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Research Paper

Pathologic fracture and healthcare resource utilisation: A retrospective study in eight European countries

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ABSTRACT

Background: Skeletal-related events (SREs; pathologic fracture [PF], spinal cord compression and radiation or surgery to bone) are common complications of bone metastases or bone lesions and can impose a considerable burden on patients and healthcare systems. In this study, the healthcare resource utilisation (HRU) associated with PFs in patients with bone metastases or lesions secondary to solid tumours or multiple myeloma was estimated in eight European countries.

Methods: Eligible patients were identified in Austria, the Czech Republic, Finland, Greece, Poland, Portugal, Sweden and Switzerland. HRU data were extracted from hospital charts from 3.5 months before the index PF (defined as a PF preceded by a 6.5-month period without a SRE) until 3 months after the last SRE during the study period. Changes from baseline in the number and duration of inpatient stays, number of outpatient visits and number of procedures provided were recorded.

Results: Overall, 118 patients with PFs of long bones (those longer than they are wide, e.g. the femur) and 241 patients with PFs of other bones were included. Overall, HRU was greater in patients with long bone PFs than in those with PFs of other bones. A higher proportion of patients with long bone PFs had multiple SREs (79.7%), and more of their SREs were considered to be linked (73.4%) compared with patients with PFs of other bones (51.0% and 47.2%, respectively).

Conclusion: The increased number and duration of inpatient stays for PFs of long bones compared with those for PFs of other bones may be due in part to the requirement for complicated and lengthy rehabilitation in patients with long bone PFs. Implementing strategies to delay or reduce the number of PFs experienced by patients with bone metastases or lesions may therefore reduce the associated HRU and patient burden.

1. Introduction

Bone metastases affect up to two-thirds of patients with advanced solid tumours such as breast, prostate or lung cancer [1], and osteolytic bone lesions are typical of multiple myeloma [2]. Individuals with bone metastases or lesions are at a high risk of experiencing skeletal-related events (SREs), including pathologic fractures (PFs), spinal cord compression and radiation or surgery to bone [3–6].

PFs have commonly been reported in the placebo arms of clinical trials that evaluated the effect of bisphosphonates in patients with bone metastases secondary to advanced cancers [7–9] and have been shown to be detrimental to patients' quality of life [10]. Statistically significant declines in the physical and emotional well-being of patients have been reported after experiencing PFs [11]. Patients with PFs often require

AbbreviationsHRUhealthcare resource utilisationICDInternational Classification of DiseasesPFpathologic fractureSDstandard deviationSREskeletal-related event

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substantial orthopaedic treatment, including rehabilitation and supportive care, such as pain relief, and therefore utilise considerable healthcare resources. Furthermore, the occurrence of PFs has been correlated with reduced survival rates in patients with bone metastases [12].

Several studies worldwide have revealed that HRU and costs associated with SREs, including PFs, in patients with bone metastases or lesions are substantial [13–16]. However, these studies have focused either on single countries or on small numbers of European countries. Increasing healthcare providers' knowledge of the HRU associated with PFs in patients with bone metastases or lesions in Europe would highlight the potential economic value of using treatments that prevent or delay SREs. Such treatments may also reduce HRU and maintain patients' quality of life. This study aimed to estimate the HRU associated with PFs in patients with bone metastases secondary to solid tumours or lesions secondary to multiple myeloma in eight European countries.

2. Methods

This was a multinational, retrospective study to assess hospital-related HRU associated with PFs in patients with bone metastases or lesions from Austria, the Czech Republic, Finland, Greece, Poland, Portugal, Sweden and Switzerland. Patients eligible to participate in the study were aged 20 years or older, had bone metastases secondary to breast, lung or prostate cancer, or bone lesions due to multiple myeloma. Patients also had to have experienced an index PF (defined as a PF preceded by a SRE-free period of at least 6.5 months) during the study period (from 1 July 2004 to 1 July 2009) to be included. Exclusion criteria included current enrolment or previous participation in a denosumab clinical trial, death less than 2 weeks after the index PF and patient chart data of insufficient quality. Relevant patient charts were identified at each site from electronic or paper patient lists using the International Classification of Diseases (ICD) Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes. Data from consecutive patient charts for those fulfilling the inclusion criteria and not meeting the exclusion criteria were captured during the study period. The patient chart with the most recent PF was analysed first (even if this is not the most recent Index SRE), then the second most recent was analysed (i.e. systematically in reverse consecutive order) until the planned number of PFs were documented on a country level.

According to European legislation for this type of retrospective research, informed consent is generally not required. However, it was provided when specifically requested by local authorities or the institution. This study was approved by official government institutions and ethics committees, where required.

2.1. PF data collection

PFs were grouped into those affecting long bones (i.e. bones that are longer than they are wide, such as the femur) or those involving other bones. Long bone fractures are usually major clinical events, whereas fractures of some other bones may be asymptomatic and may be discovered only by routine bone scanning. In this study, all PFs were symptomatic but the HRU for these fracture types may differ. Based on epidemiology and feasibility studies, the target number was 10 patients with at least one PF of a long bone and 30 patients with at least one PF of other bones for each participating country. In addition to HRU data, patients' baseline demographics and disease characteristics were documented.

2.2. HRU attribution

Retrospective HRU data were collected from patient charts during the study period. For patients who experienced only the index PF during the study period, data were extracted from hospital charts for a period beginning 3.5 months before and ending 3 months after the index PF [17] (Fig. 1a). In order to attribute HRU in patients with multiple SREs, it was necessary to set a diagnostic window. In line with a previous study [18], a period of 3 months starting 3.5 months before the index PF was used to establish baseline HRU, and a 14-day (2 week) period immediately before the index PF was used to estimate any diagnostic HRU [18]. For patients with multiple SREs, the data-extraction period was extended until 3 months after the last SRE that the patient experienced during the study period (Fig. 1b). There was no limit to the number of SREs included in the period following the index PF. To ensure lack of carry-over of HRU from a previous SRE that occurred before the 3.5-month period immediately preceding the index PF, a clean window of an additional 3 months without a SRE was required.

If multiple SREs were present at the same anatomical site and occurred within a 21-day window, they were considered to be linked and the total HRU was attributed to the index PF. In cases in which SREs occurred at the same anatomical site but outside the 21-day window, or at different anatomical sites, the SREs were considered to be unlinked and HRU was attributed to the appropriate SRE type following chart review by an expert panel. Patients could experience several linked and/or unlinked SREs simultaneously.

Primary HRU outcome measures were: the number and duration of inpatient stays (overall and by type of hospital unit); the number of outpatient visits (overall and by healthcare provider type); the number of day-care hospital visits (visits to day-care centres were made by patients who required more prolonged treatment or investigations than outpatients, but who did not require an overnight stay); the number of emergency room visits; and the number and types of procedures provided. The proportion of patients receiving bisphosphonate medications at baseline and post-SRE (and the dose frequency) was recorded.

2.3. Statistical analyses

To estimate HRU associated with an index PF, the following calculation was used.

Estimate of HRU associated with PF
= HRU recorded during post–PF period
+ HRU during diagnosis period
–HRU recorded during the baseline period[a]

[a]Adjusted to allow for the different lengths of the periods.

Statistical analyses were descriptive in nature; data are presented as mean (standard deviation [SD]), because this better describes the total HRU for the study population.

3. Results

3.1. Patients

In total, 118 patients with long bone PFs and 241 patients with PFs of other bones were included. The baseline demographics of participants were generally consistent across all countries; however, the mean age of patients with PF of long bones was higher in Finland (74.5 [SD 4.2] years; *n*=8) and Sweden (75.8 [SD 7.4] years; *n*=9) compared with the other countries (range 61.5–68.9 years) (Table 1). Overall, the most common cancer types were breast cancer (long bones 37.3%; other bones 32.4%) and multiple myeloma (long bones 23.7%; other bones 40.7%) (Tables 1 and 2). The mean time since initial diagnosis of bone metastases or lesions was approximately 1 year in both patients with long bone PFs and those with PFs of other bones. The mean duration of follow-up was similar for patients with long bone PFs (3.2 months; SD 1.2 months) and other bone PFs (3.3 months; SD 1.2 months). Overall, the most common fractures affecting long bones were those of the femur (58.5%) and humerus (32.2%) (Table 3). Fractures of the vertebrae were the most common fracture type in those with PFs

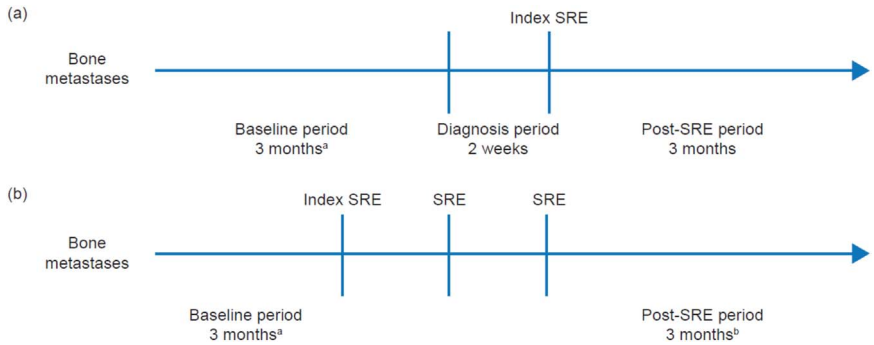

Fig. 1. Study design and data collection for patients with one SRE (a) and multiple SREs (b). (a) To ensure lack of carry-over of HRU from a previous SRE that occurred before the 3.5-month period preceding the index PF, a clean window of an additional 3 months without a SRE was required. (b) For multiple SREs, the observational period after the index PF was extended to 3 months following the last observed SRE. To ensure that any HRU used to diagnose the SRE is included in the HRU burden for the SRE, a 14-day (2 week) period immediately before the index PF was used to estimate any diagnostic HRU. The following calculation was used to estimate HRU: Estimate of HRU associated with PF=HRU recorded during post-PF period+HRU during diagnosis period – HRU recorded during the baseline period· (a) Adjusted to allow for the different lengths of the periods. The diagnosis period was adjusted to allow for the different lengths of the baseline and post-baseline periods. To calculate the HRU attributed to multiple SREs, for those observed at the same anatomical site and within a 21-day window, the HRU was attributed to the index PF. For multiple SREs observed at the same anatomical site but outside the 21-day window, the expert panel attributed HRU to the appropriate SRE. In the case of multiple SREs observed at different anatomical sites on the same or different days, the expert panel attributed HRU to the appropriate SRE. HRU, healthcare resource utilisation; PF, pathologic fracture; SRE, skeletal-related event.

Table 1
Baseline demographics and disease characteristics of patients with pathologic fractures of long bones.

	All countries (*N*=118)	**Austria (*n*=25)**	**Czech Republic (*n*=18)**	**Finland (*n*=8)**	**Greece (*n*=8)**	**Poland (*n*=28)**	**Portugal (*n*=14)**	**Sweden (*n*=9)**	**Switzerland (*n*=8)**
Mean age, years (SD)	65.7 (11.9)	62.9 (12.5)	66.3 (10.9)	74.5 (4.2)	68.9 (10.9)	62.8 (11.5)	61.5 (13.2)	75.8 (7.4)	66.9 (12.9)
Female, *n* (%)	64 (54.2)	14 (56.0)	10 (55.6)	2 (25.0)	5 (62.5)	17 (60.7)	8 (57.1)	2 (22.2)	6 (75.0)
Age group, *n* (%)									
< 65 years	50 (42.4)	13 (52.0)	9 (50.0)	0 (0.0)	2 (25.0)	14 (50.0)	9 (64.3)	1 (11.1)	2 (25.0)
≥65 years	68 (57.6)	12 (48.0)	9 (50.0)	8 (100.0)	6 (75.0)	14 (50.0)	5 (35.7)	8 (88.9)	6 (75.0)
≥75 years	30 (25.4)	4 (16.0)	4 (22.2)	3 (37.5)	3 (37.5)	5 (17.9)	3 (21.4)	6 (66.7)	2 (25.0)
ECOG status, *n* (%)									
0	8 (6.8)	1 (4.0)	1 (5.6)	1 (12.5)	1 (12.5)	2 (7.1)	0 (0.0)	1 (11.1)	1 (12.5)
1	29 (24.6)	3 (12.0)	5 (27.8)	1 (12.5)	2 (25.0)	8 (28.6)	4 (28.6)	4 (44.4)	2 (25.0)
2	28 (23.7)	2 (8.0)	6 (33.3)	2 (25.0)	3 (37.5)	8 (28.6)	1 (7.1)	2 (22.2)	4 (50.0)
3	18 (15.3)	1 (4.0)	4 (22.2)	2 (25.0)	0 (0.0)	8 (28.6)	2 (14.3)	1 (11.1)	0 (0.0)
4	3 (2.5)	0 (0.0)	1 (5.6)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	1 (11.1)	0 (0.0)
Unknown	32 (27.1)	18 (72.0)	1 (5.6)	2 (25.0)	2 (25.0)	1 (3.6)	7 (50.0)	0 (0.0)	1 (12.5)
Primary tumour diagnosis, *n* (%)									
Breast cancer	44 (37.3)	11 (44.0)	10 (55.6)	2 (25.0)	1 (12.5)	8 (28.6)	5 (35.7)	1 (11.1)	6 (75.0)
Lung cancer	20 (16.9)	4 (16.0)	0 (0.0)	1 (12.5)	1 (12.5)	8 (28.6)	4 (28.6)	1 (11.1)	1 (12.5)
Prostate cancer	26 (22.0)	1 (4.0)	7 (38.9)	3 (37.5)	2 (25.0)	3 (10.7)	2 (14.3)	7 (77.8)	1 (12.5)
Multiple myeloma	28 (23.7)	9 (36.0)	1 (5.6)	2 (25.0)	4 (50.0)	9 (32.1)	3 (21.4)	0 (0.0)	0 (0.0)
SRE status, *n* (%)									
Single	24 (20.3)	3 (12.0)	7 (38.9)	0 (0.0)	3 (37.5)	3 (10.7)	2 (14.3)	2 (22.2)	4 (50.0)
Multiple	94 (79.7)	22 (88.0)	11 (61.1)	8 (100.0)	5 (62.5)	25 (89.3)	12 (85.7)	7 (77.8)	4 (50.0)
Time since diagnosis of bone metastases/ lesions, months									
n	85	13	15	6	4	19	11	9	8
Mean (SD)	11.9 (25.9)	10.3 (15.7)	19.8 (36.4)	16.4 (26.3)	9.4 (11.2)	2.4 (5.8)	7.4 (18.7)	25.3 (50.5)	10.8 (16.7)
Median (Q1, Q3)	0.7 (0.0, 13.0)	3.1 (0.0, 15.4)	4.5 (0.0, 26.7)	7.1 (0.0,16.3)	8.2 (–0.18, 18.9)	0.0 (0.0, 1.3)	0.0 (0.0, 3.6)	0.7 (0.0, 31.5)	5.9 (0.5, 11.6)
Bone metastases sites, *n* (%)									
1–2	76 (64.4)	15 (60.0)	13 (72.2)	4 (50.0)	4 (50.0)	16 (57.1)	11 (78.6)	8 (88.9)	5 (62.5)
3–4	6 (5.1)	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	2 (7.1)	0 (0.0)	0 (0.0)	1 (12.5)
≥5	8 (6.8)	1 (4.0)	1 (5.6)	2 (25.0)	0 (0.0)	1 (3.6)	0 (0.0)	1 (11.1)	2 (25.0)
Missing	28 (23.7)	9 (36.0)	1 (5.6)	2 (25.0)	4 (50.0)	9 (32.1)	3 (21.4)	0 (0.0)	0 (0.0)

ECOG, Eastern Cooperative Oncology Group; Q, quartile; SD, standard deviation; SRE, skeletal-related event.

affecting other bones (66.7% overall; thoracic vertebrae 40.2%; lumbar vertebrae 23.2%; cervical vertebrae 3.3%) (Table 4). Retrospective review of those patients who had a long bone or other bone PF, 28.0% (n=33) and 25.3% (n=61), respectively were receiving a bisphosphonate at baseline. After a SRE, the number of patients receiving a bisphosphonate was 61.9% (n=73) in those patients with a long bone PF and 69.3% (n=167) in those patients with a PF of other bones. The most commonly used bisphosphonate was zoledronic acid (Tables 5 and 6).

3.2. SREs in patients with PFs

In the long bone PF group, more patients had multiple SREs than

Table 2
Baseline demographics and disease characteristics of patients with pathologic fractures of bones other than long bones.

	All countries (*N*=241)	Austria (*n*=22)	Czech Republic (*n*=33)	Finland (*n*=30)	Greece (*n*=32)	Poland (*n*=30)	Portugal (*n*=29)	Sweden (*n*=27)	Switzerland (*n*=38)
Mean age, years (SD)	64.5 (11.6)	63.6 (11.6)	64.8 (9.0)	64.6 (10.6)	63.3 (10.1)	63.0 (11.7)	62.9 (12.2)	62.7 (15.3)	69.1 (11.6)
Female, *n* (%)	119 (49.4)	11 (50.0)	20 (60.6)	16 (53.3)	12 (37.5)	17 (56.7)	16 (55.2)	7 (25.9)	20 (52.6)
Age group, *n* (%)									
< 65 years	111 (46.1)	12 (54.5)	14 (42.4)	13 (43.3)	15 (46.9)	15 (50.0)	15 (51.7)	14 (51.9)	13 (34.2)
≥65 years	130 (53.9)	10 (45.5)	19 (57.6)	17 (56.7)	17 (53.1)	15 (50.0)	14 (48.3)	13 (48.1)	25 (65.8)
≥75 years	46 (19.1)	4 (18.2)	5 (15.2)	5 (16.7)	2 (6.3)	4 (13.3)	3 (10.3)	8 (29.6)	15 (39.5)
ECOG status, *n* (%)									
0	16 (6.6)	4 (18.2)	2 (6.1)	0 (0.0)	4 (12.5)	0 (0.0)	1 (3.4)	0 (0.0)	5 (13.2)
1	68 (28.2)	7 (31.8)	15 (45.5)	7 (23.3)	7 (21.9)	10 (33.3)	4 (13.8)	2 (7.4)	16 (42.1)
2	69 (28.6)	0 (0.0)	10 (30.3)	14 (46.7)	16 (50.0)	15 (50.0)	3 (10.3)	2 (7.4)	9 (23.7)
3	19 (7.9)	0 (0.0)	3 (9.1)	3 (10.0)	2 (6.3)	4 (13.3)	0 (0.0)	3 (11.1)	4 (10.5)
4	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)	1 (3.3)	0 (0.0)	1 (3.7)	0 (0.0)
Unknown	66 (27.4)	11 (50.0)	3 (9.1)	6 (20.0)	2 (6.3)	0 (0.0)	21 (72.4)	19 (70.4)	4 (10.5)
Primary tumour diagnosis, *n* (%)									
Breast cancer	78 (32.4)	11 (50.0)	21 (63.6)	10 (33.3)	1 (3.1)	8 (26.7)	14 (48.3)	0 (0.0)	13 (34.2)
Lung cancer	23 (9.5)	3 (13.6)	0 (0.0)	9 (30.0)	3 (9.4)	3 (10.0)	4 (13.8)	0 (0.0)	1 (2.6)
Prostate cancer	42 (17.4)	1 (4.5)	9 (27.3)	7 (23.3)	3 (9.4)	1 (3.3)	5 (17.2)	10 (37.0)	6 (15.8)
Multiple myeloma	98 (40.7)	7 (31.8)	3 (9.1)	4 (13.3)	25 (78.1)	18 (60.0)	6 (20.7)	17 (63.0)	18 (47.4)
SRE status, *n* (%)									
Single	118 (49.0)	8 (36.4)	25 (75.8)	3 (10.0)	22 (68.8)	17 (56.7)	7 (24.1)	19 (70.4)	17 (44.7)
Multiple	123 (51.0)	14 (63.6)	8 (24.2)	27 (90.0)	10 (31.3)	13 (43.3)	22 (75.9)	8 (29.6)	21 (55.3)
Time since diagnosis of bone metastases, months									
n	142	14	30	26	7	12	23	10	20
Mean (SD)	12.2 (24.8)	6.8 (16.1)	15.8 (24.4)	15.8 (29.4)	2.2 (3.6)	1.6 (2.9)	9.1 (20.7)	15.5 (12.0)	17.6 (39.6)
Median (Q1, Q3)	0.5 (0.0, 11.4)	0.0 (0.0, 5.0)	1.0 (0.0, 22.6)	0.7 (0.0, 19.3)	0.2 (0.0, 5.6)	0.0 (0.0, 1.9)	0.7 (0.0, 6.1)	12.9 (8.4, 27.4)	0.4 (0.0, 15.8)
Bone metastases sites, *n* (%)									
1–2	108 (44.8)	11 (50.0)	26 (78.8)	11 (36.7)	7 (21.9)	9 (30.0)	23 (79.3)	7 (25.9)	14 (36.8)
3–4	19 (7.9)	3 (13.6)	2 (6.1)	9 (30.0)	0 (0.0)	1 (3.3)	0 (0.0)	2 (7.4)	2 (5.3)
≥5	16 (6.6)	1 (4.5)	2 (6.1)	6 (20.0)	0 (0.0)	2 (6.7)	0 (0.0)	1 (3.7)	4 (10.5)
Missing	98 (40.7)	7 (31.8)	3 (9.1)	4 (13.3)	25 (78.1)	18 (60.0)	6 (20.7)	17 (63.0)	18 (47.4)

ECOG, Eastern Cooperative Oncology Group; Q, quartile; SD, standard deviation; SRE, skeletal-related event.

Table 3
Site of fracture in patients with pathologic fractures of long bones.

Fracture site, *n* (%)	All countries (*N*=118)	Austria (*n*=25)	Czech Republic (*n*=18)	Finland (*n*=8)	Greece (*n*=8)	Poland (*n*=28)	Portugal (*n*=14)	Sweden (*n*=9)	Switzerland (*n*=8)
Femur	69 (58.5)	15 (60.0)	14 (77.8)	4 (50.0)	1 (12.5)	19 (67.9)	10 (71.4)	2 (22.2)	4 (50.0)
Humerus	38 (32.2)	8 (32.0)	4 (22.2)	3 (37.5)	3 (37.5)	7 (25.0)	4 (28.6)	7 (77.8)	2 (25.0)
Tibia	3 (2.5)	1 (4.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Radius	4 (3.4)	1 (4.0)	0 (0.0)	1 (12.5)	2 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ulna	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)
Other	3 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)

had a single SRE (i.e. only the index PF) (79.7% [*n*=94] and 20.3% [*n*=24], respectively; Table 1). However, in patients with PFs of other bones, the proportions with multiple or single SREs were similar (51.0% [*n*=123] and 49.0% [*n*=118], respectively; Table 2). SREs could be classified as being linked or unlinked; subsequent linked SREs were more frequent in patients with long bone PFs (73.4% of multiple SREs; *n*=69) than in those with other bone PFs (47.2%; *n*=58). The most common linked SREs were surgery to bone (long bones 42.4% [*n*=50]; other bones 6.6% [*n*=16]) and radiation to bone (long bones 18.6% [*n*=22]; other bones 17.4% [*n*=42]).

3.3. Analyses of inpatient stays

The mean number of inpatient stays per PF increased from baseline for both PF of long bones (1.2 [SD 1.2]) and other bones (0.8 [SD 1.2] (Fig. 2a). The mean duration of inpatient stays also increased in both groups (long bones 20.9 [SD 22.1] days; other bones 12.3 [SD 19.5] days) (Fig. 2b). For individuals with long bone PFs, the greatest increases in duration of stay per PF were reported in Portugal (32.1 [SD 19.8] days; *n*=14) and Finland (29.4 [SD 34.6] days; *n*=8). The smallest increase was reported in Greece (5.8 [SD 8.3] days; *n*=8) (Fig. 2b).

The types of hospital units that patients stayed in differed according to the type of fracture they experienced. The largest mean change from baseline in the number of stays per PF of long bones occurred in orthopaedic units (0.5 [SD 0.6]), but stays in oncology units and 'other' units (including trauma surgery, casualty units, cardiology units and nursing units) also increased slightly (0.1 [SD 0.3]) and 0.1 [SD 0.8], respectively). For individuals with PFs of other bones, the largest mean increases from baseline in the number of inpatient stays per PF were observed in internal medicine units (0.2 [SD 0.6]) and oncology units (0.2 [SD 0.7]).

Table 4
Site of fracture in patients with pathologic fractures of bones other than long bones.

Fracture site, *n* (%)	All countries (*N*=241)	Austria (*n*=22)	Czech Republic (*n*=33)	Finland (*n*=30)	Greece (*n*=32)	Poland (*n*=30)	Portugal (*n*=29)	Sweden (*n*=27)	Switzerland (*n*=38)
Thoracic vertebrae	97 (40.2)	5 (22.7)	13 (39.4)	8 (26.7)	18 (56.3)	12 (40.0)	16 (55.2)	12 (44.4)	13 (34.2)
Lumbar vertebrae	56 (23.2)	2 (9.1)	7 (21.2)	5 (16.7)	7 (21.9)	13 (43.3)	9 (31.0)	5 (18.5)	8 (21.1)
Cervical vertebrae	8 (3.3)	2 (9.1)	0 (0.0)	2 (6.7)	0 (0.0)	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)
Ribs	29 (12.0)	5 (22.7)	3 (9.1)	11 (36.7)	3 (9.4)	0 (0.0)	0 (0.0)	2 (7.4)	5 (13.2)
Ilium	6 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)	0 (0.0)	3 (11.1)	1 (2.6)
Sacrum	4 (1.7)	2 (9.1)	1 (3.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clavicle	9 (3.7)	3 (13.6)	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	1 (3.4)	2 (7.4)	2 (5.3)
Ischium	3 (1.2)	0 (0.0)	1 (3.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Pubis	6 (2.5)	2 (9.1)	2 (6.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	1 (2.6)
Sternum	2 (0.8)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Scapula	2 (0.8)	0 (0.0)	1 (3.0)	0 (0.0)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other	19 (7.9)	1 (4.5)	5 (15.2)	2 (6.7)	0 (0.0)	0 (0.0)	3 (10.3)	2 (7.4)	6 (15.8)

Table 5
Patients receiving bisphosphonate medication by dose frequency at baseline and in the post-SRE interval in patients with pathologic fractures of long bones.

	All countries (*N*=118)	Austria (*n*=25)	Czech Republic (*n*=18)	Finland (*n*=8)	Greece (*n*=8)	Poland (*n*=28)	Portugal (*n*=14)	Sweden (*n*=9)	Switzerland (*n*=8)
Patients receiving bisphosphonates at baseline, *n* (%)	33 (28.0)	9 (36.0)	8 (44.4)	5 (62.5)	3 (37.5)	5 (17.9)	1 (7.1)	0 (0.0)	2 (25.0)
Disodium pamidronate	4 (3.4)					4 (14.3)			
Ibandronic acid	6 (5.1)	3 (12.0)	2 (11.1)		1 (12.5)				
Pamidronate disodium	1 (0.8)						1 (7.1)		
Sodium clodronate	8 (6.8)		4 (22.2)	3 (37.5)		1 (3.6)			
Zoledronic acid	14 (11.9)	6 (24.0)	2 (11.1)	2 (25.0)	2 (25.0)				2 (25.0)
Patients receiving bisphosphonates after a pathologic fracture, *n* (%)[a]	73 (61.9)	17 (68.0)	16 (88.9)	6 (75.0)	4 (50.0)	15 (53.6)	8 (57.1)	2 (22.2)	5 (62.5)
Bisphosphonate type and dosing frequency, *n* (%)[b]									
Clodronate disodium	2 (1.7)		**2 (11.1)**						
Once a day	1 (0.8)		1 (5.6)						
Other	1 (0.8)		1 (5.6)						
Disodium pamidronate	**19 (16.1)**			**1 (12.5)**		**13 (46.4)**	**5 (35.7)**		
Every 4 weeks	11 (9.3)			1 (12.5)		9 (32.1)	1 (7.1)		
Once a month	6 (5.1)					4 (14.3)	2 (14.3)		
Other	2 (1.7)						2 (14.3)		
Ibandronic acid	**8 (6.8)**	**5 (20.0)**	**2 (11.1)**		**1 (12.5)**				
Once a day	4 (3.4)	4 (16.0)							
Every 4 weeks	4 (3.4)	1 (4.0)	2 (11.1)		1 (12.5)				
Pamidronate disodium	**1 (0.8)**						**1 (7.1)**		
Other	1 (0.8)						1 (7.1)		
Sodium clodronate	**16 (13.6)**	**1 (4.0)**	**8 (44.4)**	**4 (50.0)**		**3 (10.7)**			
Once a day	11 (9.3)		7 (38.9)	2 (25.0)		2 (7.1)			
Other	5 (4.2)	1 (4.0)	1 (5.6)	2 (25.0)		1 (3.6)			
Zoledronic acid	**31 (26.3)**	**11 (44.0)**	**4 (22.2)**	**4 (50.0)**	**3 (37.5)**		**2 (14.3)**	**2 (22.2)**	**5 (62.5)**
Once a day	1 (0.8)			1 (12.5)					
Every 4 weeks	19 (16.1)	8 (32.0)	4 (22.2)		2 (25.0)		2 (14.3)	1 (11.1)	2 (25.0)
Once a month	5 (4.2)	1 (4.0)						1 (11.1)	3 (37.5)
Every 3 months	1 (0.8)			1 (12.5)					
Other	5 (4.2)	2 (8.0)		2 (25.0)	1 (12.5)				

SRE, skeletal-related event.
[a] Patients may have received more than one type of bisphosphonate and more than one dose regimen during the post-SRE period.
[b] For clarity, the type of bisphosphonate received after a pathologic fracture is shown in bold.

3.4. Analyses of outpatient visits

Collectively, the mean number of outpatient visits per PF increased in both groups. There was a larger increase in the number of visits per event for patients with PFs of other bones (4.0 [SD 5.8]) than for those with PFs of long bones (2.6 [SD 4.7]) (Fig. 3a). Compared with the other countries in this study, Finland recorded the largest increase in the mean number of outpatient visits per event (long bones 8.6 [SD 6.1]; *n*=8; other bones 6.8 [SD 6.1]; *n*=30). The smallest changes were reported in Greece (0.9 [SD 3.3]; *n*=8) and Poland (0.9 [SD 3.2]; *n*=28)

Table 6
Patients receiving bisphosphonate medication by dose frequency at baseline and in the post-SRE interval in patients with pathologic fractures of bones other than long bones.

	All countries (*N*=241)	Austria **(*n*=22)**	**Czech Republic (*n*=33)**	**Finland (*n*=30)**	**Greece (*n*=32)**	**Poland (*n*=30)**	**Portugal (*n*=29)**	**Sweden (*n*=27)**	**Switzerland (*n*=38)**
Patients receiving bisphosphonates at baseline, *n* (%)	61 (25.3)	4 (18.2)	10 (30.3)	10 (33.3)	2 (6.3)	12 (40.0)	5 (17.2)	9 (33.3)	9 (23.7)
Clodronate disodium	2 (0.8)		2 (6.1)						
Disodium pamidronate	17 (7.1)	1 (4.5)				12 (40.0)	4 (13.8)		
Ibandronic acid	1 (0.4)								1 (2.6)
Pamidronate disodium	6 (2.5)							6 (22.2)	
Sodium clodronate	6 (2.5)		3 (9.1)	3 (10.0)					
Zoledronic acid	29 (12.0)	3 (13.6)	5 (15.2)	7 (23.3)	2 (6.3)		1 (3.4)	3 (11.1)	8 (21.1)
Patients receiving bisphosphonates after a pathologic fracture, *n* (%)[a]	167 (69.3)	15 (68.2)	23 (69.7)	21 (70.0)	18 (56.3)	24 (80.0)	17 (58.6)	19 (70.4)	30 (78.9)
Bisphosphonate type and dosing frequency, *n* (%)[b]									
Alendronate sodium	**1 (0.4)**	**1 (4.5)**							
Every week	1 (0.4)	1 (4.5)							
Clodronate disodium	**2 (0.8)**		**2 (6.1)**						
Once a day	1 (0.4)		1 (3.0)						
Other	1 (0.4)		1 (3.0)						
Disodium pamidronate	**42 (17.4)**	**4 (18.2)**				**23 (76.7)**	**9 (31.0)**		**6 (15.8)**
Once a day	1 (0.4)								1 (2.6)
Every 4 weeks	24 (10.0)	2 (9.1)				20 (66.7)			2 (5.3)
Once a month	8 (3.3)					3 (10.0)	2 (6.9)		3 (7.9)
Other	9 (3.7)	2 (9.1)					7 (24.1)		
Ibandronic acid	**7 (2.9)**	**1 (4.5)**	**2 (6.1)**				**1 (3.4)**	**1 (3.7)**	**2 (5.3)**
Once a day	3 (1.2)		1 (3.0)				1 (3.4)	1 (3.7)	
Every 4 weeks	2 (0.8)	1 (4.5)	1 (3.0)						
Once a month	1 (0.4)								1 (2.6)
Other	1 (0.4)								1 (2.6)
Pamidronate disodium	**15 (6.2)**						**1 (3.4)**	**14 (51.9)**	
Every 4 weeks	10 (4.1)						1 (3.4)	9 (33.3)	
Once a month	3 (1.2)							3 (11.1)	
Every 3 months	2 (0.8)							2 (7.4)	
Sodium clodronate	**15 (6.2)**		**9 (27.3)**	**5 (16.7)**		**1 (3.3)**			
Once a day	13 (5.4)		7 (21.2)	5 (16.7)		1 (3.3)			
Other	2 (0.8)		2 (6.1)						
Zoledronic acid	**91 (37.8)**	**10 (45.5)**	**10 (30.3)**	**18 (60.0)**	**18 (56.3)**		**7 (24.1)**	**5 (18.5)**	**23 (60.5)**
Once a day	4 (1.7)		1 (3.0)	1 (3.3)	1 (3.1)				1 (2.6)
3–4 times a week	1 (0.4)			1 (3.3)					
Every week	1 (0.4)			1 (3.3)					
Every 4 weeks	45 (18.7)	7 (31.8)	8 (24.2)	3 (10.0)	14 (43.8)		3 (10.3)	2 (7.4)	8 (21.1)
Once a month	18 (7.5)			2 (6.7)	1 (3.1)		1 (3.4)	1 (3.7)	13 (34.2)
Every 3 months	3 (1.2)			2 (6.7)					1 (2.6)
Other	19 (7.9)	3 (13.6)	1 (3.0)	8 (26.7)	2 (6.3)		3 (10.3)	2 (7.4)	

SRE, skeletal-related event.
[a] Patients may have received more than one type of bisphosphonate and more than one dose regimen during the post-SRE period.
[b] For clarity, the type of bisphosphonate received after a pathologic fracture is shown in bold.

for those with PFs of long bones. For individuals with PFs of other bones, Poland had the smallest change in the mean number of outpatient visits (0.8 [SD 1.7]; *n*=30).

The largest changes in the mean number of outpatient visits per PF from baseline were in visits to radiation oncologists/radiotherapists (long bones 1.0 [SD 2.5]; other bones 1.5 [SD 3.8]) and oncologists (long bones 0.5 [SD 1.9]; other bones 0.8 [SD 2.3]). The increase in the number of visits to orthopaedic surgeons was greater in patients with PFs of long bones (0.3 [SD 0.7]) than in those with PFs of other bones (0.1 [SD 0.3]). The number of visits to radiologists also increased, and this change was greater in patients with PFs of other bones (0.6 [SD 1.7]) than in those with PFs of long bones (0.2 [SD 1.1]).

3.5. Analysis of day-care visits and emergency room visits

The increase in the mean number of day-care visits was smaller for individuals with long bone PFs (0.8 [SD 2.7] than for those with other bone PFs (1.4 [SD 3.6]). The mean number of emergency room visits increased from baseline per PF of long bones (0.3 [SD 0.7]) and other bones (0.2 [SD 0.9]).

3.6. Number and type of procedures

Overall, the number of procedures provided per event increased in both PF groups (long bones 6.1 [SD 7.1]; other bones 5.9 [SD 6.6]) (Fig. 3b). Finland reported the greatest increase in the mean number of procedures in patients with PFs of long bones (12.9 [SD 9.2]; *n*=8). In individuals with PFs of other bones, the greatest increase was observed in Austria (10.3 [SD 7.5]; *n*=22). For both fracture groups, the smallest changes in the number of procedures were reported in Poland (long bones 4.1 [SD 3.9]; *n*=28; other bones 2.7 [SD 2.7]; *n*=30). The largest overall increase was seen in the use of external beam radiation (long bones 2.1 [SD 3.9]; other bones 2.6 [SD 4.9]). In patients with PFs of long bones, surgery to bone was also increased (0.5 [SD 0.5]). Notably, the number of 'other' procedures increased in those with PFs of long bones (2.3 [SD 3.9]); however, these encompassed a wide range of

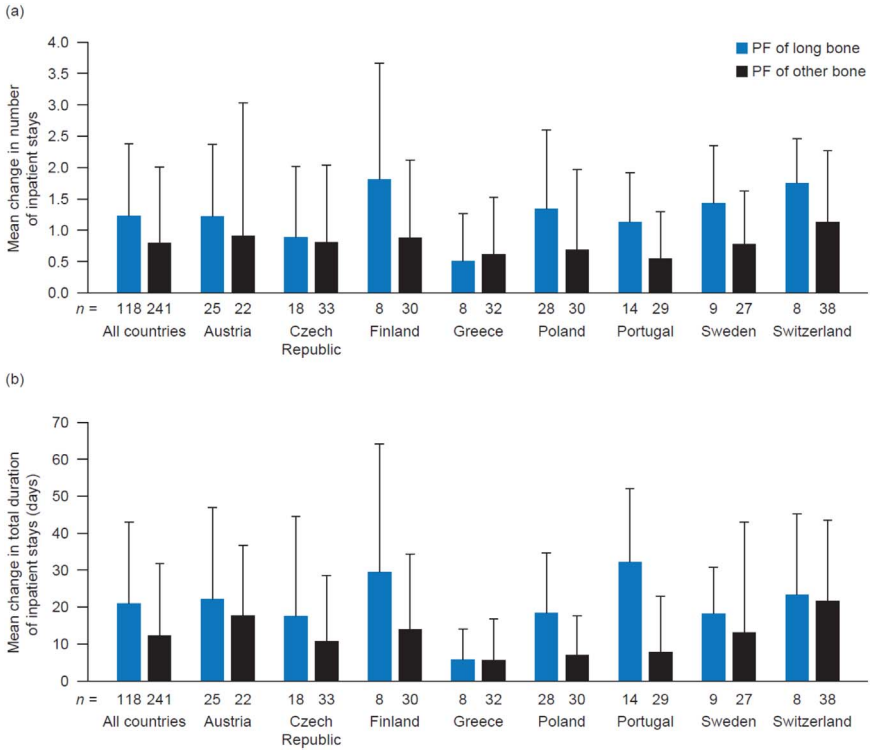

Fig. 2. Mean change from baseline in (a) the number and (b) the duration of inpatient stays per SRE. Data are shown as mean+standard deviation. *n* is the number of patients enrolled from each country with PF of long bones/PF of other bones (and the overall number is given under the first two bars). PF, pathologic fracture; SRE, skeletal-related event.

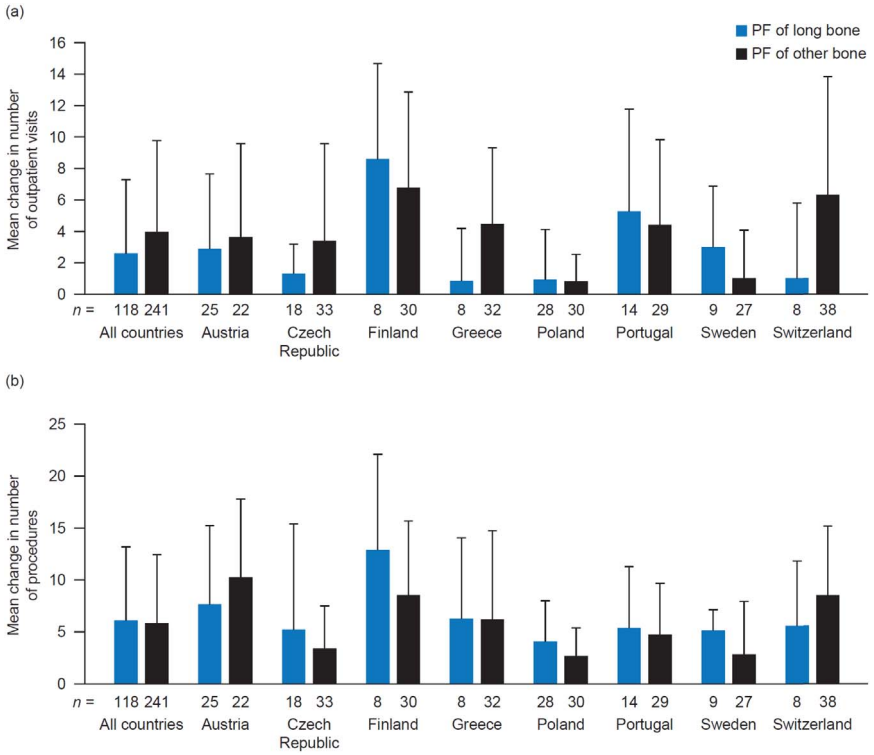

Fig. 3. Mean change from baseline in the number of (a) outpatient visits and (b) procedures per SRE. Data are shown as mean+standard deviation. *n* is the number of patients enrolled from each country with PF of long bones/PF of other bones (and the overall number is given under the first two bars). PF, pathologic fracture; SRE, skeletal-related event.

diagnostic procedures, none of which showed a large change when considered alone. In patients with PFs of other bones, the number of 'other' procedures also increased from baseline (1.7 [SD 3.3]), and use of computerised tomography also increased (0.6 [SD 1.1]).

4. Discussion

This is the first study to capture real-world changes in HRU associated with PFs of long bones and, separately, also PFs of other

bones. Overall, PFs were associated with considerable HRU owing to increases in the number of inpatient and outpatient visits, duration of inpatient stays, and number of procedures required.

Over the follow-up period of approximately 3 months, the mean number of inpatient stays and outpatient visits per PF increased in both groups. A multicentre, observational European study conducted over an 18-month period also found that the mean number of inpatient stays and outpatient visits increased in patients with PFs (range 0.4–0.5 increase in inpatient stays per PF; range 1.9–3.1 increase in outpatient visits per PF) [16]. An observational study in Spain revealed that a large proportion of patients with PFs secondary to solid tumours required hospital stays (40–60%) and outpatient visits (67–70%) [13].

In our study, the mean duration of inpatient stays also increased as a result of PF in both the long bone and other bone groups. In a previous retrospective-prospective study of HRU associated with SREs in four European countries, PFs were found to be associated with a considerable number of inpatient stays, with a duration ranging from 19 to 22 days [16], similar to the durations of inpatient stays that were observed in our study. Inpatient stays appear to be a substantial driver of overall HRU and therefore are likely to contribute considerably to the costs associated with PFs. In addition, a large study in Spain demonstrated that the mean length of hospital stay following the first admission for PF was substantial for those with breast, lung or prostate cancer (12–20 days) [19]. The results of our study indicate for the first time that the increase in the number and duration of inpatient stays is generally much higher for PFs of long bones than for PFs of other bones. This may be due in part to patients with long bone PFs requiring complicated and lengthy rehabilitation, including surgery and physiotherapy. Owing to limited resources for the care of patients with cancer and fractures in general hospitals, these individuals may have to receive inpatient care at specialised units, which will further increase the HRU costs associated with PFs of the long bones.

It has previously been shown that patients who experience one SRE are more likely to experience subsequent events [20,21]. A retrospective analysis of patients with prostate cancer found that skeletal morbidity (including PFs and bone pain) was higher in patients who had experienced a SRE than in those with no history of SREs [22]. Our study found that the majority of patients with PFs of long bones experienced multiple SREs. In some pivotal clinical trials, multiple SREs were not recorded because all SREs that occurred within a 21-day window were counted as a single event [23,24]. Our study used retrospective real-world data, and may therefore reflect clinical practice more closely than clinical trials. The treatment of multiple SREs is likely to require more outpatient hospital visits and inpatient stays than the treatment of a single SRE, and this may also contribute to the greater increases in HRU observed for long bone PFs compared with those affecting other bones. The proportion of patients receiving bisphosphonates increased from baseline at similar levels during the duration of this study for patients with PFs of long bones and those with PFs of other bones. The fact that some patients were already receiving bisphosphonate treatment yet still experienced a PF indicates that further treatment optimisation with bone-targeted agents (BTAs) and new antineoplastic agents may be required to minimise the frequency of PFs, and thereby HRU.

PFs affect a large proportion of patients with advanced cancers and require a considerable amount of healthcare resources for their treatment; this means that PFs result in substantial costs [13,15]. Another multinational European study of patients with solid tumours and multiple myeloma estimated that the mean costs associated with each individual PF ranged from €1000 to €7000 for vertebral fractures and from €1700 to €3200 for non-vertebral fractures [15]. In Spain and Belgium, the mean HRU cost per PF has also been reported to be high (€3209 and €7087 for non-vertebral fractures and €5015 and €6968 for vertebral fractures in Spain and Belgium, respectively) [13,25]. In Portugal, one of the countries included in our analysis, the estimated annual cost of PFs per patient was €8730 [26]. The costs associated with surgery to bone and radiation to bone are also substantial [15] and were the linked SREs with largest increases from baseline in our study.

A strength of this study is the ability to distinguish between the different PFs because HRU is different for each fracture type; long bone fractures are rarely asymptomatic and will have HRU requirements that are different from those of other bone fractures. The main limitation of our study was the low number of patients with PF of long bones identified in each country, reflecting a low incidence of this fracture type in patients with cancer. One study of patients with advanced breast cancer found that the incidence of long bone fracture was half that of other fracture types [27]. Furthermore, the use of bone-targeted agents in routine clinical practice may have reduced the incidence of SREs overall, as seen in clinical trials [9,28–30]. However, the baseline demographics of patients from countries with low recruitment were generally consistent with those of the other countries in the study.

5. Conclusion

This is the first study to differentiate between the HRU attributed to PFs of long bones and to those affecting other bones. Both fracture types were associated with increases from baseline in the mean number of inpatient and outpatient stays, and visits to day care centres and emergency rooms. The mean number of procedures was also increased from baseline for both fracture types. The number of SREs can be reduced by using bone-targeted agents such as bisphosphonates [9,28,31], radiopharmaceuticals [32] or denosumab [29,30,33], or new antineoplastic agents for prostate cancer such as enzalutamide [34] and abiraterone acetate [35]. Combining these new antineoplastic agents with bone-targeted agents may lead to greater reductions in HRU in patients with advanced cancer.

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