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ORIGINAL ARTICLE

Impact of fractures on quality of life in patients with osteoporosis: a US cross-sectional survey

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ABSTRACT

Objective: To evaluate the impact of osteoporosis-related fractures on health-related quality of life (HRQoL).

Methods: Data were obtained from the 2016 Adelphi US Osteoporosis Disease Specific Programme™, a cross-sectional survey of physicians and their male and female patients with osteoporosis. Patient-reported outcomes (PRO) measures included the European Quality of Life 5 Domains (EQ-5D), European Quality of Life Visual Analog Scale (EQ-VAS), and Osteoporosis Assessment Questionnaire short-version (OPAQ-SV; physical, emotional, and symptom domains). Associations between PRO scores and the number and site of fractures were evaluated using ANOVA. Multivariate analyses were conducted using linear regression.

Results: Physicians provided records for 1848 patients with osteoporosis. Of these, 981 (53.1%) completed the patient survey, data for the number of fractures were available for 935/981 (95.3%), and 185/935 (19.8%) had a history of fracture. Experiencing fractures significantly influenced scores on all PRO measures ($p < .0001$). Hip and spine fractures were associated with the greatest reduction in most PRO scores. The number of fractures, age, body mass index, and Charlson Comorbidity Index (CCI) were significantly associated with PRO measures ($p < .05$) in multivariate analyses. In patients with a fracture, fracture site, CCI, gender (EQ-5D and EQ-VAS), and age (OPAQ-SV physical only) were significantly associated with PRO measures.

Conclusions: In patients with osteoporosis, fractures are associated with lower HRQoL and lower overall health status. Fracture history, fracture site, age, and comorbidity burden significantly influence HRQoL in individuals with osteoporosis. These data suggest the need for interventions to reduce the risk of fractures in patients with osteoporosis.

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osteoporosis; fracture; health-related quality of life; EQ-5D; OPAQ-SV

Introduction

Osteoporosis is a major public health problem, that is characterized by low bone mass, structural deterioration of bone tissue, and increased risk of fractures[1]. Annually, 2 million fractures are attributed to osteoporosis in the US and this number is projected to increase to 3 million by 2025[2]. Currently, osteoporosis is the leading cause for fractures in the elderly; about 1 in 2 women aged >50 years will experience an osteoporosis-related fracture in her lifetime[3].

Osteoporotic fractures lead to >500,000 hospital admissions, >800,000 emergency room visits, >2.5 million office visits, and nearly 180,000 nursing home admissions in the US each year[3]. In US women aged >55 years, the burden of hospitalization for osteoporotic fractures is greater than for stroke, heart attack, or breast cancer, independently[4]. By 2025, annual direct fracture-related costs are projected to exceed $25 billion[2].

Hip fractures are the most burdensome of osteoporosis-related fractures[3]. Mortality among patients with hip fractures approximates 10–45% in the year following the fracture[5,6], and nearly 20% of patients require long-term nursing home care[3]. As many as two-thirds of patients do not regain their former level of function or mobility, even after lengthy rehabilitation[3,5,7]. Clinical vertebral fractures are also associated with increased risk of mortality and hospitalization in postmenopausal women with low bone density[8,9].

The high economic and societal burden of osteoporosis is related not only to the direct medical costs of acute and rehabilitative care for fractures but also to indirect costs related to other complications (e.g. depression and chronic pain) and poor health[10,11]. According to a recent Bone Health Index Survey by the National Osteoporosis Foundation, leading concerns about aging for patients with osteoporosis were loss of independence (42%) and mobility

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(25%); additionally, 50% of caregivers expressed uncertainty about their ability to manage their patient's or loved one's care[12].

The physical, psychological, and social consequences of fractures can profoundly influence health-related quality of life (HRQoL) and should be considered in addition to the economic burden of disease management. However, recent data on the HRQoL of patients with osteoporosis-related fractures in the US are limited. This report describes the impact of fractures on patient-reported outcomes (PRO) including overall health status and HRQoL in patients who are diagnosed with or suspected of having osteoporosis as assessed by their physicians.

Methods

Study design

The current study used data from the 2016 Adelphi US Osteoporosis Disease Specific Programme (DSP)[13], a cross-sectional survey of physicians and their corresponding patients with confirmed or suspected (reported by the physician, but not confirmed by review of hospitalization records or imaging studies) osteoporosis conducted in the US between August and November 2016. Four sources of data were used to select physicians and patients for inclusion in the study: (1) physician surveys; (2) physician workload questionnaires in which the physician documented the actual number of patients seen (both in total and those diagnosed with osteoporosis) for a period of 5 consecutive days after the physician survey was completed; (3) electronic case report forms (eCRFs), which the physician retrospectively completed online to provide details on patients diagnosed with osteoporosis; and (4) patient self-completed records (PSCs; patients whose information was recorded on the eCRFs were invited to complete the PSC records independently of their physician immediately after consultation).

To preserve patient confidentiality and to avoid bias during data collection and analysis, all responses were anonymized[13] and the study adhered to HIPAA regulations on data collection and patient privacy. The study was conducted under the EphMRA code of conduct and ethics and institutional review board approval was not required.

Inclusion criteria

Physicians were included in the survey if they were the prescribing decision-makers, managing at least 20 (for primary care physicians [PCPs]) or 28 (for specialists) patients in the US with confirmed or suspected osteoporosis in a typical month, and had not completed a survey-based osteoporosis study in the 12 months preceding the current study. The minimum numbers of patients were selected to ensure that physicians had a patient load sufficient to complete the necessary number of eCRFs in the timeframe required. The difference in minimums for PCPs and specialists reflects the difference in the number of patients with osteoporosis each is likely to see. Physicians had to be board certified in one of the following specialties: primary care, gynecology, rheumatology, or endocrinology.

Patients were included if they had suspected or physician-diagnosed osteoporosis (regardless of whether they were receiving the treatment); completed the PSC, which included 5 PRO measures; and were not participating in a clinical trial. Patient enrollment was completed on a prospective basis. Other than confirmation of the diagnosis as indicated by the physician's answer in the eCRF to the question, "What is this patient's current diagnosis?", no formal patient selection verification procedures were used.

Physicians were asked to provide data for 10 consecutive patients presenting with osteoporosis and 2 additional oversample patients considered to be at high risk of fractures and/or to have more severe disease (comprising 1 patient with a bone mineral density [BMD] *T*-score ≤ -2.5 and a previous history of fracture, and 1 patient with a BMD *T*-score ≤ -3.5), thereby avoiding selection bias. The same patients were invited to complete the PSCs. The minimal inclusion criteria ensured a broad inclusion of physicians and patients.

PRO measures

The Osteoporosis Assessment Questionnaire short-version (OPAQ-SV) was used to assess HRQoL across 3 domains: physical function, emotional status, and symptoms[14]. OPAQ-SV consists of 34, five-point Likert scale questions and has been validated to detect changes in HRQoL in patients with prevalent vertebral and nonvertebral fractures[14]. Scores can be calculated for each domain as well as for overall HRQoL; higher scores correspond to better HRQoL.

Generic health status was assessed using the European Quality of Life 5 Domains (EQ-5D) questionnaire, a standardized instrument that can be used in a wide array of health conditions[15,16]. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The European Quality of Life Visual Analog Scale (EQ-VAS) records the patient's self-rated health on a vertical visual analog scale and can be used as a quantitative measure of health as judged by the individual respondent.

Data collected

Demographic information was extracted and Charlson Comorbidity Index (CCI)[17] scores were calculated from information provided in the eCRFs. The history of fractures was indicated by the physician's answer in the eCRF to the question, "How many osteoporotic fracture events has this patient ever suffered?" Physicians were also asked which tests were used to aid in osteoporosis diagnosis (options in the eCRF were peripheral DXA scan, central DXA scan, conventional X-ray, ultrasound, and vertebral fracture analysis). For fracture site, patients were analyzed based on site of most recent fracture (options in the eCRF were hip, spine, wrist, rib, humerus, or other). The impact of time since fracture on PROs was analyzed by evaluating patients who had sustained a fracture $\leq$1 year previously, within the preceding 1 to 2

years, or >2 years ago based on the physician's answers in the eCRF to the question, "Time since occurrence of fracture." Disease severity was characterized as mild, moderate, severe, or very severe based on the physician's answer in the eCRF to the question, "How would you rate the severity of this patient's osteoporosis?" No formal definition of disease severity was used.

For the EQ-5D and EQ-VAS, missing values were not imputed and any missing or incomplete data were excluded from the analysis. For the OPAQ-SV, missing values were replaced following the official instructions for the questionnaire (i.e. missing values were imputed by the average of the nonmissing values if more than half of the questions in the same domain were answered)[14]. Additionally, for any analysis using PRO variables, patients were only included if they had valid values for all PRO variables. The PRO variables were derived by following the official instructions from the author/owner for each PRO.

Statistical analyses

Descriptive statistics were used to describe patient characteristics and mean PRO scores. Categorical variables are presented as numbers and percentages, whereas continuous variables are presented as the mean with standard deviation (SD) or medians with interquartile range (IQR). Analysis of variance (ANOVA) was used to determine whether the number of fractures and the fracture site in those who have experienced a fracture, affect PRO scores. Multivariate analysis included linear regression model to identify predictors of PRO adjusting for confounding variables. Standard errors were adjusted to account for physician clustering, using the Huber–White estimate of variance.

Results

Demographics

Records for 1848 patients with osteoporosis were provided by physicians (Table 1). Of the 981 patients (53.1%) who participated in the survey, 899 (91.6%) were women and 644 (65.6%) were ≥65 years. Patients who participated in the survey did not significantly differ from those who did not complete it, with the exception that patients who completed the surveys were younger ($p = .0005$). Overall, most patients (80.8%) had mild or moderate osteoporosis as rated by physicians. Of patients who completed all PRO measures, 935 had data available for number of fractures. The majority (80.2%, $n = 750$) had no history of fracture, 145 (15.5%) had 1 fracture, and 40 (4.3%) had ≥2 fractures. Physicians indicated that X-ray was used to confirm diagnosis of osteoporosis in 16% of patients with a history of fracture.

Impact of number of fractures, fracture site, and time since fracture on patient HRQoL

There was a statistically significant difference in mean PRO scores between groups based on the number of fractures for all PROs (one-way ANOVA, all $p < .0001$) (Figure 1). Health status and HRQoL measures were lower in patients with a single fracture compared with those with no fracture history, and these scores declined further in patients with ≥2 fractures.

In patients with a fracture, the fracture site had a significant effect on PRO scores ($p < .01$) (Figure 2). Although fractures of the hip and spine were associated with the greatest reduction in health status, fractures at "other" sites were also associated with lower scores for the EQ-VAS and all OPAQ-SV domains.

For all PRO measures, time since fracture (≤1 year, 1–2 years, or >2 years) was not statistically significant based on one-way ANOVA (Table 2), suggesting persistence of disease burden for years following fracture.

Multivariate regression analyses

Three linear regression models were used to identify factors associated with HRQoL and/or health status as assessed by the different PRO instruments. In the first model, changes in PRO scores by fracture site, time since fracture, and number of fractures were examined (Table 3). In order to include the number of fractures in the model, only patients with at least 1 fracture were included in the analysis. Time since fracture and fracture site of rib (with wrist as reference site) were not significant for any PRO ($p > .05$). Fracture sites of hip and spine were significant in all cases ($p < .05$). Fracture site of humerus was significant for the OPAQ-SV symptom instrument ($p < .05$) only, and fractures at "other" sites were significant ($p < .05$) for the EQ-VAS and the OPAQ-SV (physical, emotional, and symptom). Number of fractures beyond the first fracture was only significant ($p < .05$) for the EQ-VAS.

The second model in all patients with osteoporosis included the number of fractures, age, gender, body mass index (BMI), and CCI. In this model, all variables were significantly associated with variability in scoring for all PRO measures ($p < .05$) except gender (Table 4).

The third model analyzed only patients who had experienced a fracture and included fracture site (with wrist fracture as the reference), age, gender, BMI, and CCI. In this model, significant associations between fractures and PRO scores varied depending on the PRO instrument used and the site of fracture. Spine and hip fractures were significantly associated with differences in scoring for all the PRO instruments examined ($p < .05$), while rib and humerus fractures were only significantly associated with the EQ-VAS and EQ-VAS/OPAQ-SV symptom instruments, respectively (Table 5). CCI was also significantly associated with differences in scoring for all PRO instruments. Male gender was significant for the EQ-5D and EQ-VAS, and a significant association with age was observed for the OPAQ-SV physical domain.

Discussion

Data from this large US cross-sectional survey of patients with osteoporosis suggest that patients with a history of osteoporotic-fracture have lower HRQoL and lower health status compared with patients without a fracture history. Hip

Table 1. Patient and physician characteristics.

	Overall	Patient has not completed all PROs	Patient has completed all PROs
Patient age, years			
n	1848	867	981
Mean (SD)	69.2 (10.3)	70.1 (10.9)	68.4 (9.8)
Median (IQR)	69 (62.0, 76.5)	70 (63.0, 78.0)	68 (62.0, 75.0)
Patient gender, *n* (%)			
n	1848	867	981
Female	1690 (91.5)	791 (91.2)	899 (91.6)
Male	158 (8.6)	76 (8.8)	82 (8.4)
Patient BMI			
n	1848	867	981
Mean (SD)	25.4 (4.6)	25.3 (4.7)	25.5 (4.5)
Median (IQR)	24.9 (22.3, 27.8)	24.9 (22.1, 27.8)	24.9 (22.5, 27.8)
Number of days since diagnosis			
n	1251	538	713
Mean (SD)	1044.9 (1100.2)	1092.9 (1152.5)	1008.7 (1058.3)
Median (IQR)	732 (336.0, 1422.0)	734 (287.0, 1475.0)	731 (351.0, 1258.0)
Physician reported severity, *n* (%)			
n	1848	867	981
Mild	549 (29.7)	257 (29.6)	292 (29.8)
Moderate	944 (51.1)	415 (47.9)	529 (53.9)
Severe	304 (16.5)	171 (19.7)	133 (13.6)
Very severe	51 (2.8)	24 (2.8)	27 (2.8)
Physician type grouping, *n* (%)			
n	1848	867	981
PCP	771 (41.7)	343 (39.6)	428 (43.6)
Specialist	1077 (58.3)	524 (60.4)	553 (56.4)
Charlson Comorbidity Index			
n	1848	867	981
Mean (SD)	0.9 (1.3)	1.0 (1.4)	0.8 (1.2)
Site of most recent fracture, *n* (%)			
n	369	184	185
Hip	69 (18.7)	40 (21.7)	29 (15.7)
Spine	137 (37.1)	66 (35.9)	71 (38.4)
Wrist	90 (24.4)	45 (24.5)	45 (24.3)
Rib	17 (4.6)	7 (3.8)	10 (5.4)
Humerus	12 (3.3)	9 (4.9)	3 (1.6)
Other	44 (11.9)	17 (9.2)	27 (14.6)
Number of days since most recent fracture			
n	367	182	185
Mean (SD)	1165 (1300)	1366 (1600)	968 (874)
EQ-5D Health Index score			
n	1025	44	981
Mean (SD)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
EQ-VAS			
n	1021	40	981
Mean (SD)	75.2 (16.0)	75.9 (13.5)	75.2 (16.1)
OPAQ-SV—normalized physical score			
n	1075	94	981
Mean (SD)	75.7 (15.8)	68.5 (16.9)	76.4 (15.5)
OPAQ-SV—normalized emotional score			
n	1039	58	981
Mean (SD)	69.4 (15.1)	66.1 (18.1)	69.6 (14.9)
OPAQ-SV—normalized symptom score			
n	1074	93	981
Mean (SD)	68.1 (20.5)	63.5 (21.4)	68.6 (20.3)

Abbreviations. BMI, body mass index; EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; IQR, interquartile range; PCP, primary care physician; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version; PRO, patient-reported outcomes; SD, standard deviation.

or vertebral fractures were associated with lower HRQoL than fractures at sites other than the hip or spine. Quality of life was also influenced by age and existing comorbidities.

The DSP used in this study provides comprehensive real-world insights and evidence in osteoporosis management through clinical, behavioral, and patient-reported data[13]. Other observational and prospective studies have reported an inverse association between the number of osteoporotic fractures and HRQoL[18–22]. Our results show that the impact of the number of fractures (beyond the first fracture) on HRQoL and/or health status varied by PRO instrument. These results suggest that the first fracture is the most important in terms of HRQoL. However, the small sample size of patients with at least 1 fracture ($n = 185$) and differences in sensitivity of the PRO instruments used need to be considered when interpreting these data.

Our finding that decrements in HRQoL vary by type of fracture is consistent with data from other studies[18–22]. For example, Hallberg et al reported significant reductions in HRQoL using the general Short Form 36 (SF-36) health survey for at least 2 years following hip or vertebral fracture compared with a forearm or humeral fracture[21]. The observed association between vertebral fractures and HRQoL may be related to back pain and limitations in physical activity,

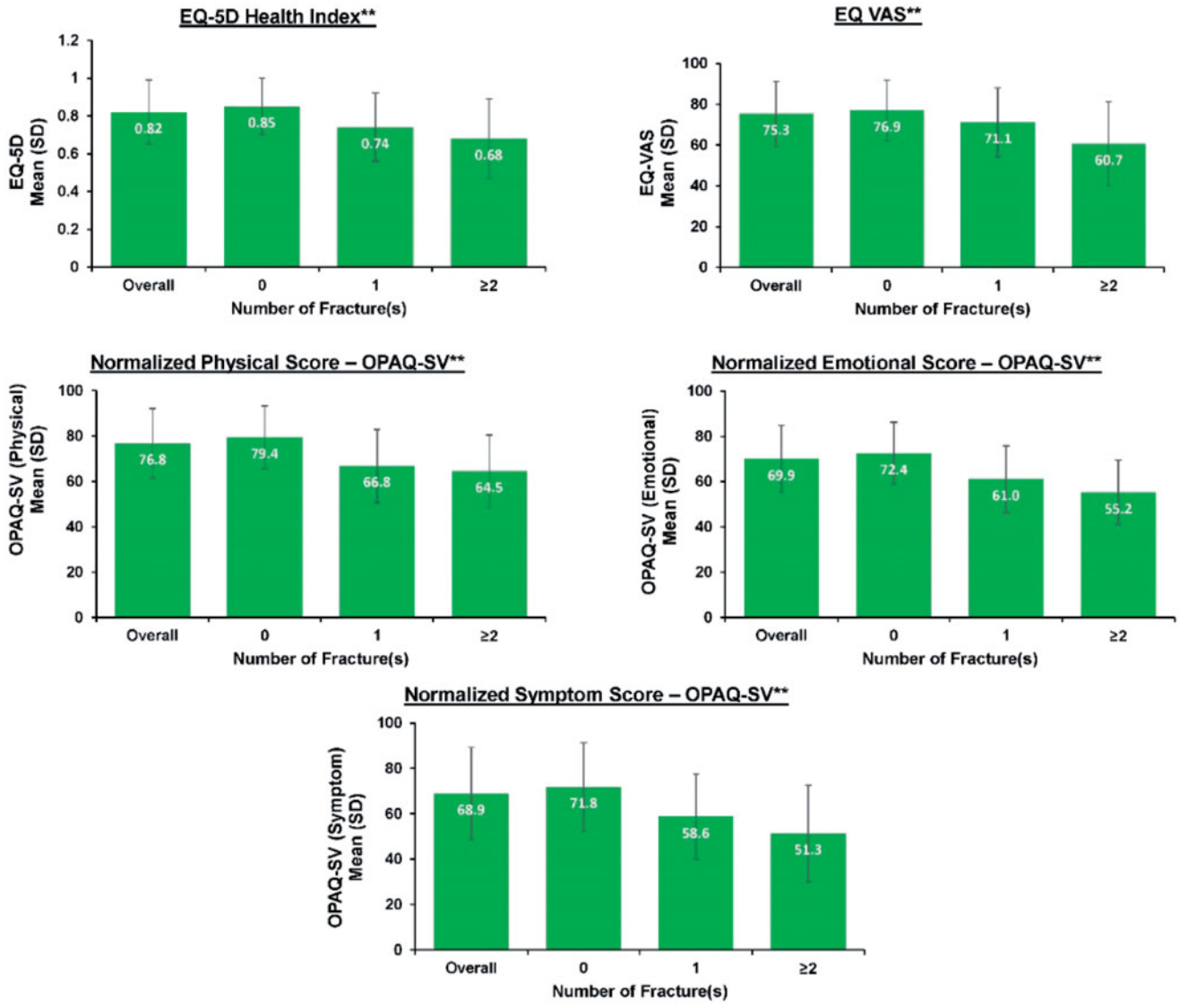

Figure 1. Mean PRO scores by number of fractures ($n = 935$). **ANOVA $p < .0001$. Abbreviations. EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version; PRO, patient-reported outcomes; SD, standard deviation. Number of patients in each group were as follows: overall, $n = 935$; 0 fractures, $n = 750$; 1 fracture, $n = 145$; ≥ 2 fractures, $n = 40$. Includes participants who completed all PROs and had values for all variables used in the analysis.

accompanied by the emotional impact of changed appearance, functional decline, and inability to participate in usual activities. For patients with hip fractures, loss of independence following fracture may be a major factor contributing to lower HRQoL. Prior studies have also shown an association between site of vertebral fracture and HRQoL[23–25]. For example, thoracic fractures may be associated with a greater disease burden given the impact on the respiratory system[26]. In the current study, fragility fractures were captured in the spine (along with hip, wrist, rib, humerus, and other), but were not further classified by site of vertebral fracture.

We also observed a decline in all PROs for the category "other fractures," which were experienced by 15% of patients, almost as many as experienced hip fractures. Non-hip, non-vertebral fractures have previously been shown to have a significant effect on HRQoL. In the Canadian Multicentre Osteoporosis Study, pelvic, lower limb, and rib fractures were associated with low HRQoL scores[20]. Similarly, data from the Global Longitudinal Study of Osteoporosis in Women suggest that previous fractures at a variety of locations may be associated with reduced HRQoL[22]. Unfortunately, we did not have a breakdown of fractures by fracture sites for "other" category, hence, further evaluation of PROs was not possible.

Because osteoporotic fractures affect people later in life, a substantial proportion of such patients have other comorbidities. Our findings show that in patients with fractures, the presence of comorbidity as assessed by the CCI was associated with lower health status and HRQoL for all PRO measures examined. Other studies have also reported that HRQoL is modified by the presence and number of comorbidities in patients with osteoporosis[27,28].

When addressing HRQoL, the temporal relationship between the occurrence of an event and the potential consequences of that event needs to be considered. Our data suggest that in patients with a fracture, HRQoL impairment persists over time. No improvement in any PRO measures was noted between fractures sustained less than a year

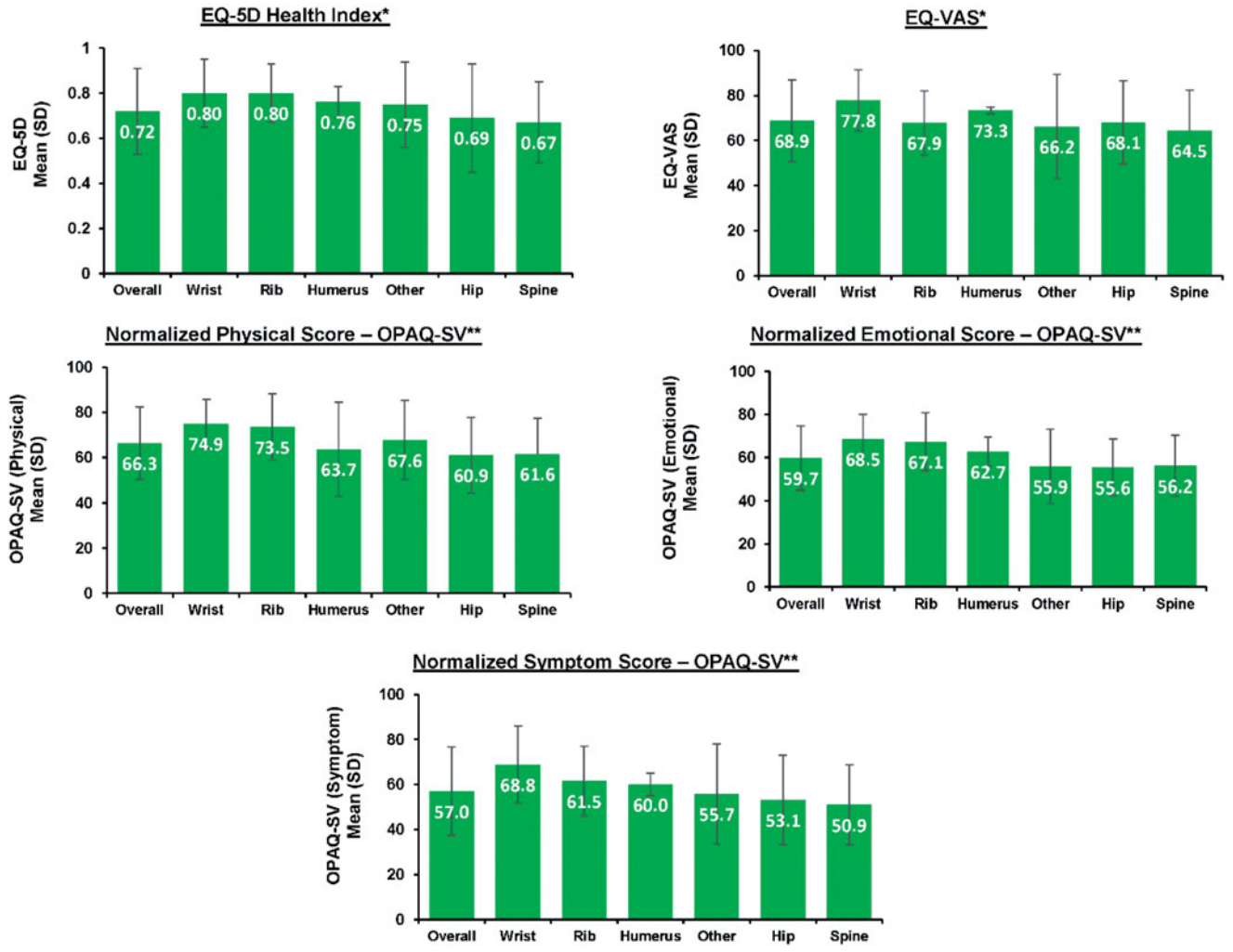

Figure 2. Mean PRO scores by site of most recent fracture ($n = 185$). *ANOVA $p < .01$; **ANOVA $p < .0001$. Abbreviations. EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version; PRO, patient-reported outcomes; SD, standard deviation. Number of patients in each group were as follows: overall, $n = 185$; wrist, $n = 45$; rib, $n = 10$; humerus, $n = 3$; other, $n = 27$; hip, $n = 29$; spine, $n = 71$.

Table 2. Mean PRO scores by time since most recent fracture.

	Overall ($n = 185$)	≤1 year ago ($n = 40$)	1–2 years ago ($n = 41$)	>2 years ago ($n = 104$)	*p*-Value
EQ-5D Health Index					
Mean ± SD	0.72 ± 0.19	0.70 ± 0.19	0.75 ± 0.15	0.72 ± 0.20	.4841
Median (IQR)	0.77 (0.59, 0.83)	0.71 (0.64, 0.81)	0.77 (0.69, 0.83)	0.77 (0.59, 0.83)	
EQ-VAS					
Mean ± SD	68.85 ± 18.23	68.55 ± 18.31	69.05 ± 18.23	68.89 ± 18.38	.992
Median (IQR)	70 (55.0, 80.0)	70 (59.5, 80.0)	70 (60.0, 80.0)	70 (52.0, 82.5)	
Normalized physical score - OPAQ-SV					
Mean ± SD	66.3 ± 16.03	62.13 ± 16.96	67.95 ± 13.93	67.25 ± 16.31	.1731
Median (IQR)	66 (55.0, 78.0)	59 (48.5, 74.0)	70 (58.0, 78.0)	68 (56.0, 78.5)	
Normalized emotional score - OPAQ-SV					
Mean ± SD	59.72 ± 14.78	58.25 ± 15.42	60.95 ± 12.63	59.81 ± 15.38	.7125
Median (IQR)	60 (47.0, 69.0)	57 (46.5, 67.0)	64 (51.0, 71.0)	60 (47.0, 71.0)	
Normalized symptom score - OPAQ-SV					
Mean ± SD	57.03 ± 19.59	57.00 ± 17.31	59.88 ± 15.91	55.91 ± 21.66	.5501
Median (IQR)	55 (40.0, 70.0)	55 (45.0, 65.0)	55 (50.0, 70.0)	55 (40.0, 75.0)	

Abbreviations. EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; IQR, interquartile range; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version; PRO, patient-reported outcomes; SD, standard deviation.

previously and those sustained >2 years previously. Even when the analysis was adjusted for type of fracture, patients reported poor health status as assessed by all PROs. Similar findings on the long-term decrement in HRQoL after fracture have been reported in the cross-sectional Canadian Multicentre Osteoporosis Study[29]. Studies have also shown that the impact of vertebral fractures on pain, disability, psychological impairment, and HRQoL persists even after the fractures have healed[30,31].

The study has some limitations. Because it was a cross-sectional study, we cannot make an inference of causality. Although several potential confounding variables were

Table 3. Regression analysis for association between fracture site, time since fracture, and number of fractures with PROs in patients with fractures ($n = 185$)[a].

Variable	Coefficient (95% CI)				
			OPAQ-SV		
	EQ-5D	EQ-VAS	Physical	Emotional	Symptom
Days since fracture	0.0000	−0.0021	0.0017	0.0016	0.0007
	(−0.00003, 0.00004)	(−0.0018, 0.0060)	(−0.0019, 0.0052)	(−0.0016, 0.0048)	(−0.0036, 0.0050)
	$p = .895$	$p = .285$	$p = .363$	$p = .319$	$p = .752$
Fracture site[b]					
Hip	−0.110	−8.6285	−13.834	−12.561	−15.274
($n = 29$)	(−0.1947, −0.0253)	(−16.4079, −0.8491)	(−21.1488, −6.5184)	(−17.9830, −7.1384)	(−23.3411, −7.2076)
	$p = .011$	$p = .030$	$p < .001$	$p < .001$	$p < .001$
Spine	−0.129	−11.454	−13.205	−11.765	−17.131
($n = 71$)	(−0.1937, −0.0644)	(−18.0936, −4.8151)	(−18.2881, −8.1209)	(−16.7712, −6.7583)	(−24.0758, −10.1868)
	$p < .001$	$p = .001$	$p < .001$	$p < .001$	$p < .001$
Rib	0.004	−7.935	−1.422	−0.881	−6.495
($n = 10$)	(−0.0851, 0.0930)	(−17.8313, −1.9604)	(−10.8690, 8.0241)	(−9.9859, 8.2233)	(−17.4503, 4.4605)
	$p = .930$	$p = .115$	$p = .766$	$p = .848$	$p = .243$
Humerus	−0.040	−4.702	−11.060	−5.761	−8.914
($n = 3$)	(−0.1209, 0.0411)	(−9.9148, 0.5102)	(−31.0558, 8.9356)	(−14.4575, 2.9356)	(−16.2919, −1.5364)
	$p = .331$	$p = .077$	$p = .275$	$p = .192$	$p = .018$
Other	−0.044	−10.756	−7.660	−12.619	−12.666
($n = 27$)	(−0.1310, 0.0433)	(−20.8036, −0.7080)	(−14.8730, −0.4470)	(−20.4102, −4.8284)	(−22.6770, −2.6559)
	$p = .321$	$p = .036$	$p = .038$	$p = .002$	$p = .014$
Number of fractures	−0.021	−5.751	−0.663	−1.930	−2.278
	(−0.0588, 0.0167)	(−10.4627, −1.0391)	(−4.1802, 2.8540)	(−4.7582, 0.8978)	(−6.2619, 1.7068)
	$p = .272$	$p = .017$	$p = .709$	$p = .179$	$p = .260$

Abbreviations. CI, confidence interval; EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version.
[a]Model included number of fractures, fracture site, and days since fracture only. *p*-values were adjusted to account for physician clustering.
[b]Reference fracture site was the wrist.

Table 4. Regression analyses for association between the number of fractures and demographic and clinical variables with PROs[a] ($n = 935$)[b].

	Coefficient (95% CI)				
			OPAQ-SV		
Variable	EQ-5D	EQ-VAS	Physical	Emotional	Symptom
Number of fractures	−0.0543	−4.682	−5.2196	−5.5403	−6.7456
	(−0.0722, −0.0363)	(−7.3076, −2.0573)	(−6.8898, −3.5493)	(−7.3200, −3.7607)	(−8.9615, −4.5298)
	$p < .001$	$p = .001$	$p < .001$	$p < .001$	$p < .001$
Age	−0.0046	−0.2843	−0.5164	−0.5217	−0.5137
	(−0.0058, −0.0034)	(−0.4175, −0.1512)	(−0.6680, −0.3647)	(−0.6627, −0.3807)	(−0.6807, −0.3466)
	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .001$
Male gender[c]	0.0045	2.6280	−0.1021	2.9503	−1.060
	(−0.0364, 0.0455)	(−0.8718, 6.1278)	(−3.7036, 3.4994)	(−0.5394, 6.4399)	(−5.6449, 3.5252)
	$p = .827$	$p = .140$	$p = .955$	$p = .097$	$p = .649$
BMI	−0.0036	−0.3243	−0.4211	−0.2736	−0.5592
	(−0.0063, −0.0009)	(−0.5697, −0.0789)	(−0.6587, −0.1836)	(−0.5031, −0.0441)	(−0.9131, −0.2054)
	$p = .009$	$p = .010$	$p = .001$	$p = .020$	$p = .002$
CCI	−0.0332	−3.4995	−2.703	−1.9865	−3.2203
	(−0.0430, −0.0235)	(−4.5141, −2.4849)	(−3.8029, −1.6035)	(−2.8830, −1.0899)	(−4.4874, −1.9532)
	$p < .001$	$p < .001$	$p < .001$	$p < .001$	$p < .001$

Abbreviations. BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version.
[a]Model included number of fractures, age, gender, BMI, and CCI only. *p*-values were adjusted to account for physician clustering.
[b]Includes participants who completed all PROs and had values for all variables used in the regression analysis.
[c]Reference was female gender.

included in the analysis, residual confounding factors may also exist; only known confounders were controlled for. Further, fracture events were reported by physicians, but were not confirmed by X-ray. Although 16% of physicians indicated utilizing X-ray to confirm the diagnosis of osteoporosis in patients with fractures, the survey did not specify whether X-rays were specifically performed to confirm the presence of fracture. In addition, only a small proportion of patients had a past history of fracture and information regarding treatment of osteoporosis was not available. Further, the number of fractures was low at some fracture sites (i.e. $n = 3$ for humerus and $n = 3$ for rib). Furthermore, because data capture was based on patients presenting to the physician within a stipulated time frame, the sample may contain a higher proportion of patients who consult a physician more frequently and may not be generalizable to the overall population of patients with osteoporosis. Patients who participated in the survey, however, were on average younger than those who did not complete the survey, suggesting that the disease burden may be underestimated. We observed no difference in PRO measures with respect to time since fracture. It is important to note that the pre-index (baseline) PRO measures were not available. It is therefore not possible to determine whether a decrement in PRO

Table 5. Regression analyses for associations between the site of fracture and demographic and clinical variables with PROs in patients with fractures ($n = 185$)[a].

Variable	Coefficient (95% CI)				
	EQ-5D	EQ-VAS	OPAQ-SV		
			Physical	Emotional	Symptom
Fracture site[b]					
Hip	−0.0854	−8.1315	−11.0303	−10.4118	−12.6570
($n = 29$)	(−0.1644, −0.0064)	(−14.0580, −2.2050)	(−17.5155, −4.5451)	(−15.8833, −4.9403)	(−20.0996, −5.2143)
	$p = .034$	$p = .008$	$p = .001$	$p < .001$	$p = .001$
Spine	−0.1277	−13.1196	−11.7272	−11.7648	−16.5482
($n = 71$)	(−0.1904, −0.0650)	(−20.4239, −5.8154)	(−16.6302, −6.8241)	(−16.6327, −6.8969)	(−23.0725, −10.0238)
	$p < .001$	$p = .001$	$p < .001$	$p < .001$	$p < .000$
Rib	−0.0164	−12.6208	−0.9039	−1.1075	−8.3533
($n = 10$)	(−0.1023, 0.0695)	(−22.2924, −2.9492)	(−8.9915, 7.1836)	(−9.2450, 7.0300)	(−18.0183, 1.3117)
	$p = .706$	$p = .011$	$p = .825$	$p = .788$	$p = .090$
Humerus	−0.0408	−5.3668	−9.7721	−6.3037	−8.0426
($n = 3$)	(−0.1310, 0.0494)	(−9.9976, −0.7361)	(−28.5261, 8.9819)	(−16.2690, 3.6616)	(−14.9761, −1.1090)
	$p = .372$	$p = .024$	$p = .304$	$p = .213$	$p = .023$
Other	−0.0551	−11.8812	−7.8692	−13.3592	−13.6090
($n = 27$)	(−0.1361, 0.0259)	(−20.9066, −2.8559)	(−14.8121, −0.9262)	(−20.1668, −6.5515)	(−22.9135, −4.3044)
	$p = .180$	$p = .010$	$p = .027$	$p < .001$	$p = .005$
Age	−0.0021	−0.0286	−0.3140	−0.2111	−0.2472
	(−0.0045, 0.0003)	(−0.2706, 0.2135)	(−0.5354, −0.0927)	(−0.4338, 0.0116)	(−0.5292, 0.0348)
	$p = .084$	$p = .815$	$p = .006$	$p = .063$	$p = .085$
Male gender[c]	0.0728	6.6171	2.4228	5.3676	4.7063
	(0.0011, 0.1446)	(0.8050, 12.4291)	(−2.7352, 7.5807)	(−0.3703, 11.1056)	(−1.7510, 11.1637)
	$p = .047$	$p = .026$	$p = .354$	$p = .066$	$p = .151$
BMI	−0.0004	−0.0790	−0.2158	0.2609	−0.2078
	(−0.0064, 0.0057)	(−0.7225, 0.5646)	(−0.7221, 0.2906)	(−0.2863, 0.8082)	(−0.7653, 0.3496)
	$p = .900$	$p = .808$	$p = .400$	$p = .347$	$p = .462$
CCI	−0.0437	−4.3839	−3.2585	−2.1882	−4.7962
	(−0.0648, −0.0225)	(−6.3593, −2.4085)	(−4.9125, −1.6046)	(−3.8457, −0.5306)	(−6.8591, −2.7334)
	$p < .001$	$p < .001$	$p < .001$	$p = .010$	$p < .001$

Abbreviations. BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; EQ-5D, European Quality of Life 5 Domains; EQ-VAS, European Quality of Life Visual Analog Scale; OPAQ-SV, Osteoporosis Assessment Questionnaire short-version.
[a]Model included fracture site, age, gender, BMI, and CCI only. *p*-values were adjusted to account for physician clustering.
[b]Reference fracture site was the wrist.
[c]Reference was female gender.

measures was indeed observed following the fracture episode and whether patients' overall status or HRQoL returned to baseline sometime after the event. Evaluation of disease burden is in relation to the timing of the fracture, but this is an approximation as no diagnostic validation was carried out.

A strength of the study is that the minimal inclusion criteria ensured a broad representation of patients and physicians. Also, by asking physicians to provide data for a prospective, consecutive series of patients, selection bias, which may be present in retrospective patient selection, could be avoided. This selection process allowed the evaluation of a range of patients across treatment types. Additionally, patients with more severe disease were oversampled. Finally, the study included use of multiple measures to estimate utility and health state decrements. Different instruments may have variable sensitivity to capture decrements associated with different fracture sites. The inclusion of multiple measures in the current study provides the opportunity to capture impact on PRO from various fracture sites.

Conclusions

This large cross-sectional study conducted in US patients with osteoporosis shows that osteoporotic fractures, particularly those of the hip and vertebrae, have a detrimental impact on HRQoL and overall health status. The occurrence of a previous fracture and the presence of comorbidities are associated with worse HRQoL in patients with fracture. In addition to developing interventions to reduce fracture risk, strategies must be developed to prevent secondary fractures.

Transparency

Declaration of funding

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Declaration of financial/other relationships

DTG is a consultant for Amgen, Eli Lilly, and Radius Health, Inc. SAW, RJW, YW, and CW are employees of, and own company stock in, Radius Health, Inc. JC and CM are employees of Adelphi Real World, Bollington, UK, and are paid consultants of Radius Health, Inc. SS is a consultant for Amgen, Eli Lilly, and Radius Health, Inc.

Author contributions

SAW and JC contributed to the conception or design of the study. JC contributed to the acquisition of the data. All authors had access to the data and contributed to the data analysis or interpretation. All authors provided a critical review and final approval of the manuscript for publication.

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Data availability statement

The data supporting the findings of this study are commercially available from the 2016 Adelphi US Osteoporosis Disease Specific Programme™. The analysis was conducted using Stata 15.1. Analysis of variance was conducted using command "oneway." Regression analyses were conducted using command "regress," with option "VCE cluster" to account for physician clustering. The Protocol Synopsis is available on request by contacting swilliams@radiuspharm.com.

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