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ORIGINAL ARTICLE

Experience gained from the implementation of the fracture liaison service in Greece

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Abstract

Introduction We present the second implementation of a fracture liaison service (FLS) at a national level in Greece.

Methods This was a multicenter prospective study, organized by the Hellenic Society for the Study of Bone Metabolism, aiming to investigate the tracking and outcome of patients with low-trauma fractures visiting four university orthopedic departments across the country. The primary endpoint was the participation rate of eligible patients with low-trauma fractures in the program within a time frame of 1 year. Secondary outcomes included the percentage of patients initiating osteoporosis treatment, adherence to treatment, and the percentage of patients experiencing subsequent fractures. A major difference with previous reports was the designed implication of the orthopedic surgeon managing the fracture.

Results Among the 1350 eligible patients with major osteoporotic fractures, only 396 (29.3%; mean age 78.1 ± 11.6 years; female/male ratio: 4.4) agreed to participate, nearly all of the latter ($n = 392$) completing the study. With the exception of seven patients, all participants were receiving anti-osteoporotic treatment at the end of the study. Twelve new fractures were recorded at completion of the 12-month follow-up, which were all sustained in patients who either declined to receive anti-osteoporotic treatment or who discontinued treatment despite advice to the contrary.

Conclusion The participation rate remains low and needs improvement. However, we report herein that whenever the treating physician is involved in the FLS structure, patients are more easily convinced to complete the program, to receive anti-osteoporotic treatment, and to stay connected throughout with the outpatient clinic.

Keywords Osteoporosis · Fracture · Treatment · Fracture liaison service

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Introduction

Fracture liaison services (FLS) are coordinated fracture prevention programs that have evolved over the last few decades targeting osteoporotic patients, who, in most cases, present with their first fracture, in an effort to enhance the management of the underlying osteoporosis and frailty [1].

Despite their effectiveness, however, FLS programs are still far from achieving optimal outcomes in the increase of disease awareness and guidance of appropriate management. In addition, FLS implementation in different countries has produced a wide range of results [2–6], most of which document the need to upgrade the service to being one of standardized and universal design and structure.

Following the results of the pilot study of FLS implementation in Greece in a single center in Athens [6], the Hellenic Society for the Study of Bone Metabolism (HSSBM) organized and implemented the second FLS program in Greece targeting a larger pool of fractured patients at a national level.

Patients and methods

Patients

"Secondary Prevention of Osteoporotic Fractures: a Multiple Center Fracture Liaison Service in Greece" was a multicenter prospective study run by the Departments (Dpts) of Orthopedics of four different hospitals in four large cities of Greece (NCT 02637180). The initial study design included five University Orthopedic Dpts; however, one center was finally not included for administrative reasons and thus did not recruit any patients. There are 85 Orthopedic Dpts in Greece receiving trauma cases and therefore patients with fractures of any kind at a 24-h base. The selection of the four included Dpts was mainly based on their location in order to be representative of a large area of Greece, although the study was not designed to include a randomly selected, specific percentage of the total number of Orthopedic Dpts. There was no established FLS both in the four Orthopedic Dpts as well as in their hosting hospitals before this study. In specific and with the exception of the previously published FLS [6], there were no other FLS programs running in Greece at the time of the study's onset. Therefore, the previous workflow in these Dpts following the identification of a fragility fracture did not include any diagnostic procedure regarding osteoporosis, and there was no established link with the relevant outpatient clinic. In addition, the participating centers were free to continue the specific FLS program at their own resources following the end of the study; however, there are no available collected records following the conclusion of the study from any of the four Dpts.

From April 2015 through December 2016, the study targeted all hospitalized patients as well as all outpatients of each referral center who fulfilled the following simple eligibility criteria: (i) age ≥ 50 years and (ii) presence of at least one low-energy fragility fracture (defined as a fracture resulting spontaneously or after minimal trauma such as falling from standing height or less) of the following skeletal sites: hip, spine, proximal humerus, distal forearm, and pelvis. The enrollment period was 365 days for each Dpt, starting from the first patient's enrollment date in each center; the overall enrollment period did not start at the same time for each Dpt due to administrative issues at each hospital, and this is the reason for the 18-month total enrollment period of the whole study. Patients' follow-up was 365 days; therefore, the total duration of the program in each center could extend up to 2 years in accordance with the protocol's design. The study was completed in December 2017.

Exclusion criteria were the presence of osteomalacia and/or other clinical entities predisposing to low-energy fractures, apart from osteoporosis, such as primary or secondary hyperparathyroidism, Paget's disease of the bone, osteogenesis imperfecta, paraplegia, etc.

The study was in accordance with the Declaration of Helsinki and was approved by the local medical ethical committees, while all patients provided written informed consent after being informed in detail of the program's terms and conditions.

Methods

All eligible patients were interviewed by the FLS personnel in full cooperation with the treating physician (orthopedic surgeon managing the fracture) according to the steps described in supplemental Fig. 1 and in accordance with the previously published IOF CSA Fracture Working Group recommendations [7].

In specific:

1. The patients were informed about the program and were given the relevant informative printed material by the FLS personnel (dedicated nurse and/or resident) and the treating physician.

2. Patients willing to participate were asked to sign the informed consent form; the time frame of the recruitment period for each patient was that of 48 h following the identification of the fracture.

3. Each patient's file was completed and updated with all appropriate data including: hip and lumbar spine BMD, thoracic and lumbar spine X-rays, and the minimum required laboratory tests according to the Greek osteoporosis guidelines [8]. The completion of each patient's file was organized by the FLS personnel in cooperation with the Dpt personnel for inpatients or with the treating physician for outpatients.

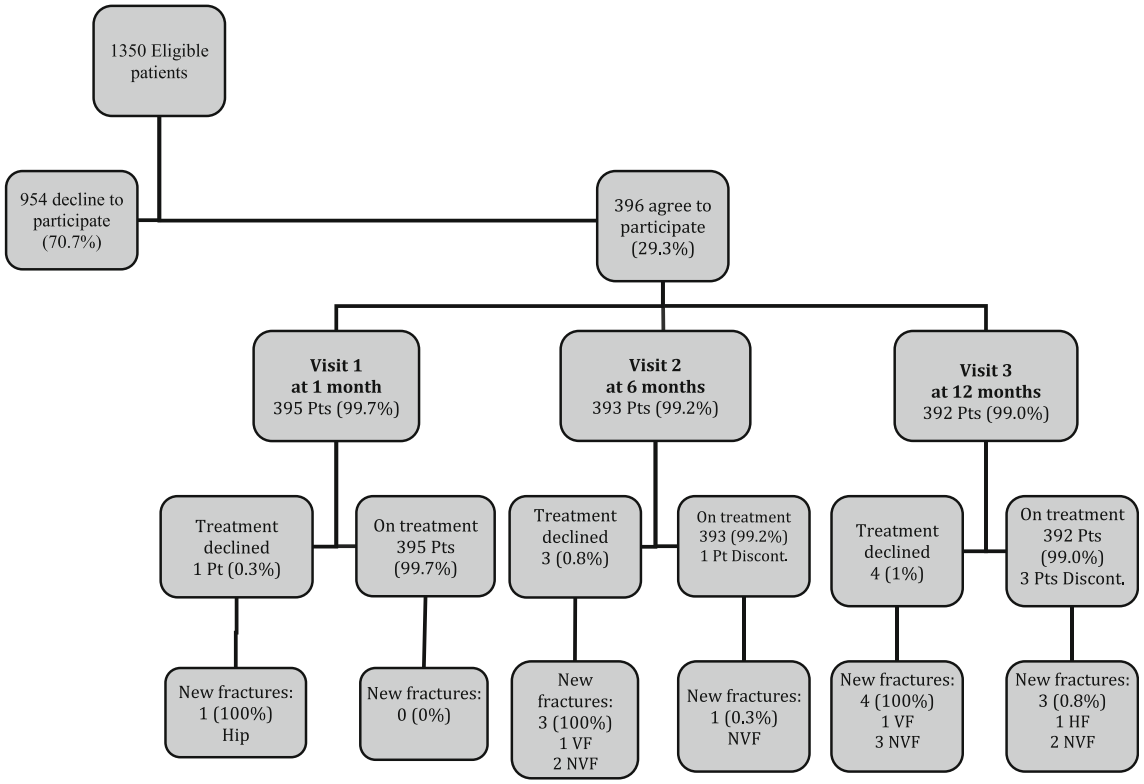

Fig. 1 Workflow of patients recruited and finally enrolled in the study

4. Calculation of the FRAX score was performed in all treatment-naive patients, and the need for treatment was recorded using specific thresholds for the Greek population [9].

5. FLS personnel assured the patient that his/her physician (either treating physician or the physician specialized in metabolic bone disorders) recommended the specific anti-osteoporotic treatment, where appropriate, before the patient's discharge. Clear written instructions were always given regarding the recommended therapeutic approach and the time schedule of future visits, while patients were instructed and encouraged to inform any other physicians dealing with their health issues about their participation in the FLS program.

6. A patient support program with regular telephone contacts was organized and carried out by the FLS personnel who provided further information when needed, alerted the patients and/or their relatives as to the necessity for close monitoring, and facilitated the next appointment in the specialized outpatient clinic for metabolic bone diseases.

Patients could opt to be monitored in other healthcare settings as well. Overall, this FLS program can be described as a modified type B model of care [10], as it included identification, investigation, and treatment recommendations as defined by the FLS, while treatment initiation or continuation was supported both within the FLS and in other healthcare settings.

During each telephone contact, specific data were collected and recorded regarding (a) new fracture(s), (b) regular supervision/follow-up by a bone specialist, and (c) the patient's adherence to specific anti-osteoporotic treatment through the number of executed prescriptions, which is available in the online national prescription system. In cases of treatment discontinuation, the reason was identified and recorded. The telephone contacts were scheduled for 1, 6, and 12 months after discharge from the hospital or from the initial visit to the outpatient clinic.

Study outcomes

The primary outcome measure was the participation rate of eligible patients with low-trauma fractures in the FLS program within the time frame of 2 years. Secondary outcomes included the percentage of patients initiating osteoporosis treatment, the percentage of patients experiencing subsequent fractures, and adherence to anti-osteoporotic treatment during the follow-up period based on the calculation of the medication possession ratio (MPR).

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or frequencies and percentages for quantitative and qualitative variables, respectively. Comparisons of qualitative variables between treatment groups were performed using the z score for two population proportions. All tests were two-sided, and

statistical significance was set at $p < 0.05$. Analyses were conducted using the statistical package SPSS v. 21.00 (IBM Corporation, Somers, NY, USA).

Results

Across the four Orthopedic Dpts that participated in this FLS program, 1350 patients were referred (either hospitalized or visiting the outpatient clinic) and considered eligible for the study, although only 396 (29.3%) agreed to participate (Fig. 1), while 954 patients (70.7%) declined for personal reasons. In specific, the vast majority of patients declined to participate as they believed that the whole procedure was time-consuming offering no additional benefits for their health status as they were already under some kind of supervision for osteoporosis; the second most common reason for nonparticipation was the concern for the use of medications for osteoporosis which reflects on the general problem of suboptimal awareness about the disease. The distribution of the initially eligible and finally enrolled patients across the four centers is shown in Fig. 2, while the type of their fragility fractures is depicted in Table 1.

The mean age of the patients finally enrolled in the study ($n = 396$) was 78.1 ± 11.6 years (range 52–104 years), with a female to male ratio of 4.4. More than 50% of the recorded fractures were of the hip (54.3%), while vertebral (VF) and non-vertebral (NVF) fractures accounted for 4.7% and 41% of the total recorded fractures, respectively. At baseline 57.3% of the enrolled patients were under supervision for osteoporosis by a physician and were previously prescribed anti-osteoporotic treatment. However, 86.4% of them had stopped their treatment during the preceding year from the recorded fracture despite their physician's contrary recommendation.

At the first month telephone visit (Visit 1), all except one patient were under supervision by a bone specialist and were receiving anti-osteoporotic treatment. No treatment interruption and no new fractures were recorded among patients under treatment. The one participant who did not get any anti-osteoporotic treatment during the first month had sustained a new hip fracture (Table 2).

At the 6-month telephone visit (Visit 2), all except three patients were under medical supervision and were receiving anti-osteoporotic treatment. There was only one treatment discontinuation based on the doctor's decision, and four new fractures were recorded (one VF and three NVFs) among the patients. Specifically, the new NVFs were reported in the three patients who were not receiving anti-osteoporotic treatment, while the one patient who had discontinued treatment suffered a new VF. Although the number of fractures is too low to reach a solid statistical conclusion, fracture incidence was significantly lower in patients under anti-osteoporotic treatment compared to those that were not receiving any treatment ($z = 17.21$ $p < 0.001$).

At the 12-month telephone visit (Visit 3), with the exception of four patients, all participants were being medically followed up and were receiving anti-osteoporotic treatment. Three patients had discontinued treatment, one after the doctor's decision and two on their own. Seven new fractures were recorded: one VF, five NVFs, and one hip fracture. As at Visit 2, and with the same limitations, there was a significant increase in new fractures among patients who were not receiving any anti-osteoporotic treatment compared to those that were under medication [4 (100%) vs. 3 (0.8%) $z = 14.98$ $p < 0.001$]. In addition, three patients who had discontinued treatment suffered a new fragility fracture (one hip and two NVFs).

Of the 12 new fractures that were recorded during the 12-month follow-up period, 1 was sustained by a male patient who was not under anti-osteoporotic treatment at 6 months after the initial record, and the rest were recorded in female patients (Table 3). However, there was no statistically significant difference in fracture incidence between males and females at 6 ($p = 0.477$) or 12 months ($p = 0.992$) evaluation time.

The majority of the new fractures that were recorded were NVFs ($n = 8$, 66%), two were hip fractures, and two were VFs. All fractures were reported in patients who had declined or discontinued anti-osteoporotic treatment. In a subgroup analysis between patients under or over the age of 75 years, there was no statistically significant difference in fracture incidence either at 6 ($p = 0.638$) or at 12 months ($p = 0.406$).

Discussion

This is the second report of FLS implementation in Greece conducted in a multicenter design evaluating the efficacy of secondary prevention over a 2-year period. Despite the large number of patients considered eligible to participate in the program, the recruitment efficacy was very low (29.3%), and significantly lower compared with the first FLS Greek report (54.5%) [6], or other national programs, e.g., in The Netherlands, Spain, and the UK [11–14]. As in most other FLS programs, the majority of eligible patients who agreed to participate had suffered a hip fracture [1].

However, despite the disappointingly low recruitment rate, the percentage of recruited participants who completed the study, having attended the 12-month follow-up visit, reached 99%. This is in discordance with the first FLS Greek report performed in the setting of a single hospital, where the completion rate was lower than 20% [6], but in line with other studies that reported percentages of adherence to treatment and follow-up visits of between 65 and 80% [12, 13, 15]. This striking difference, both in the recruitment rate and in

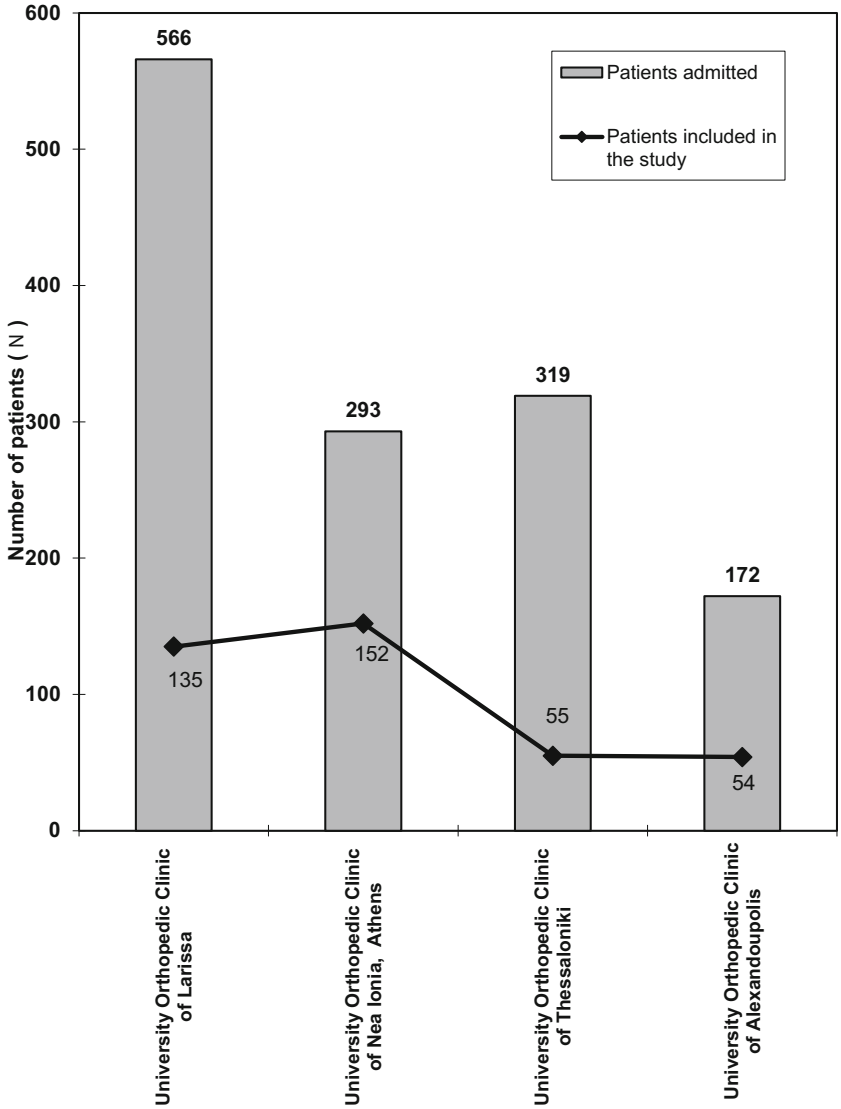

Fig. 2 Distribution of eligible patients across the four Orthopedic Departments in General Hospitals around Greece

the percentage of patients who finally completed the follow-up visits, can be attributed to differences in the structure of the two FLS programs. In the first FLS program [6], screening and recruitment of eligible patients were performed by the registered nurse who was specifically assigned to this task and therefore was both motivated and dedicated. In the current study, in which Orthopedic Dpts were involved rather than hospitals, the treating physicians were required to be involved in the recruitment of the eligible patients during their routine clinical work at the hospital, and this might have influenced the final outcome. In other words, the recruitment of patients was an additional task for the orthopedic surgeons on top of a usually overloaded work schedule. Another probable reason for the high percentage of reluctant patients might have been the relatively high percentage (57.3%) of patients under osteoporosis treatment. Therefore, patients probably opted to be followed by their own physician rather with an FLS setting. In addition this high percentage of patients with previous osteoporosis follow-up might indicate a selection bias of the study's population. We cannot provide a solid explanation for this. Given that a patient in Greece can usually choose among the hospitals of his/her residential area, a probable reason would be the urban and rather central location of these University Dpts, which probably makes them easily accessible to patients with unrestricted access to health services and thus adequately treated for several medical conditions. On the other hand, and despite the low recruitment rate of eligible patients, the role of the treating physician in the completion rate of the recruited patients proved to be extremely important, since almost 100% of them completed the follow-up visits for up to 1 year. We could not identify any specific characteristics among these adherent patients, and there were no particularities either in their management within the FLS or outside of it. In addition, as this was a common finding in all four centers, we cannot attribute it to special communication abilities of the FLS personnel. Therefore, it seems rational to conclude that

Table 1 Type of fractures in eligible and finally included patients across the four Orthopedic Departments

	University Orthopedic Clinic of Larissa	University Orthopedic Clinic of Nea Ionia, Athens	University Orthopedic Clinic of Thessaloniki	University Orthopedic Clinic of Alexandroupolis
Hip	348	134	157	95
Vertebral	25	17	8	14
Proximal humerus	34	32	27	20
Distal forearm	152	96	116	40
Pelvis	7	14	11	3
Eligible patients (n)	566	293	319	172
Patients included in the study (n, %)	135 (23.9%)	152 (51.9%)	55 (17.2%)	54 (31.4%)

whenever the treating physician is involved in the process of recruitment and motivation, the patient remains under medical supervision.

It appears that the recruitment success of osteoporotic patients depends largely on the time dedicated by the assigned personnel to explaining the risks of osteoporosis and the treatment benefits. As shown by similar studies [6, 16], the FLS personnel are usually not exclusively employed, but instead, the task comes in tandem with the rest of their duties and is, moreover, mainly voluntary. However, from our experience in Greece, it is clear that even when such a multitask and time-consuming program as is FLS is carried out by dedicated and motivated personnel who are willing and able to explain to patients in detail the risks of osteoporosis and convince them of the urgent need for treatment, the results are, on the whole, highly satisfactory and successful.

In Greece, osteoporosis management is supported by specific guidelines [8, 17], clear FRAX thresholds for cost-effective treatment [9, 18], and easy access to BMD measurements with appropriate reimbursement. However, whenever there is a lack of financial support, the national registry and audit FLS programs will have poor results, at least in terms of disease awareness. Osteoporosis, like other silent and asymptomatic chronic diseases such as diabetes and hypertension, need prophylactic and chronic management in order to reduce the risk of future complications; nevertheless, for various reasons, adherence to treatment is at present rather low [19–21]. In a recent study, only 19% of patients with hip fractures had been receiving bone-active osteoporosis treatment before the occurrence of the fracture, and this percentage barely changed, rising to 21% after the fracture [22]. This kind of diagnostic gap is too high given the fact that effective therapies exist to reduce a future fracture, this underscoring the need for a more focused public health approach [23, 24]. In this study, the percentage of hip fractures was quite high, representing more than 50% of eligible and finally included cases, and this might point to a possible selection bias; however, this is attributed to the fact that almost all hip fractures are admitted in an Orthopedic Dpt in Greece, while other less severe fractures might receive medical care in public or private outpatient settings. Therefore, any Greek FLS occurring in an orthopedic Dpt receiving trauma cases will have a high percentage of hip fractures.

In the first Greek report, it was shown that the profile of osteoporotic patients reluctant to participate in an FLS program

Table 2 Clinical characteristics of patients during the follow-up period

		Visit 1 (1st month)	Visit 2 (6 months)	Visit 3 (12 months)
Under follow-up: no/yes; n (%)		1 (0.3%)/395 (99.7%)	3 (0.8%)/393 (99.2%)	4 (1.0%)/392 (99.0%)
Under treatment: no/yes; n (%)		1 (0.3%)/395 (99.7%)	3 (0.8%)/393 (99.2%)	4 (1.0%)/392 (99.0%)
Treatment interruption: no/yes; n(%)		396 (100%)/0 (0%)	392 (99.7%)/1 (0.3%)	393 (99.2%)/3 (0.8%)
Reason for interruption (n, %)	Doctor's decision	0 (0%)	1 (0.3%)	1 (0.3%)
	Adverse event	0 (0%)	0 (0%)	0 (0%)
	No compliance	0 (0%)	0 (0%)	0 (0%)
	Patient's decision	0 (0%)	0 (0%)	2 (0.6%)
	Death	0 (%)	0 (0%)	0 (0%)
Type of fracture (n,%)	Vertebral	0 (0%)	1 (0.3%)	1 (0.3%)
	Hip	1 (0,3%)	0 (0%)	1 (0.3%)
	Non vertebral	0 (0%)	3 (1.0%)	5 (1.5%)
Number of fractures (n,%)	Treatment	0 (0%)	1 (0.3%)	3 (0.8%)
	No Treatment	1 (100%)	3 (100%)	4 (100%)

Table 3 Characteristics of patients who sustained a new fracture during the follow-up period

Patient with fracture	Treatment status	Gender	Age group	Type of fracture
1	Declined	M	< 75	Non-vertebral
2	Discontinued	F	< 75	Hip
3	Declined	F	< 75	Non-vertebral
4	Declined	F	< 75	Non-vertebral
5	Declined	F	< 75	Vertebral
6	Declined	F	< 75	Vertebral
7	Declined	F	> 75	Hip
8	Discontinued	F	> 75	Non-vertebral
9	Discontinued	F	>75	Non-vertebral
10	Discontinued	F	> 75	Non-vertebral
11	Declined	F	> 75	Non-vertebral
12	Declined	F	> 75	Non-vertebral

F female; *M* male

was that of a male of a relatively younger age, with a single NVF other than the hip. In addition, patients older than 75 years old with a hip fracture and several comorbidities appeared more prone to discontinue the project. These are the patients who show poor adherence to treatment as they either do not realize that fractures are life-threatening or they experience great difficulties in visiting an outpatient clinic because of an inadequate transportation system. Greece lacks a patient-centered public facility for nonemergency transportation, which is critical for older patients, especially when they live alone. One limitation of this study, however, is that relevant data on the patients who declined to participate or who were lost to follow-up are missing, and thus we could not confirm whether the above factors were applicable to our subjects.

Finally, during the follow-up visits of our current study, 12 new fragility fractures occurred in the total of 392 patients who completed the project. Despite the fact that all of these fractures were reported in patients who had declined or discontinued anti-osteoporotic treatment, the numbers were too small to draw any solid conclusions, and the treatment period is too small to effectively influence the re-fracture rates. This finding appears to illustrate somewhat of a fortuitous event rather than an event clearly associated with or driven by the lack of anti-osteoporotic treatment.

The present study has several limitations, some of them being common with the first Greek report: (i) data on treatment adherence was based only on information retrieved by the patients and the national prescription system, which provides information regarding the executed prescriptions but not about the actual intake of medication; (ii) we did not have any information regarding the participants who preferred to visit other outpatient clinics or other physicians in private practice during the follow-up; (iii) in contrast with the first report, we did not have data on the eligible patients who refused to participate, which would have enabled us to identify any specific characteristics; and (iv) telephone visits might have missed any morphological vertebral fractures leading to underestimation of their number.

In conclusion, and based on the experience gained from FLS implementation in Greece, recruitment rates need to be further improved. In order to boost both the recruitment and completion rate, it is important for the treating physician to be well educated, motivated, and able to spend the appropriate amount of time needed to encourage patients to enroll. Furthermore, specific target groups need special attention, such as young people and older people with comorbidities and/or polypharmacy. In addition, a national fracture database is urgently needed, and HSSBM is collaborating with the ministry of health and other medical societies to reach this goal. This will certainly help all FLS efforts, especially at a national level, as it is the case in other countries such as the UK (https://www.nhfd.co.uk). Finally, our results have clearly demonstrated what a crucial role is played in the final outcome by the operational structure of the FLS, which, as a highly demanding and time-consuming effort, should be adequately and systematically supported by the national healthcare system.

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Compliance with ethical standards

Conflicts of interest PM has received lecture fees and research grants from Amgen and lecture fees and/or advisory board fees from Glaxo, Eli-Lilly, Pfizer, Leo, Genesis, Elpen, Vianex, Rafarm, Galenica, UCB, and UniPharma. GCB has received grants/research supports from ZIMMER GmBh (Academic Support) and Bayer. EC has received lecture fees from Eli-Lilly and Vianex. MP has received research grants and lecture fees from Bayer, Amgen, Pharmaserve-Lilly, and Vianex. CK has received lecture and/or advisory board fees from Amgen, Eli-Lilly, and VIANEX and lecture fees from Galenica. TK, KK, DP, A-NT, and CV have nothing to disclose.

References

1. Shipman KE, Doyle A, Arden H, Jones T, Gittoes NJ (2017) Development of fracture liaison services: what have we learned? Injury 48(Suppl 7):S4–S9. https://doi.org/10.1016/j.injury.2017.08.030
2. Axelsson KF, Jacobsson R, Lund D, Lorentzon M (2016) Effectiveness of a minimal resource fracture liaison service. Osteoporos Int 27(11):3165–3175. https://doi.org/10.1007/s00198-016-3643-2
3. Miller AN, Lake AF, Emory CL (2015) Establishing a fracture liaison service: an orthopaedic approach. J Bone Joint Surg Am 97(8):675–681. https://doi.org/10.2106/JBJS.N.00957
4. Noordin S, Allana S, Masri BA (2018) Establishing a hospital based fracture liaison service to prevent secondary insufficiency fractures. Int J Surg 54 (Pt B):328-332. https://doi.org/10.1016/j.ijsu.2017.09.010
5. Amphansap T, Stitkitti N, Dumrongwanich P (2016) Evaluation of police general hospital's fracture liaison service (PGH's FLS): the first study of a fracture liaison service in Thailand. Osteoporos Sarcopenia 2(4):238–243. https://doi.org/10.1016/j.afos.2016.09.002
6. Makras P, Panagoulia M, Mari A, Rizou S, Lyritis GP (2017) Evaluation of the first fracture liaison service in the Greek healthcare setting. Arch Osteoporos 12(1):3. https://doi.org/10.1007/s11657-016-0299-7
7. Marsh D, Akesson K, Beaton DE, Bogoch ER, Boonen S, Brandi ML, McLellan A, Mitchell PJ, Sale JE, Wahl DA, IOF CSA Fracture Working Group (2011) Coordinator-based systems for secondary prevention in fragility fracture patients. Osteoporos Int 22:2051–2065. https://doi.org/10.1007/s00198-011-1642-x
8. Makras P, Vaiopoulos G, Lyritis GP, Greek National Medicine A (2012) 2011 guidelines for the diagnosis and treatment of osteoporosis in Greece. J Musculoskelet Neuronal Interact 12(1):38–42
9. Makras P, Athanasakis K, Boubouchairopoulou N, Rizou S, Anastasilakis AD, Kyriopoulos J, Lyritis GP (2015) Cost-effective osteoporosis treatment thresholds in Greece. Osteoporos Int 26(7):1949–1957. https://doi.org/10.1007/s00198-015-3055-8
10. Ganda K, Puech M, Chen JS, Speerin R, Bleasel J, Center JR, Eisman JA, March L, Seibel MJ (2013) Models of care for the secondary prevention of osteoporotic fractures: a systematic review and meta-analysis. Osteoporos Int 24(2):393–406. https://doi.org/10.1007/s00198-012-2090-y
11. McLellan AR, Gallacher SJ, Fraser M, McQuillian C (2003) The fracture liaison service: success of a program for the evaluation and management of patients with osteoporotic fracture. Osteoporos Int 14(12):1028–1034. https://doi.org/10.1007/s00198-003-1507-z
12. Dehamchia-Rehailia N, Ursu D, Henry-Desailly I, Fardellone P, Paccou J (2014) Secondary prevention of osteoporotic fractures: evaluation of the Amiens University Hospital's fracture liaison service between January 2010 and December 2011. Osteoporos Int 25(10):2409–2416. https://doi.org/10.1007/s00198-014-2774-6
13. Eekman DA, van Helden SH, Huisman AM, Verhaar HJ, Bultink IE, Geusens PP, Lips P, Lems WF (2014) Optimizing fracture prevention: the fracture liaison service, an observational study. Osteoporos Int 25(2):701–709. https://doi.org/10.1007/s00198-013-2481-8
14. Ojeda-Bruno S, Naranjo A, Francisco-Hernandez F, Erausquin C, Rua-Figueroa I, Quevedo JC, Rodriguez-Lozano C (2011) Secondary prevention program for osteoporotic fractures and long-term adherence to bisphosphonates. Osteoporos Int 22(6):1821–1828. https://doi.org/10.1007/s00198-010-1414-z
15. Boudou L, Gerbay B, Chopin F, Ollagnier E, Collet P, Thomas T (2011) Management of osteoporosis in fracture liaison service associated with long-term adherence to treatment. Osteoporos Int 22(7):2099–2106. https://doi.org/10.1007/s00198-011-1638-6
16. Huntjens KM, van Geel TA, Blonk MC, Hegeman JH, van der Elst M, Willems P, Geusens PP, Winkens B, Brink P, van Helden SH (2011) Implementation of osteoporosis guidelines: a survey of five large fracture liaison services in the Netherlands. Osteoporos Int 22(7):2129–2135. https://doi.org/10.1007/s00198-010-1442-8
17. Makras P, Anastasilakis AD, Antypas G, Chronopoulos E, Kaskani EG, Matsouka A, Patrikos DK, Stathopoulos KD, Tournis S, Trovas G, Kosmidis C (2019) The 2018 guidelines for the diagnosis and treatment of osteoporosis in Greece. Arch Osteoporos 14(1):39. https://doi.org/10.1007/s11657-019-0584-3
18. Makras P, Boubouchairopoulou N, Katsarolis I, Athanasakis K (2017) Cost-effective osteoporosis treatment thresholds for people living with HIV infection in Greece. J Musculoskelet Neuronal Interact 17(4):292–298
19. Silverman S, Gold DT (2010) Compliance and persistence with osteoporosis medications: a critical review of the literature. Rev Endocr Metab Disord 11(4):275–280. https://doi.org/10.1007/s11154-010-9138-0
20. Peacock E, Krousel-Wood M (2017) Adherence to antihypertensive therapy. Med Clin North Am 101(1):229–245. https://doi.org/10.1016/j.mcna.2016.08.005
21. Polonsky WH, Henry RR (2016) Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence 10:1299–1307. https://doi.org/10.2147/PPA.S106821
22. Munson JC, Bynum JP, Bell JE, Cantu R, McDonough C, Wang Q, Tosteson TD, Tosteson AN (2016) Patterns of prescription drug use before and after fragility fracture. JAMA Intern Med 176:1531–1538. https://doi.org/10.1001/jamainternmed.2016.4814
23. Kanis JA, Svedbom A, Harvey N, McCloskey EV (2014) The osteoporosis treatment gap. J Bone Miner Res 29(9):1926–1928. https://doi.org/10.1002/jbmr.2301
24. The Lancet Diabetes E (2018) Osteoporosis: a roadmap to close the treatment gap. Lancet Diabetes Endocrinol 6(11):833. https://doi.org/10.1016/S2213-8587(18)30292-4