. In this way, we identified two groups of patients: those who received their first AOM prescription, either elsewhere or at our FLS, within 2 months from the index FF (“early treatment” group), and those who did not (“untreated” group), either because they started taking AOM treatment after 2 months from the index FF, or because they were never treated before being referred to

our FLS and two months from the index FF had already elapsed (Figure 1).

Our second endpoint was to compare the “early treatment” group and the “untreated” group in terms of refracture risk and refracture-free survival. Refracture was defined as the first clinically evident major osteoporotic FF (vertebral, hip, proximal humerus, wrist, or pelvis) occurring after the index FF. Refracture was considered only if either radiologic documentation for image review or a hospital or emergency department discharge letter demonstrating the diagnosis were available. In the case of refracture, we collected the month and year of occurrence, its site, and the time elapsed from the index FF.

For patients identified as “early treatment,” we investigated the occurrence of refracture after AOM prescription by retrieving documentation from each FLS follow-up visit (either every 6 or 12 months, according to the monitoring needs of the specific AOM taken by the patient) until the last available visit; in case a patient of the “early treatment” group did not have at least one follow-up visit, the patient was excluded from the survival analysis. For patients identified as “untreated,” we investigated the occurrence of refracture in the period between the index FF and the date of the first AOM prescription; therefore, for the “untreated” group, the period after the AOM prescription was not assessed for refracture occurrence. For any patient, independent of group, the date of the first refracture would correspond to the end of the retrospective analysis. The occurrence of a second (or subsequent) refracture was not investigated or considered in this study.

We carried out a survival analysis with the data obtained on refracture occurrence. Since AOM treatment prescription for

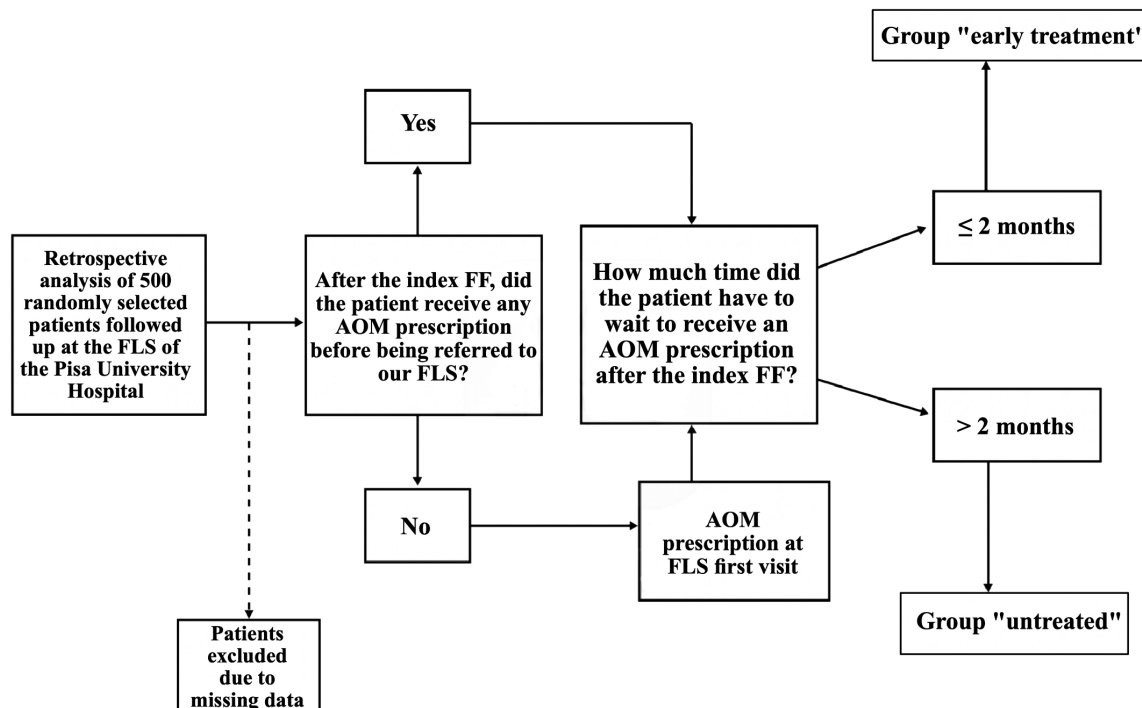


FIGURE 1  
Flowchart for identification of the “early treatment” and “untreated” groups.

patients in the “early treatment” group did not always coincide with the immediate timeframe around the index FF, this could lead to a potential immortal time bias in our analysis. We employed a landmark analysis (19) to counter this issue. Because patients of the “early treatment” group started taking AOM treatment within 2 months from the index FF, the landmark (i.e., time zero of the survival analysis) was moved from the index FF date to the end of a 2-month (62 days) “ascertainment window” for both groups. Since for patients of the “untreated” group we did not consider the period after AOM prescription, moving the landmark as previously explained was sufficient to solve a potential immortal time bias issue. Patients of the entire cohort who had the first refracture during the 2-month “ascertainment window” (i.e., within 2 months from index FF) were excluded from the survival analysis (Figure 2).

## 2.2 Sample size calculation and statistical analysis

Considering the results of the previously mentioned survey carried out by the region of Tuscany (15) and that no references in the previous literature could drive a specific target sample size, we designed a pilot study on 500 patients and calculated the *post hoc* statistical power with the “PowerSurvEpi” package of R to verify the robustness of the results.

Based on the results of the Shapiro–Wilk test, continuous data were described as median and interquartile range (IQR) in case of non-Gaussian distribution, or as mean and standard deviation (SD) in case of Gaussian distribution. Categorical variables were expressed as numbers and proportions related to the available data. The groups were compared using the Chi-squared test and the Mann–Whitney *U*-test for qualitative and quantitative

variables, respectively. Missing data were not imputed. *p*-value was set at 0.05 level.

A Cox regression was carried out to model the survival time. The Cox regression model included group assignment (“early treatment” vs. “untreated”) as the primary covariate. We verified the proportional hazards assumption through visual inspection of log–log survival plots. The model assumed independence of observations, non-informative censoring, and proportional hazards over time.

The Kaplan–Meier method was then applied, with a log-rank test, divided by group.

Statistical elaborations were performed using the STATA 15.1 software package (StataCorp) and R 4.4.2 for MacOS (Apple Inc.).

## 3 Results

Five hundred subjects were randomly selected for our retrospective study. Forty-one were excluded due to missing data; therefore, 459 patients (414 women, 90.2%) made up the definitive cohort. According to our definition of AOM treatment, only two patients among the 500 who were randomly selected had been prescribed appropriate AOM therapy (alendronate in both cases) elsewhere before the first FLS visit; due to incomplete data regarding their medical history, they were among the 41 excluded patients. Therefore, all 459 patients in the definitive cohort had never received AOM treatment by the time of the first FLS visit.

The median age at the index FF was 70 years (IQR 12). The index FFs were most frequent at the vertebrae ( $n = 373$ ; 81.3%), followed by the hip ( $n = 37$ ; 8.1%), the distal forearm or wrist ( $n = 28$ ; 6.1%), the proximal humerus ( $n = 16$ ; 3.5%), and the pelvis ( $n = 5$ ; 1%). The remaining patient characteristics are summarized in Table 1.

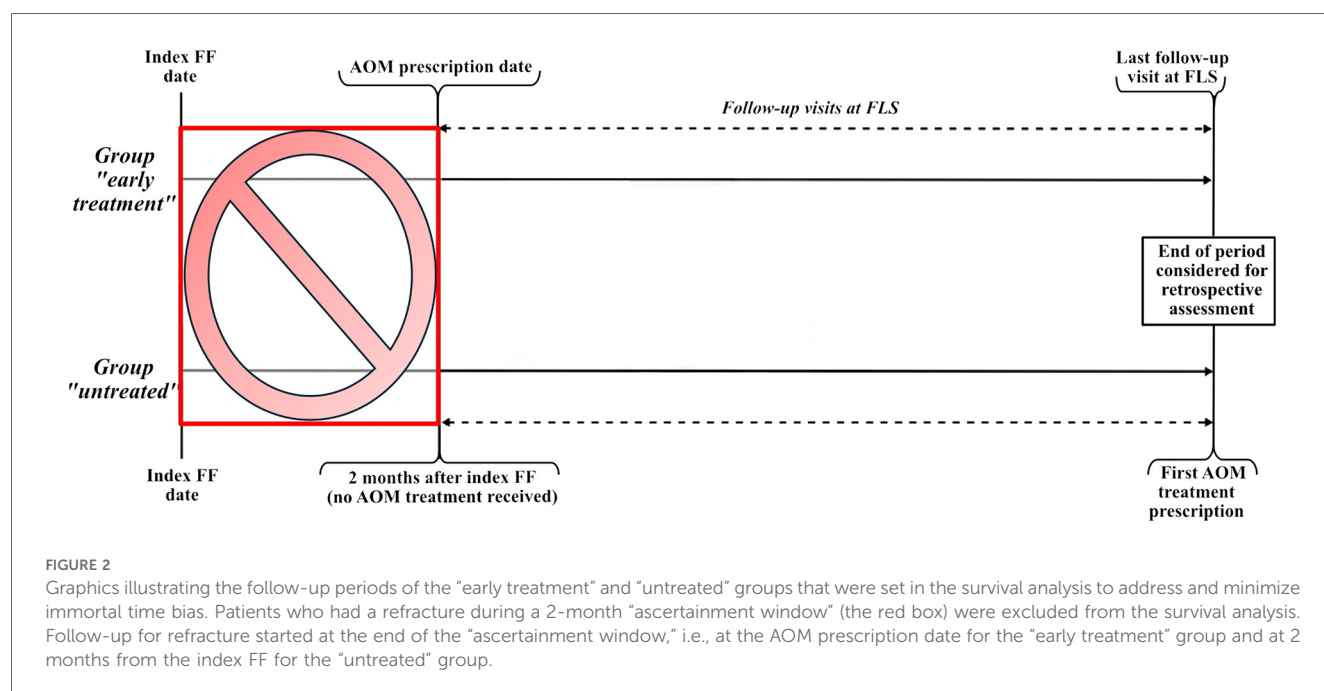


TABLE 1 Patient characteristics of the entire cohort ( $n = 459$ ).

Patient characteristics (dichotomous)	N (%)
Female sex	414 (90.2)
Smokers	90 (19.6)
Ongoing glucocorticoid therapy	79 (17.2)
Rheumatoid arthritis	27 (5.9)
Family history of vertebral or femoral FFs	97 (21.1)
Use of psychotropic drugs	104 (22.6)
<b>Site of index FF</b>	
Vertebra	373 (81.3)
Hip	37 (8.1)
Distal forearm/wrist	28 (6.1)
Proximal humerus	16 (3.5)
Pelvis	5 (1)
Patients who sustained a clinical refracture	251 (54.7)
<b>Site of first clinical refracture</b>	
Vertebra	204 (81.3)
Hip	23 (9.2)
Distal forearm/wrist	10 (4)
Pelvis	8 (3.2)
Proximal humerus	6 (2.4)
Patient characteristics (continuous)	Median (IQR)
Age (years) at the index FF	70 (12)
BMI ( $\text{kg}/\text{m}^2$ ) at the index FF	25 (5.5)
FRAX value (%) following the index FF	21 (15)
Charlson comorbidity index (score) after the index FF	6 (6)
T-score at total hip (DXA scan)	-2.2 (1.3)

All 459 patients received their first AOM prescription after the index FF at the first FLS visit. Based on the retrospectively retrieved time between index FF and AOM prescription date, we observed that 374 (81.5%) patients did not receive AOM therapy within 2 months from the index FF. In these patients, identified as the “untreated” group, the median time delay between the index FF and first AOM prescription was 24 months (IQR 52 months) (range 3–312; mean 47 months). The remaining 85 (18.5%) patients received the first AOM prescription within 2 months from the index FF and thus were identified as the “early treatment” group. The two groups were comparable in terms of all considered variables except for ongoing glucocorticoid therapy

which was significantly more frequent in the “early treatment” group (Table 2).

At the time of the index FF and before arrival at our FLS, out of 374 patients in the “untreated” group, 187 (50%) received vitamin D supplementation, 25 (6.7%) received calcium + vitamin D supplementation, and 201 (53.4%) were prescribed intramuscular clodronate, a non-nitrogen-containing bisphosphonate which is not included among drugs listed in *Nota 79* (18). The persistence of clodronate treatment was very low, with 8% of the patients still on therapy after 1 year from the first prescription.

In our cohort, 251 (54.7%) patients had a refracture. Approximately 91% ( $n = 228$ ) of these patients belonged to the “untreated” group. The most frequent sites of refracture were the vertebrae ( $n = 204$ ; 81.3%), followed by the hip ( $n = 23$ ; 9.2%), the distal forearm or the wrist ( $n = 10$ ; 4%), the pelvis ( $n = 8$ ; 3.2%), and the proximal humerus ( $n = 6$ ; 2.4%).

For the second endpoint of the study, we carried out a survival analysis. To address a potential immortal time bias, 12 patients (11 of whom belonged to the “untreated” group and one belonged to the “early treatment” group) who had a refracture during the previously mentioned 2-month “ascertainment window” were excluded. Therefore, the final survival analysis included 447 individuals (363 in the “untreated” group and 84 in the “early treatment” group). The comparability of the two groups (Table 2) was unaffected by the exclusion of the 12 patients (data not shown). The log-rank test showed that patients in the “untreated” group were significantly more prone to refracture as opposed to patients in the “early treatment” group (78% vs. 48%, respectively;  $\chi^2 = 19.1$ ;  $p = 0.0001$ ). The Cox regression analysis revealed a 44% lower probability of refracture in the “early treatment” group compared with the “untreated” group [hazard ratio (HR) 0.56; 95% CI: 38%–73%;  $p = 0.004$ ].

Despite the numerical imbalance between the two groups, the statistical robustness of our results was supported by a *post hoc* power analysis; considering the overall HR, the power was 95.5% (95% CI: 95.0–95.7%).

The Kaplan–Meier estimator showed that, for patients in the “early treatment” group, the median time between AOM treatment prescription and first clinical refracture was 41 months (IQR 47

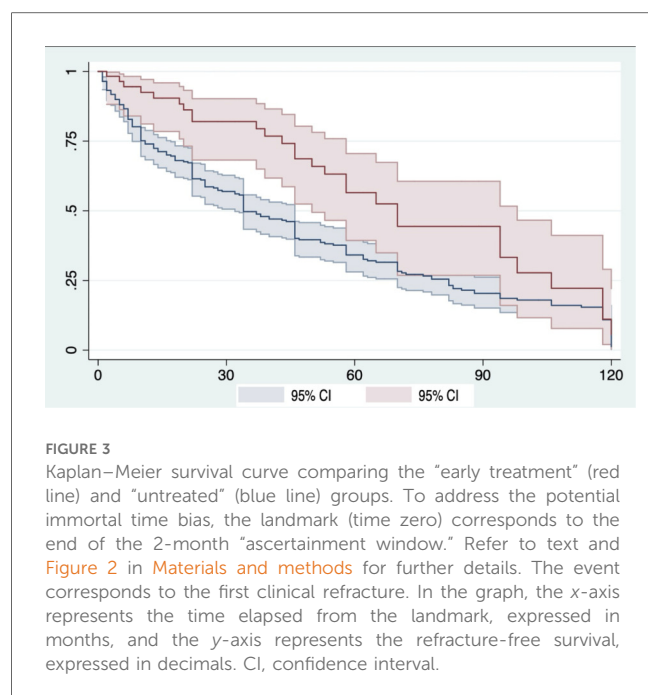
TABLE 2 Comparison between the “early treatment” and “untreated” groups.

Patient characteristics	“Early treatment” group ( $n = 85$ )	“Untreated” group ( $n = 374$ )	$p$ -value
Median age in years (IQR) at index FF	70 (13)	70 (11.5)	0.53*
Female sex (%)	78 (91.8)	337 (90.1)	0.36#
Smokers (%)	14 (16.5)	79 (21.1)	0.21#
Positive family history of vertebral/femoral FFs (%)	20 (23.5)	75 (20.1)	0.32#
Median BMI in $\text{kg}/\text{m}^2$ (IQR) at index FF	24 (5)	25 (6)	0.52*
Median Charlson comorbidity index score (IQR) after the index FF	5 (6)	6 (5)	0.054*
Median FRAX value % (IQR) after the index FF	21 (14)	21 (15)	0.48*
Median T-score at total hip (IQR)	-2.2 (0.9)	-2.1 (1.0)	0.4*
Rheumatoid arthritis (%)	9 (10.6)	19 (5.1)	0.06#
Use of psychotropic drugs (%)	17 (20)	90 (24.1)	0.31#
Ongoing glucocorticoid therapy	22 (25.8)	56 (15)	0.04#
Mean follow-up duration (months)	50	44	0.7*

# $p$ -values were calculated using the Chi-squared test for dichotomous variables.

\* $p$ -values were calculated with the Mann–Whitney  $U$ -test for continuous variables.





months), whereas for patients in the “untreated” group, the median time between the end of the 2-month “ascertainment window” and the first clinical refracture was 26 months (IQR 50 months), over a considered follow-up time of 120 months (Figure 3).

## 4 Discussion

To our knowledge, our retrospective study represents the first description of the entity of the OP treatment gap in the catchment area of an Italian FLS and of its impact on refracture recurrence.

Our first finding is that only 18.5% of the patients living in the catchment area of our hospital’s FLS received an AOM prescription within 2 months from the index FF (“early treatment” group). This finding is in accordance with a recent study which reported that only 20% of 915 patients recruited at eight Austrian centers were prescribed AOM treatment at the time of the index FF (8).

Moreover, 81.5% of the cohort received the first AOM prescription after the index FF with a median delay of 24 months, with some patients receiving AOM therapy for the first time >10 years after the index FF. These data are worrisome since it is known that the risk of refracture is time-dependent, with an imminent risk that is highest in the first 2 years after the index FF (20). Although the patients in the “untreated” group did not receive AOM therapy, we observed that many had been identified as osteoporotic in the months after the index FF; as a matter of fact, before the first visit in our FLS, a considerable proportion had been treated with calcium, vitamin D supplementation, and/or intramuscular clodronate, a non-nitrogen-containing bisphosphonate not included in Nota 79 (18). Although a randomized, double-blind, placebo-controlled trial in women unselected for osteoporosis showed that 3-year oral daily 800 mg clodronate reduced the incidence of any

clinical FF by 20% with respect to placebo, hip FF incidence was unaffected, and vertebral FF incidence was not specifically addressed (21). To the best of our knowledge, no randomized controlled trial has been carried out to test the ability of either oral or intramuscular clodronate to prevent FF recurrence, i.e., secondary FF prevention, in an osteoporotic population.

Our second finding is that AOM prescription within 2 months from the index FF reduced the risk of refracture by 44%. Thus, our data provide evidence of the importance of timely and efficacious AOM prescription following FFs.

Despite continuous advancements in OP diagnosis and treatment over the decades, it is evident that still too many osteoporotic patients with FFs are not offered timely AOM treatment. This phenomenon has been recently defined as a global “crisis” because of its disastrous consequences in terms of both refracture rate and economic burden on society (22). It is worrisome to observe that the OP treatment gap is widening in several countries over time, as reported in a recent study from Switzerland (13), showing that this worldwide problem is not being addressed in the manner it deserves. Several elements have been suggested to inflate the treatment gap. It is possible that there are not as many OP specialists as it is needed considering the population aging currently occurring worldwide (23). Furthermore, healthcare providers may incorrectly consider OP an inevitable degenerative process of the bone that would not benefit from any treatment (24), and others may ignore or disregard the latest treatment guidelines. Importantly, the fear of treatment-related side effects, in particular the osteonecrosis of the jaw following treatment with bisphosphonates and denosumab, may lead to omission of AOM prescription by physicians and avoidance of AOM treatment by patients, despite the evidence that serious adverse events occur only in a small minority of AOM-treated patients as opposed to the large-scale benefits that AOM therapy has been shown to yield in FF prevention (25). Last, but not least, the absence of an effective action by those in charge of clinical governance at either regional or national level may play a role. Potential strategies to reduce the OP treatment gap may include the creation of FLS and Bone Units, i.e., of departments aimed at capturing the largest possible proportion of FFs to promptly prescribe AOM treatment.

Our study has limitations within which our results should be interpreted. Firstly, the retrospective design of the study did not allow the systematic collection of data such as the specific reason(s) behind the lack of timely AOM prescription in the “untreated” group, and thus we could not draw any overall conclusion on this aspect. Nevertheless, all patients with missing data were excluded from the final analysis to compensate for the retrospective design, still resulting in a sample size that proved more than sufficient for high statistical power and a definitive cohort with comprehensive and uniform data. Furthermore, we acknowledge that the retrospective nature of the study may introduce potential confounding variables. However, we addressed this by comparing baseline characteristics between groups (Table 2), which showed comparable distributions (except for glucocorticoid use), and by collecting comprehensive clinical data including several risk factors for osteoporosis among the considered variables. While we did not perform multivariable

adjustments due to the pilot nature of the study, the groups were well-balanced for most potential confounders. Future prospective studies should include multivariable Cox regression to adjust for all potential confounders, such as the number of falls in the previous 12 months, which may not be effectively monitored with retrospective studies.

Secondly, the low proportion of male patients did not allow us to conclude on any inter-gender differences regarding the impact of the OP treatment gap. Due to the limited number of male patients ( $n=45$ , 9.8%), with only seven males in the “early treatment” group, formal sex-stratified analyses would have been underpowered and potentially misleading. Descriptive data showed refracture rates of 35.9% vs. 60.7% in females (“early treatment” vs. “untreated”) and 14.3% vs. 47.4% in males, suggesting potential sex differences. However, with only one refracture event among males receiving early treatment, these estimates are highly unstable. This represents an important area for future investigation in larger multicenter studies with adequate power to detect sex-specific effects, particularly given the known differences in bone metabolism between sexes.

Another limitation of our study could be that our FLS is addressed specifically at patients who had a history of at least one vertebral FF, either as index FF or refracture (or both). Therefore, we acknowledge that the results of our pilot study may not be generalizable to the entire fractured population and that a nationwide multicentric study, involving more accurate data from a more uniform population with regard to FF sites, is warranted to overcome this issue. Nevertheless, vertebrae are the most common site of FF in osteoporotic patients (3), and our cohort still featured a relevant proportion of patients (18.7% and 18.8%) who had their index FF and first clinical refracture, respectively, at a non-vertebral site (hip, wrist, proximal humerus, and pelvis). Furthermore, we focused on clinically evident FFs, vertebral or non-vertebral, that have come under medical attention. From this point of view, we believe that the treatment gap in the real world is even wider than what we found in this study, since many vertebral FFs are often not diagnosed.

Another potential limitation may arise from the fact that, for the “early treatment” group, only clinical FFs were considered during the retrospective assessment for refracture, since we do not regularly carry out serial dorsolumbar spine X-rays to search for possible clinically silent vertebral refractures.

In conclusion, the osteoporosis treatment gap in this cohort of patients was wide, with 81.5% of the patients not receiving appropriate and timely AOM treatment after the index FF, with a median delay of 24 months in AOM prescription. When prescribed within 2 months from the index FF, AOM therapy can reduce the occurrence of clinical refracture by 44% and proportionally reduce the economic burden on the health system. Since the elderly population and the annual number of OP-related FFs in Italy are expected to increase (2), it is of utmost importance to address the OP treatment gap to avoid an even more amplified impact in the future. Our pilot, local study is intended to prompt larger studies at a national level and to persuade health authorities to prioritize the implementation of strategies aimed at reducing the OP treatment gap.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Ethical Committee of Area Vasta Toscana Nord-Ovest (CEAVNO). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

GDM: Writing – original draft, Writing – review & editing, Data curation, Methodology, Investigation, Conceptualization. MM: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. VB: Investigation, Writing – review & editing. DA: Investigation, Writing – review & editing. AM: Writing – review & editing, Investigation. MiM: Investigation, Writing – review & editing. MaM: Writing – review & editing, Supervision. MMA: Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Writing – original draft, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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