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Healthcare resource utilisation associated with skeletal-related events in European patients with multiple myeloma: Results from a prospective, multinational, observational study

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Abstract

Objectives: Patients with multiple myeloma (MM) often experience debilitating skeletal-related events (SREs: pathologic fracture, radiation to bone [RB], surgery to bone [SB] or spinal cord compression [SCC]). This is the first comprehensive, prospective, observational analysis of healthcare resource utilisation (HRU), independently attributed to SREs by investigators, in patients with MM.

Methods: Eligible patients had lytic bone lesions, life expectancy ≥ 6 months, Eastern Cooperative Oncology Group performance status ≤ 2 and ≥ 1 SRE in the 97 days before enrolment. Data were collected retrospectively for 97 days before enrolment and prospectively for 18–21 months.

Results: Altogether, 153 patients were enrolled from Germany, Italy, Spain and the United Kingdom. Of the 281 observed SREs, 36.7% required inpatient stays (mean duration: 20.6 days per SRE [standard deviation (SD): 22.9]). SB and SCC were the SREs most likely to require stays (72.3% and 50.0% of SREs, respectively); SCC required the longest mean (SD) stay per event (40.5 [40.8] days). Overall, 179 SREs required outpatient visits; this was most likely for RB (74.8%) and least likely for non-vertebral fracture (50.0%).

Conclusions: All SREs were associated with substantial HRU; therefore, preventing SREs in MM will reduce the economic and resource burden on healthcare systems.

KEYWORDS

advanced cancer, bone lesions, healthcare resource utilisation, multiple myeloma, observational research, skeletal-related events

1 | INTRODUCTION

Multiple myeloma (MM) accounts for roughly 1% of all cancers and approximately 10% of haematological malignancies worldwide.¹ Bone lesions are a hallmark of MM²; up to 95% of patients will develop osteolytic bone lesions at some point during their treatment.^{2–4} These bone lesions are often associated with severe pain, nerve compression syndromes and skeletal-related events (SREs).^{3–5}

By definition, SREs include pathologic fracture and spinal cord compression, as well as radiation or surgery to bone (which are surrogate markers for skeletal pain and fractures).⁵ SREs increase the risk of death,⁶ are often debilitating and result in severe pain; they can impact a patient's ability to carry out daily activities and to work and reduce their quality of life.^{7,8} SREs are common in individuals with MM; it is estimated that up to 60% of patients will suffer a pathologic fracture during their treatment journey,² resulting in pain, reduced

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load-bearing capacity and, frequently, restricted movement.⁵ Spinal cord compression is a medical emergency that can lead to paralysis.⁵

In addition to the effect on patients' well-being, SREs also place a significant burden on healthcare systems. Previous studies have shown that, in particular, surgery to bone is associated with long inpatient stays in patients with solid tumours or MM.^{3,9} Several retrospective studies in the United States of America (USA) and Europe that included patients with MM demonstrated increased healthcare resource utilisation (HRU) and/or costs associated with SREs.^{3,4,10-13} Although these data provide some insight into the impact that SREs have on HRU by these patients, they may be limited by the scope and completeness of the available HRU data and by the use of codes (clinical and/or administrative) as proxies for diagnosis and resource use. Prospective data, collected from a broader European population, could provide more extensive, complete and robust information on the real-life use of healthcare resources in the treatment of SREs to better inform optimum approaches for patient management and healthcare planning.

A prospective, observational, multinational study was conducted to evaluate the HRU associated with SREs in patients with bone lesions secondary to prostate, breast or lung cancer and MM in Canada, Germany, Italy, Spain, the United Kingdom (UK) and the USA. Data on the HRU associated with SREs in breast cancer, lung cancer and prostate cancer in the four European countries (Germany, Italy, Spain and the UK) have been previously reported.¹⁴⁻¹⁶ Here, we report the European data for patients with MM.

2 | METHODS

2.1 | Patients

The methods used in this study have been described previously.³ Eligible patients were aged 18 years or older with bone lesions that were secondary to MM and had a life expectancy of at least 6 months. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and to have experienced at least one SRE in the 97 days before signing informed consent or up to 7 days afterwards.¹⁶ Patients were excluded from the study if they were enrolled in an investigational drug trial for treatment of bone lesions or prevention of SREs.

2.2 | Study design

This was a multicentre, prospective, observational study conducted in centres across Europe (Germany, Italy, Spain and the UK), Canada and the USA. Analysis by country and tumour type was prespecified in the protocol. This analysis reports only on data from the four European countries in patients with bone lesions secondary to MM. Enrolment began in 2008, and the data cut-off date for the final analysis was 31 May 2010.

Patient demographics and information on disease history were collected at enrolment. HRU data for each patient were collected retrospectively by chart review for all SREs occurring in the 97-day

period before enrolment and prospectively for the duration of their involvement in the study. SREs were defined as pathologic fracture (either vertebral or non-vertebral), radiation to bone, surgery to bone or spinal cord compression, and events were recorded according to the results of physicians' assessments as per their routine clinical practice. Full data collection occurred at 90-day, mandatory milestones (calculated from the enrolment date), but with SRE-related HRU recorded as soon as the site was made aware of the SRE. The planned follow-up period was 18-21 months. In the case of a patient who experienced more than one SRE in the 97 days preceding study entry, the index SRE was classified based on the following hierarchy: (i) spinal cord compression; (ii) surgery to bone; (iii) pathologic fracture (vertebral or non-vertebral); and (iv) radiation to bone.

For patients who experienced multiple SREs at the same anatomical site, HRU was attributed to the first SRE (ie, the index SRE) if subsequent events occurred within 21 days of the index event. If subsequent SREs occurred at a different anatomical site or occurred more than 21 days after the index event at the same anatomical site, the investigator decided to which SRE the HRU was attributed. HRU outcome measures included the following: number, duration and facility type of inpatient stays; number and facility type of outpatient visits; number of emergency department visits; number, duration and facility type of nursing home/long-term care facility stays; number of home health visits; and type of procedure.

2.3 | Statistical analysis

All analyses were descriptive and the HRU outcome measures were categorised by SRE type. For each of the HRU measures, the mean values (eg, number or duration of inpatient stay) for each SRE type were calculated by dividing the total HRU attributed to SREs by the total number of SREs of the same type. The mean duration of inpatient stay per SRE was calculated as the total number of inpatient days divided by the total number of SREs that were associated with an inpatient stay; if an SRE resulted in multiple inpatient stays, the total duration of all inpatient stays was used.

Data on inpatient stays by facility type reported SREs with at least one inpatient stay within the facility type and SRE type. When an SRE required stays in more than one facility type, a stay was attributed to each facility type. If an SRE required multiple inpatient stays within one facility type, the total duration of inpatient stays was counted.

If radiation or surgery to bone was carried out as a result of another SRE (ie, treatment of a primary SRE, such as pathologic fracture), the investigator had the option of attributing HRU to the primary SRE. SREs determined to be secondary to a primary SRE were excluded from the analysis, as reported previously.¹⁶

3 | RESULTS

3.1 | Study population

At the time of the final analysis, 153 patients with MM who met the eligibility criteria were enrolled across the four European countries.

**TABLE 1** Baseline demographics and disease history

Characteristic	Germany (N = 51)	Italy (N = 39)	Spain (N = 38)	UK (N = 25)
Follow-up time (mo)				
Mean (SD)	9.6 (6.0)	9.3 (5.5)	8.7 (6.1)	6.0 (5.0)
Median (Q1, Q3)	9.0 (5.0, 15.4)	10.8 (3.9, 13.5)	7.8 (3.9, 13.6)	5.5 (1.2, 9.2)
Mean age, y (SD)	65.8 (10.4)	64.8 (9.0)	63.7 (9.9)	67.9 (10.0)
Female, n (%)	21 (41.2)	22 (56.4)	17 (44.7)	3 (12.0)
Race, n (%)				
Caucasian	50 (98.0)	39 (100.0)	37 (97.4)	23 (92.0)
Other	1 (2.0)	0 (0)	1 (2.6)	2 (8.0)
ECOG status, n (%)				
0	18 (35.3)	4 (10.3)	5 (13.2)	6 (24.0)
1	25 (49.0)	20 (51.3)	14 (36.8)	8 (32.0)
2	8 (15.7)	15 (38.5)	19 (50.0)	11 (44.0)
Time since primary MM diagnosis (mo)				
Mean (SD)	26.7 (36.0)	30.5 (40.8)	32.5 (39.2)	29.2 (49.6)
Median	10.7	13.2	13.0	8.7
Time since diagnosis of bone metastasis/lesion to enrolment (mo)				
Mean (SD)	21.7 (32.3)	25.4 (41.3)	21.5 (37.6)	22.1 (44.3)
Median	4.1	5.8	1.6	3.7
History of SREs ^a , n (%)	30 (58.8)	25 (64.1)	31 (81.6)	11 (44.0)
Previous bisphosphonate use ^b , n (%)	42 (82.4)	19 (48.7)	19 (50.0)	22 (88.0)
Duration of previous bisphosphonate use ^b (mo)				
Mean (SD)	20.1 (29.4)	22.2 (33.7)	28.8 (37.8)	23.1 (49.7)
Median (Q1, Q3)	2.9 (1.0, 32.2)	2.6 (0.4, 41.5)	3.2 (0.7, 52.7)	3.2 (1.1, 11.0)

ECOG, Eastern Cooperative Oncology Group; Q, quarter; MM, multiple myeloma; SD, standard deviation; SREs, skeletal-related events; UK, United Kingdom.

^aPatients who experienced an SRE > 97 d before enrolment.

^bPatients who received bisphosphonates before or at enrolment (more than 90 d prior to enrolment and within 90 d prior to enrolment).

Mean (standard deviation; SD) length of follow-up ranged from 6.0 (5.0) to 9.6 (6.0) months, and median follow-up ranged from 5.5 to 10.8 months (Table 1). While generally consistent, there was some variation in baseline characteristics and disease history across the four countries (Table 1); for example, there were fewer women enrolled in the UK (12.0%) than in the other countries (range, 41.2%-56.4%). There was a higher proportion of patients with an ECOG performance status of 0 in Germany (35.3%) than in the other countries (range, 10.3%-24.0%), and a lower proportion of patients with ECOG performance status of 2 (15.7% vs 38.5%-50.0%). Patients in Germany and the UK were more likely to receive bisphosphonates prior to treatment on study (82.4% and 88.0% of patients, respectively) compared with Italy or Spain (48.7% and 50.0% of patients, respectively). The median time from bone lesion detection to enrolment was shorter in Spain (1.6 months) than in the other countries (range, 3.7-5.8 months). A total of 42 patients (27.5%) discontinued the study before the primary data analysis cut-off date (Germany: 20/51, 39.2%

[14 owing to death, 4 lost to follow-up, 2 other]; Italy: 7/39, 17.9% [5 owing to death, 2 lost to follow-up]; Spain: 7/38, 18.4% [5 owing to death, 2 lost to follow-up]; UK: 8/25, 32% [all owing to death]).

3.2 | Skeletal-related events

Eligible patients experienced a total of 321 SREs. Analysis of the raw SRE data (which included SREs secondary to primary SREs and was ultimately excluded from the final HRU analysis) showed that the event rate in this population of patients (who had all experienced an SRE) was consistent across Germany, Italy and Spain (2.2, 1.9 and 2.2 SREs per patient-year, respectively), but slightly higher in the UK (2.6 SREs per patient-year). In total, 281 of the 321 SREs were suitable for inclusion in the HRU analysis (Figure 1). Overall, radiation to bone (38.1%) and pathologic fracture (34.5%) were the most common SREs; spinal cord compression was the least common, accounting for 10.7% of SREs.

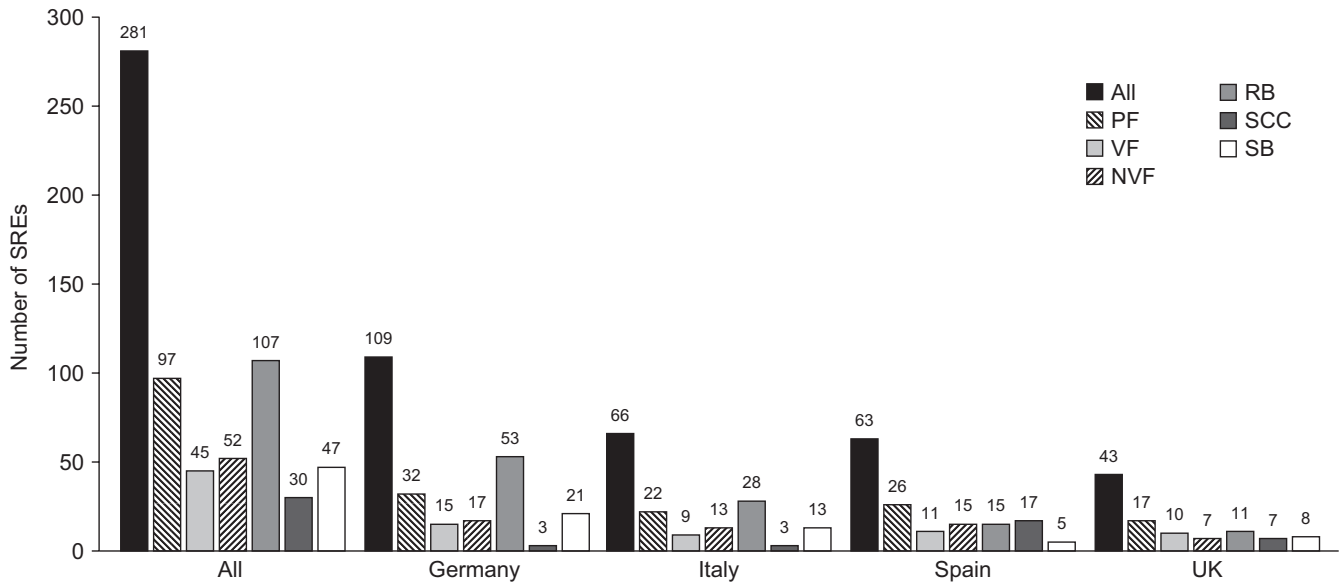


FIGURE 1 Number of SREs included in the HRU analysis, by country and by SRE type. VF and NVF are subsets of PF. HRU, healthcare resource utilisation; NVF, non-vertebral fracture; PF, pathologic fracture; RB, radiation to bone; SB, surgery to bone; SCC, spinal cord compression; SREs, skeletal-related events; UK, United Kingdom; VF, vertebral fracture

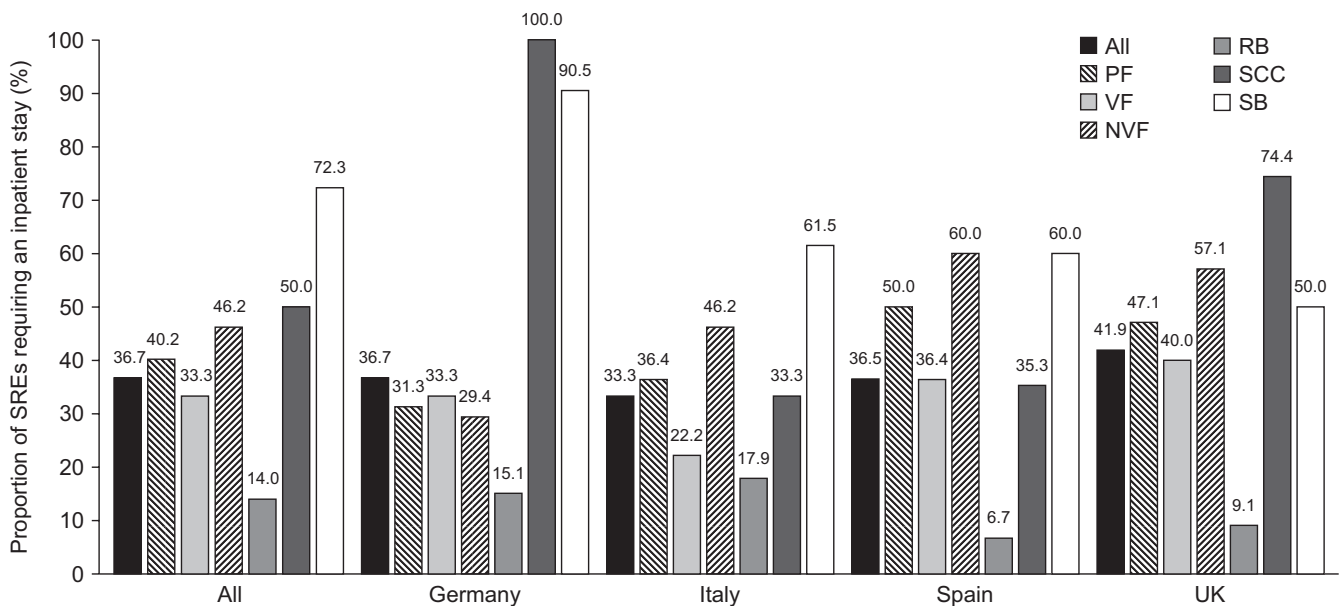


FIGURE 2 Proportion of SREs requiring at least one inpatient stay, by country and by SRE type. VF and NVF are subsets of PF. NVF, non-vertebral fracture; PF, pathologic fracture; RB, radiation to bone; SB, surgery to bone; SCC, spinal cord compression; SREs, skeletal-related events; UK, United Kingdom; VF, vertebral fracture

There were some differences observed in the pattern of SREs between countries (Figure 1). In Spain and the UK, spinal cord compression was reported more often (27.0% and 16.0%, respectively) than in Germany (2.8%) or Italy (4.5%). There were fewer reports of surgery to bone in Spain (7.9%) than in the other countries (range, 18.6%–19.7%). Vertebral fractures were reported less often in Italy (13.6%) than in the other countries (range, 13.8%–23.3%). The frequency of radiation to bone in the UK (25.6%) and Spain (23.8%) was around half of that reported in Germany (48.6%) and Italy (42.4%).

3.3 | Healthcare resource utilisation

3.3.1 | Inpatient stays

Overall, 103 of 281 patients experiencing SREs (36.7%) required hospitalisation. Although all types of SRE were associated with inpatient stays, the proportion requiring an inpatient stay varied considerably between SRE types (Figure 2). Overall, surgery to bone (72.3%), spinal cord compression (50.0%) and non-vertebral

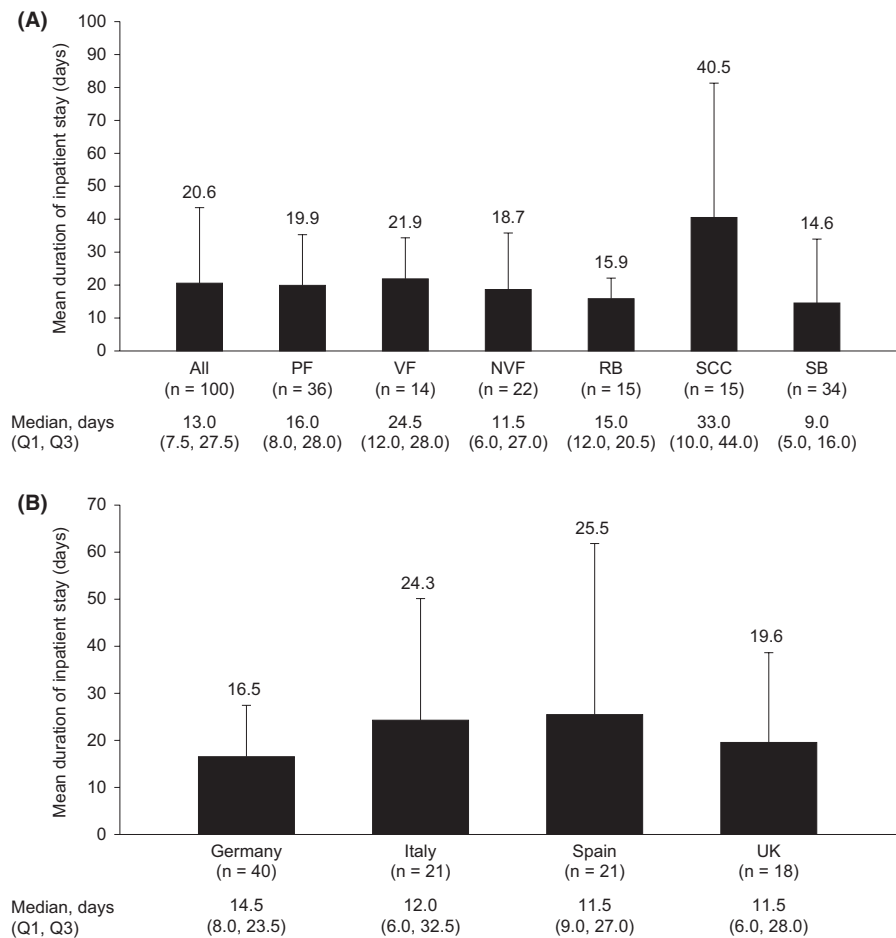


FIGURE 3 Mean duration of inpatient stay per SRE that required at least one inpatient stay (A) by SRE type and (B) by country. VF and NVF are subsets of PF. Data include only SREs requiring an inpatient stay. If an SRE contributed to multiple inpatient stays, the total duration of all of the inpatient stays was used. Error bars indicate SD. NVF, non-vertebral fracture; PF, pathologic fracture; Q, quarter; RB, radiation to bone; SB, surgery to bone; SCC, spinal cord compression; SD, standard deviation; SRE, skeletal-related event; UK, United Kingdom; VF, vertebral fracture

fracture (46.2%) were most likely to require inpatient stays; radiation to bone (14.0%) was the least likely. For certain types of SREs, the proportion requiring an inpatient stay also varied across countries (Figure 2).

Regarding duration of inpatient stay, data were collected for the first 100 SREs. All SREs were associated with substantial lengths of inpatient stay (Figure 3A). The mean (SD) length of inpatient stay per SRE that required an inpatient stay was 20.6 (22.9) days. Spinal cord compression required the longest mean (SD) stay per event (40.5 [40.8] days), while surgery to bone (14.6 [19.4] days) and radiation to bone (15.9 [6.3] days) required the shortest stays per event. Across the four countries, the overall mean length of inpatient stay ranged from 16.5 to 25.5 days, with Germany having the shortest mean duration and Spain the longest (Figure 3B).

Across all SREs, the most common facility types for inpatient stays were surgical units/wards and oncology units/wards, with general units/wards, radiation units/wards and “other” units/wards also used frequently (Table S1). Radiation to bone was most likely to be administered in an oncology unit/ward (mean [SD] length of stay, 13.2 [6.5] days). Patients with pathologic fracture or surgery to bone were most likely to be treated in a surgical unit/ward (mean [SD] length of stay, 16.9 [16.8] and 8.3 [4.5] days, respectively).

3.3.2 | Outpatient visits

Outpatient visits were also common across all SREs (Figure 4). Overall, 179 SREs (63.7%) required an outpatient visit, with 74.8% of radiation to bone events and 73.3% of vertebral fractures, compared with 50.0% of non-vertebral fracture events, requiring at least one visit. The pattern of outpatient visits was generally consistent across countries (Figure 4).

The overall mean (SD) number of outpatient visits per SRE was 5.2 (7.1) (Figure S1). Radiation to bone was associated with the highest mean (SD) number of outpatient visits per SRE (8.9 [8.2] visits), with the number of visits required for other SREs ranging from 2.1 (5.0) for surgery to bone to 3.9 (5.3) for vertebral fractures. There was some variation in the number of outpatient visits between countries (Figure S1).

3.3.3 | Procedures performed

External beam radiation therapy was the most common procedure type, with a mean of 4.3 (95% confidence interval [CI], 3.41-5.10) procedures per SRE (Figure S2).

Overall, each SRE required a mean (SD) of 7.4 (6.9) procedures (Figure 5). Radiation to bone and spinal cord compression were associated with the highest mean (SD) number of

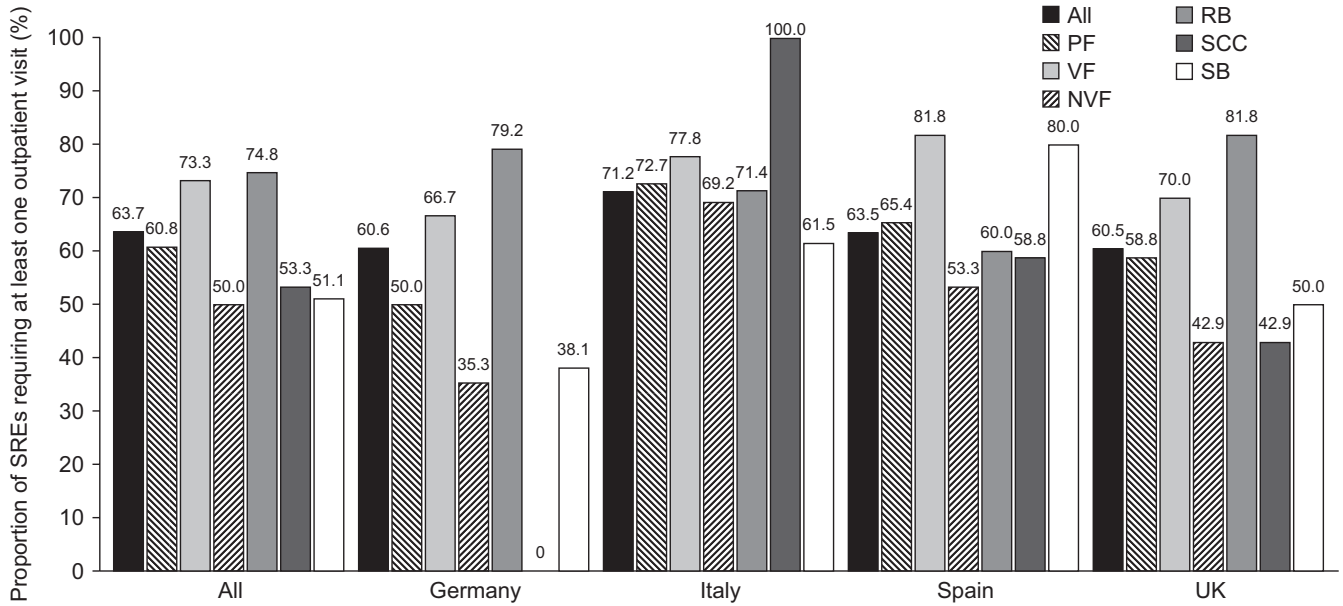


FIGURE 4 Proportion of SREs requiring at least one outpatient visit, by country and by SRE type. VF and NVF are subsets of PF. NVF, non-vertebral fracture; PF, pathologic fracture; RB, radiation to bone; SB, surgery to bone; SCC, spinal cord compression; SRE, skeletal-related event; UK, United Kingdom; VF, vertebral fracture

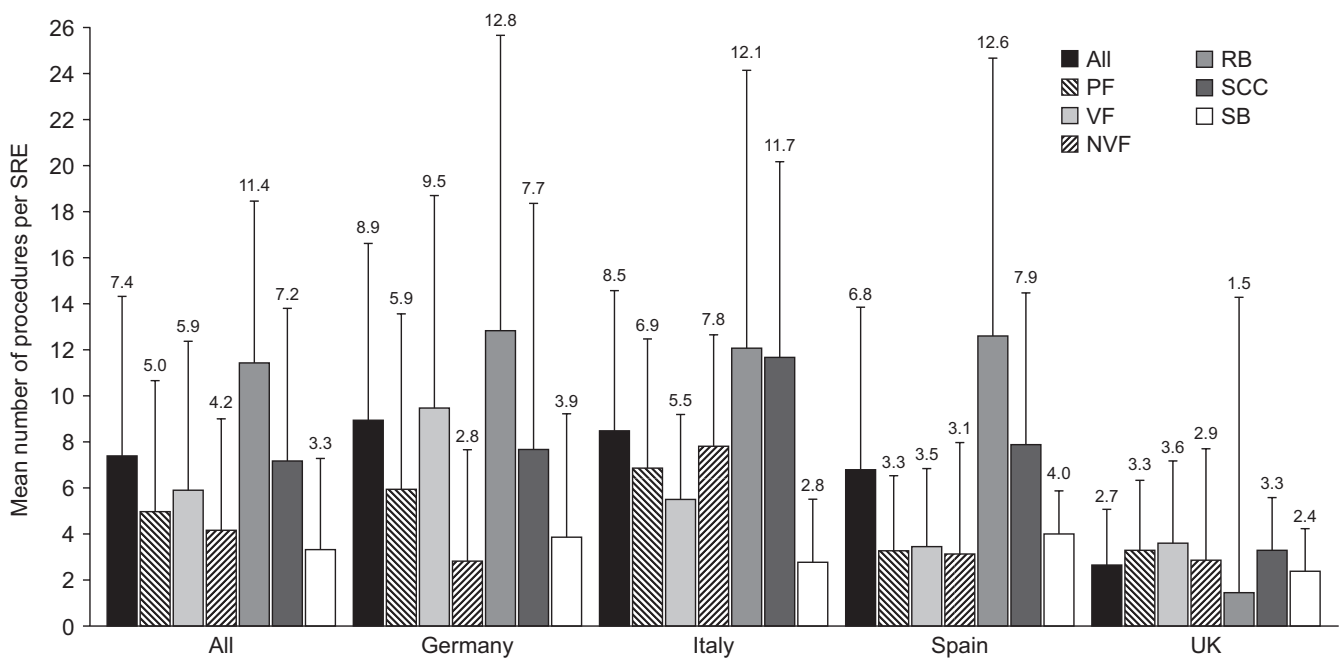


FIGURE 5 Mean number of procedures per SRE, by country and by SRE type. VF and NVF are subsets of PF. Error bars show SDs. NVF, non-vertebral fracture; PF, pathologic fracture; RB, radiation to bone; SB, surgery to bone; SCC, spinal cord compression; SD, standard deviation; SRE, skeletal-related event; UK, United Kingdom; VF, vertebral fracture

procedures per SRE (11.4 [7.0] and 7.2 [6.6], respectively). There was some variation between countries (Figure 5). Most procedures were performed in an outpatient setting (5.1 [7.0] procedures per SRE); 2.1 (3.8) procedures per SRE required an overnight stay, with spinal cord compression most likely to require this.

3.3.4 | Emergency room and home health visits, and nursing home/long-term care facility stays

No home health visits were required, and very few emergency room visits (2 per 100 SREs) were reported. No nursing home/long-term facility care stays associated with SREs were reported.



4 | DISCUSSION

To the best of our knowledge, this is the first prospective study to investigate HRU associated with SREs secondary to bone lesions in patients with MM in Europe. In addition, this is the first study in which HRU was assigned to specific SREs by the investigators. This ensured that HRU was included in the analysis only when it was considered, in the expert opinion of the investigators, to be directly related to the SRE and not to the underlying disease.

Patient characteristics at enrolment were broadly similar across the countries, although there was a tendency for better ECOG performance status in Germany than in the other countries. Overall, radiation to bone (38.1%) and pathologic fracture (34.5%) were the most common SREs, and spinal cord compression was the least common (10.7%). In Spain and the UK, spinal cord compression was reported considerably more often than in Germany and Italy; radiation to bone was reported about half as often. The proportion of patients who had previous treatment with bisphosphonates for the prevention of SREs was approximately 50% in Italy and Spain and considerably higher in Germany and the UK (over 80%). This variation could possibly reflect intercountry differences in patient management pathways; recruitment of patients in our study was according to pre-defined targets and enrolment criteria and may not fully reflect the distribution of SREs in the real-world setting. Therefore, more studies would be required to verify such differences.

In line with studies of prostate cancer, breast cancer and lung cancer, all SREs were associated with substantial HRU.¹⁴⁻¹⁶ Inpatient stays were common (36.7% of SREs), at a rate similar to that previously reported for lung cancer (41.0%)¹⁵ and higher than that reported for breast and prostate cancers (both 26.0%),^{14,16} with an average duration of stay of approximately 3 weeks. The reason for the differences in the proportions of SREs requiring an inpatient stay across tumour types cannot be firmly concluded from these analyses, but it may be due to the high incidence of comorbidities in patients with MM; patients with MM are often immunocompromised, with an increased risk of severe infection, while 20%-40% have renal impairment.^{17,18} Yet, interestingly, the proportion of patients with MM who discontinued the study (27.5%, primarily owing to death) was lower than for other cancer types: breast cancer, 36.3%; lung cancer, 69.6%; MM, 27.5%; and prostate cancer, 45.0% (data not published). These differences may reflect the longer survival times of patients with MM compared with patients with metastatic solid tumours and also any associated differences in disease status in these latter patients at the point of SRE development; for example, patients with prostate cancer were at an advanced stage,¹⁴ whereas patients with MM frequently have bone disease at diagnosis, earlier in the disease course.¹⁹

All SRE types were associated with hospitalisation and substantial lengths of inpatient stay. Compared with other tumour subtypes included in this observational study, the proportion of patients with MM and SREs requiring an inpatient stay varied considerably across SRE types. Surgery to bone, spinal cord compression and non-vertebral fracture were most likely to require inpatient stays,

and radiation to bone was the least likely. Spinal cord compression represents a significant burden because it often requires hospitalisation and, in this study, was associated with the longest duration of inpatient care (nearly 6 weeks). In patients with MM, 50% of spinal cord compressions required hospitalisation. This is a smaller proportion than in patients with other cancer types (lung cancer, 80%; prostate cancer, 74%; breast cancer, 58%).¹⁴⁻¹⁶ The reasons for this difference are unclear and are beyond the scope of this study, but a speculative explanation could be that the threshold to initiate imaging of the spine is much lower in patients with MM compared with other cancer types, possibly because there is great awareness of the propensity of MM to cause spinal cord compression. Indeed, such investigation is often a standard of care at diagnosis in patients with MM. Some between-country differences were noted in the duration of inpatient stay. Duration was longer in Italy and Spain than in Germany or the UK. Across all SREs, the most common facility types for inpatient stays were surgical units/wards and oncology units/wards, with general units/wards, radiation units/wards and "other" units/wards also used frequently.

Outpatient visits were necessary for the majority of SREs (63.7%) and were most frequently required for radiation to bone (74.8%) and vertebral fracture (73.3%). In the UK, the mean number of outpatient visits required per SRE was less than one-third of that of the overall mean. This is probably owing to the fact that radiotherapy is predominantly an outpatient procedure in the UK,²⁰ unless other medical requirements necessitate an inpatient stay. Nevertheless, the data presented here indicate that outpatient visits impose a considerable burden on healthcare resources in Europe, similar to findings reported for other cancer types in this study.^{3,14-16}

This study has identified that almost every SRE required a procedure, and multiple procedures were common. Overall, a mean of 7.4 procedures per SRE was required. Most procedures were performed in an outpatient setting, and external beam radiation therapy was the most common type of procedure. Radiation to bone was associated with the highest number of procedures per SRE (11.4), which—coupled with the high number of outpatient visits for this procedure—makes it a major contributor to the burden that SREs place on healthcare systems. This is consistent with the findings of previous studies.²¹⁻²³ The high numbers of outpatient visits and procedures observed probably reflect the use of multiple fractions of radiotherapy.¹⁶ Considering the differences in the characteristics of the patients enrolled, the relatively small sample size and any variations in clinical practices across the countries, overall, patterns of HRU were broadly consistent. However, in the UK, the numbers of outpatient visits, procedures overall and procedures per SRE were all substantially lower than in the other countries. Differences in clinical practice between the countries may help to explain this variation; for example, multiple-fraction radiation sessions are more commonplace in mainland Europe, while single-fraction radiation is used more often in the UK.¹⁴ Also in the UK, radiotherapy is not necessarily available in all hospitals, so some patients may have to travel to alternative centres.²⁰



There are some limitations to this study, as previously reported by Hoefeler et al³. The differences in baseline characteristics between countries and physician clinical practice may explain some of the heterogeneity in outcomes. The duration of follow-up for this study was shorter than planned (median of 5.5–10.8 months vs 18–21 months) owing to slow recruitment (possibly because the trial was non-interventional) and early withdrawal from the study due to patient death. However, conclusions can still be drawn as the data showed a generally consistent approach to patient management across the countries. The numbers of patients enrolled per country were also limited, leading to small sample sizes in some SRE subsets. Some data were not accessible to investigators at all study sites (eg, home health visits). HRU for secondary SREs may have been assigned to a previous SRE; for example, HRU for spinal cord compression may have been assigned to a previous pathologic fracture or radiation to bone. Thus, despite the known burden of this SRE, not all events were expected to be associated with an inpatient stay. It should also be noted that numbers of SRE types are not representative of the real-world distribution, because they are affected by the index SRE recruitment and the inclusion criteria (stating that patients must have an ECOG status ≤ 2 and a life expectancy ≥ 6 months). These limitations, however, would be expected to result in an underestimation of the overall HRU associated with SREs; therefore, the true burden of SREs may be even greater than that suggested by these results.

Although data collection for this study commenced in 2007, the findings described here remain pertinent. It is likely that HRU resulting from the management of SREs in these patients has not changed significantly. While novel treatments are available, there is no evidence that these treatments reduce the risk of SREs in patients, and their impact on HRU is currently unknown. Additionally, with more effective treatments for MM available which may result in an increased life expectancy, patients may have a longer exposure to the risk of SREs. In these patients, non-drug-related costs (such as those resulting from bone complications) will remain a key cost driver. Therapies that preserve bone (eg, bisphosphonates or denosumab) and that help to reduce the incidence of SREs may have an important role to play in reducing the related HRU and the economic and clinical burden associated with this disease. Bisphosphonates have been shown to reduce pathologic fractures, SREs and pain in patients with MM.²⁴ In patients with bone lesions due to solid tumours (excluding breast or prostate cancers) or MM, denosumab was non-inferior to zoledronic acid in prolonging the time to first on-study SRE.²⁵ In patients with newly diagnosed MM in a phase 3 study of denosumab ($n = 859$) and zoledronic acid ($n = 859$), denosumab was non-inferior to zoledronic acid ($P = .01$) in prolonging the time to first on-study SRE (hazard ratio [95% CI]: 0.98 [0.85–1.14]).²⁶

The timing of the initiation of treatment with agents that preserve bone in patients with MM is an issue that should be considered. The International Myeloma Working Group (IMWG) recommends that bisphosphonates should be initiated in patients with MM, with or without detectable osteolytic bone lesions on conventional radiography.²⁷ The American Society of Clinical Oncology recommends

that bone-targeted therapy should be considered in all patients with MM receiving first-line, antimyeloma therapy, regardless of the presence of osteolytic bone lesions on conventional radiography.²⁷ IMWG guidelines, published in 2017, for the optimal use of ¹⁸fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) in patients with MM, recommend this technique to provide an earlier evaluation of response to therapy compared with MRI scans.²⁸ It is therefore feasible that, with increased use of these imaging techniques to visualise the burden of myeloma disease, the number of patients who are eligible for treatment and hence the use of bone-preserving agents will increase and thus reduce the HRU associated with SREs in MM. The data reported here indicate that studies directly examining the impact of bisphosphonates and denosumab on SRE-associated HRU would be warranted.

5 | CONCLUSIONS

SREs secondary to bone lesions are frequently observed in patients with MM, with radiation to the bone and pathologic fracture being the most common. This study highlights that SREs in these patients are associated with substantial HRU across the four European countries. All types of SRE were associated with hospitalisation, multiple procedures and substantial periods of inpatient stay. Mean inpatient stay was shortest in Germany where both the proportion of patients with ECOG performance status of 2 and incidence of spinal cord compression were lowest. This is in addition to the impact that SREs have on patients' well-being, activities of daily life and ability to work. Initiating treatments that delay or prevent SREs will, therefore, help not only to reduce the healthcare burden and reduce costs, particularly associated with inpatient stay, but also to have a positive effect on the quality of life of patients. Consequently, physicians involved in the management of MM should initiate prompt treatment with agents that preserve bone.

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DISCLOSURES

John Ashcroft has received honoraria and participated in advisory boards and consultancy for Amgen, Celgene, Janssen and Takeda. Diana Lueftner has been a speaker for Amgen and participated in advisory boards for Amgen. Amit Bahl has received honoraria for advisory boards from Amgen and Novartis. Ignacio Duran has participated in advisory boards for Amgen and Novartis. Herbert Hoefeler



has participated in advisory boards for Amgen. Vito Lorusso has participated in advisory boards for Amgen. Marco Campioni and Michele Intorcchia are employees of Amgen and hold stock.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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