Effect of improved medication adherence on health care costs in osteoporosis patients

Hyemin Cho, MSc, Ji-Hye Byun, PhD, Inmyung Song, PhD, Ha Y. Kim, MD, Yong-Chan Ha, MD, Tae-Young Kim, MD, Young-Kyun Lee, MD, Sunmee Jang, PhD

Abstract

Osteoporosis is a chronic disease that requires continuous health care spending for pharmacotherapy and examinations. Osteoporotic fractures are a major economic burden. However, little is known about the economic effects of osteoporosis and osteoporotic fractures in Korea.

The purpose of this study was to determine the predictors of osteoporosis-related health care costs and to evaluate the economic effects of fracture prevention through medication adherence among osteoporosis patients.

Using the Korea National Health Insurance Claims Database (KNHICD), we identified osteoporosis patients aged 50 years and older from 2011 to 2012. Annual health care costs of osteoporosis were analyzed from the insurer’s perspective and compared between patients with fractures and those without fractures. Adherents were defined as patients with a medication possession ratio of ≥80%.

The major predictors of osteoporosis-related health care costs were age, medication adherence, and the occurrence of fractures (P < .001). The proportion of fractures among non-adherents was approximately 1.1 times the proportion among adherents. Health care costs per patient with fractures were 3.8 times the costs per patient without fractures. Patients with fractures had higher health care costs due to hospitalization and outpatient costs but lower pharmacy costs than non-adherents. We estimated that about $5 million of health insurance expenses could be saved annually if all non-adherents became adherents.

Improved osteoporosis medication adherence can reduce osteoporosis-related health care costs by preventing fractures. Persistent pharmacotherapy for osteoporosis is necessary to prevent osteoporotic fractures and to reduce osteoporosis-related health care costs.

Abbreviations: CCI = Charlson Comorbidity Index, GLM = Generalized Linear Model, ICD-10 = International Classification of Diseases, 10th revision, KNHICD = Korea National Health Insurance Claims Database, KRW = Korean Won, MPR = medication possession ratio, NHIS = National Health Insurance Service, OTC = over-the-counter, SD = standard deviation, SERMs = selective estrogen receptor modulators, USD = United States dollar, VIF = variance inflation factor.

Keywords: generalized linear model, health care cost, medication adherence, osteoporosis, osteoporotic fractures

1. Introduction

Osteoporosis can lead to numerous clinical and health-related consequences, including fractures, and becomes a greater concern as an individual ages.[2] With rapid aging of the population, the prevalence of osteoporosis has increased.[2–4] Between 2005 and 2008, the prevalence of osteoporosis increased by 34.6% for females and 42.7% for males in Korea.[5]

Osteoporosis is the main risk factor for fractures.[6,7] Fractures reduce quality of life by decreasing mobility and limiting daily and social activities.[8] Moreover, fractures have been reported to greatly increase excess mortality.[4,6,7] The mortality rate due to osteoporotic fractures within a year has been reported to be 21.0% for males and 15.0% for females.[9] Osteoporotic fractures are also known to impose a huge economic and social burden.[10–12] There are many studies on health care costs of osteoporotic fractures in Asia and other countries.[11,13–18] In Korea, the societal costs of osteoporotic fractures increased from $88.8 million in 2007 to $149.3 million in 2011.[19] Another study in Korea reported that total health care costs of osteoporotic fractures of the elderly increased by 31.6% from $549 million in 2008 to $722 million in 2011.[20]

Medication adherence among osteoporosis patients is low although osteoporosis medication significantly reduces the risk of fractures[13,21,22] Adherents to the medication have higher drug costs than non-adherents but adherence can lower the disease-
related health care costs associated with fractures, such as inpatient service and surgery.\cite{13,15} Nonetheless, research on the predictors that increase the cost burden and the economic effects of high adherence to osteoporosis medication is lacking.\cite{13,23} Therefore, the present study sought to compare health care costs of osteoporosis according to the incidence of fractures. Moreover, this study aims to identify the predictors of osteoporosis-related health care costs and to evaluate the economic effects of medication adherence.

2. Methods

2.1. Data source

We used the Korea National Health Insurance Claims Database (KNHICD) for the 2011 to 2012 periods. Korea has a mandatory national health insurance system that covers 97% of the population. The remaining 3% of the population is covered under the Medical aid, a publicly funded medical assistance program for the poor. The KNHICD contains information on inpatient or ambulatory services, prescriptions, diagnoses, costs, and patient characteristics for almost all South Korean patients who utilize medical services, with the exception of procedures that are not covered by insurance, such as cosmetic surgery.\cite{5,24,25} Diagnoses are coded according to the International Classification of Diseases, 10th revision (ICD-10).

2.2. Study population

The study participants were patients with osteoporosis aged 50 years and older. Using the KNHICD, we identified osteoporosis patients who met both of the following criteria: an ICD-10 code of osteoporosis: M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), or M82 (osteoporosis in diseases classified elsewhere); the prescription of anti-osteoporosis drugs (bisphosphonate, bisphosphonate complex, selective estrogen receptor modulators [SERMs], and calcitonin). The index date was set as the date on which patients received their first prescription in 2011. To define new users, we excluded patients who had received anti-osteoporosis drugs in one year prior to the index date,\cite{26–28} and patients with Paget disease, rare disorders, cancer, dementia, or cerebral infarction (Fig. 1).

2.3. Variables

2.3.1. Osteoporosis-related health care costs. Osteoporosis-related health care costs include costs for hospitalization, outpatient visits, and pharmacy associated with osteoporosis and osteoporotic fractures in 2011. Costs of hospitalization and outpatient visits include medical procedures, treatments and surgeries. Pharmacy costs include drug costs and prescription fees. Claims amounts for the first visit and follow-up treatments for 1 year were tallied for each patient. We included anti-osteoporosis drug, anti-inflammatory agents, and analgesic agents used for fractures.

We estimated the annual health care costs from the insurer’s perspective. When clinics or hospitals performed treatment and medical procedures, they request reimbursement of medical costs from the Korea National Health Insurance Service. Non-covered services such as caregivers’ service, assistive devices, over-the-counter (OTC) drugs, and long-term care facilities were not included in the KNHICD and therefore excluded from our analysis.

The estimated annual costs were inflation-adjusted to the 2012 Korean Won (KRW) unit cost except drug costs and then

![Figure 1. Selection of the study population.](image-url)
converted to United States dollars (USD) by using the 2012 average conversion rate of 1126 KRW per 1 USD [http://ecos/bok.or.kr].

2.4. Fracture

We identified osteoporotic fractures including fractures in the hip (S72.0 [fracture of neck of femur], S72.1 [pertrochanteric fracture], and seven procedures [open reduction of fractured extremity-femur, closed pinning-femur, external fixation-pelvis/femur, closed reduction of fractured extremity-pelvis/femur, bone traction, skin traction, hemiarthroplasty-hip]), the spine (S22.0 [fracture of the thoracic vertebra], S22.1 [multiple fractures of the thoracic spine], S32.0 [fracture of lumbar spine and pelvis], M48.4 [fatigue fracture of vertebra] and M48.5 [collapsed vertebra, NEC]), wrist (S52.5 [fracture of lower end of radius], and S52.6 [fracture of lower end of both ulna and radius]), and the humerus (S42.2 [fracture of upper end of humerus] and S42.3 [fracture of shaft of humerus]) by using all claims records of outpatient visits or hospital admissions of patients from the KNHICD in the study period. Multiple fractures were defined as more than 1 fracture within the study period.

2.5. Medication adherence

Medication adherence was calculated using the medication possession ratio (MPR). The MPR is defined as the ratio of the number of days for which a patient is supplied with medication to the total number of days in the study period. On the basis of previous studies, we used 80% as the cutoff point to classify patients as adherents or non-adherents. Adherents were defined as patients with an MPR of ≥80%. Some studies have suggested that an MPR of 80% or higher allows patients with chronic disease to receive the benefits of their medication.

2.6. Other covariates

We include relevant confounders that could affect health care cost related osteoporosis: gender, age, area of residence, type of health coverage, medical institution, fracture history, anti-osteoporosis drugs, and Charlson Comorbidity Index (CCI). Age was categorized into 50 to 64 years, 65 to 74 years, and 75 years and over. To consider the availability of medical institutions by region, we classified area of residence into metropolitan, small to medium sized cities, and rural areas. The type of health insurance was included as a variable describing the socioeconomic status of the patient and out of pocket money. Medical Aid beneficiaries have low or no income and qualify for low or no out-of-pocket payment. As medical care costs can vary depending on the medical care institutions used, the type of medical institution was considered and defined as the institution which the patient used most often during the 1 year for the treatment of osteoporosis or osteoporotic fractures. Medical institutions were classified into general hospitals, hospitals, and clinics/public health centers. We also included anti-osteoporosis drugs as a covariate. The type and severity of comorbidities experienced by patients can influence osteoporosis-related health care costs and thus need to be adjusted for. Comorbidities were measured by using the CCI, which was converted into ICD-9 and ICD-10. We calculated the CCI, based on previous studies using national health insurance claims data, and scored it as 0, 1, 2, and 3 or over. We also included history of fractures as a covariate because it can also influence osteoporosis-related health care costs. History of fractures was defined as experience of receiving treatment due to fractures within 2 years prior to the index date. We assessed the gender, age, area of residence, and type of health coverage for the index date. Medical institution and anti-osteoporosis drugs were assessed 1 year after the index date, and the CCI was assessed within one year prior to the index date, in order to identify predictors of osteoporosis-associated health care costs.

We tested and confirmed that there was no problem of multicollinearity for all variables (variance inflation factor, VIF < 10).

2.7. Statistical analysis

Characteristics of non-adherents and adherents were tested by using χ² tests and t test, respectively. We then compared, by using the t test and ANOVA, the average health care between patients with fractures, and patient without fractures. In addition, we used a generalized linear model (GLM) with a gamma distribution and log link function to analyze the association between osteoporosis-related health care costs and predictors such as medication adherence and fractures according to patient demographics and clinical characteristics. The GLM was used to take into consideration the skewed distribution of the dependent variable, health care costs.

Using the GLM, we estimated the cost of osteoporosis treatment. The estimated osteoporosis treatment costs were then multiplied by the number of excess fractures among non-adherents. The number of excess fractures was determined as the difference in the number of fractures between non-adherents and adherents. The product is viewed as the amount of health care costs that could be saved if non-adherents become adherents and thus the economic effects of maintaining a high level of medication adherence.

All statistical analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and a 2-tailed level of statistical significance was defined as a P < .05.

2.8. Ethics statement

The study protocol was approved by the National Health Insurance Service (NHIS) Institutional Review Board (approval number: NHIS-2015-4-001).

3. Results

Of 438,845 osteoporosis patients included in this study, adherent patients accounted for 22.2% (97,469) of the study population and non-adherent patients 77.8% (Table 1). The average age (± standard deviation, SD) of non-adherents was higher than that of adherents (68.9 [±9.1] years vs 66.9 [±8.4] years, P < .001), and the greatest proportion of patients were 65 to 74 years in both groups. Males comprised 10% of non-adherents and 5% of adherents (P < .001). The proportion of Medical Aid beneficiaries were higher in non-adherents (10.4%) (P < .001). The most frequently used medical institutions were clinics/public health centers (81.8%), followed by tertiary/general hospitals (10.5%) and hospitals (7.7%). Adherents visited hospitals and bigger medical institutions (P < .001). The percentage of fractures were higher in non-adherents (7.6%) than in adherents (6.9%) (P < .001). The overwhelming majority of the patients (88%) used bisphosphonates to treat osteoporosis. The proportion of patients with a CCI of 0 was higher in non-adherents (65.9%) than in adherents (65.3%) (P < .001)
**Figure 2** shows the difference in the number of osteoporotic fracture patients by medication adherence. The proportion of fractures among non-adherents (7.6%) was approximately 1.1 times the proportion among adherents (7.0%). The proportion of fracture among non-adherents was 1.03 times that of adherents, the smallest difference between these groups. The proportion of fractures was 5.2% and 5.0% in non-adherents and adherents, respectively, and the proportion of vertebral fractures.

**Table 1**

| Characteristics of study subjects. | Total (n = 438,845) | Non-adherent (MPR < 80) (n = 341,376) | Adherent (MPR > 80) (n = 97,469) |
|------------------------------------|-------------------|--------------------------------------|----------------------------------|
| Age, y Mean ± SD                  | 68.45 ± 8.97      | 68.90 ± 9.08                         | 66.86 ± 8.41                    |
| Gender                            |                   |                                      |                                  |
| Men                               | 39,726            | 9.05                                 | 34,185                          |
| Women                             | 399,119           | 90.95                                | 307,191                         |
| Area of residence                 |                   |                                      |                                  |
| Metropolis                        | 163,741           | 37.31                                | 122,926                         |
| Small to medium cities            | 195,616           | 44.58                                | 152,561                         |
| Rural areas                       | 78,488            | 18.11                                | 65,889                          |
| Type of health coverage           |                   |                                      |                                  |
| Health insurance                  | 396,300           | 90.31                                | 305,892                         |
| Medical aid                       | 42,545            | 9.69                                 | 35,484                          |
| Medical institution               |                   |                                      |                                  |
| General hospital                  | 46,016            | 10.49                                | 30,299                          |
| Hospital                          | 33,707            | 7.68                                 | 25,609                          |
| Clinic and public health center   | 359,122           | 81.83                                | 285,468                         |
| Fracture history                  |                   |                                      |                                  |
| Yes                               | 419,372           | 95.56                                | 326,332                         |
| No                                | 19,473            | 4.44                                 | 15,044                          |
| Fracture                          |                   |                                      |                                  |
| Yes                               | 32,828            | 7.48                                 | 26,057                          |
| Hip                               | 2788              | 8.49                                 | 2179                            |
| Vertebral                         | 22,640            | 68.97                                | 17,744                          |
| Wrist                             | 5508              | 16.78                                | 4558                            |
| Human arm                         | 964               | 2.94                                 | 779                             |
| Multi fractures                   | 928               | 2.83                                 | 797                             |
| No                                | 406,017           | 92.52                                | 315,319                         |
| Anti-osteoporosis drugs           |                   |                                      |                                  |
| Bisphosphonate                    | 387,447           | 88.29                                | 296,520                         |
| SERM                              | 12,780            | 2.91                                 | 8099                            |
| Calcitonin                        | 36,618            | 8.80                                 | 36757                           |
| MPR Mean, ± SD                   | 44.69             | 32.49                                | 30.88                           |
| ≥80%                              | 97,469            | 22.21                                | 93.05                           |
| CCI Charlson comorbidity index    | 0                 | 288,741                              | 225,102                         |
|                                   | 1                 | 103,954                              | 80,713                          |
|                                   | 2                 | 31,449                               | 24,105                          |
|                                   | 3+                | 14,701                               | 11,456                          |

MPR = medication possession ratio, SD = standard deviation, SERM = selective estrogen receptor modulator.
Table 2
Difference in osteoporosis-related health care costs between fracture and non-fracture.

|               | Total          | Non-fracture  | Fracture       |   | Difference in osteoporosis-related costs |
|---------------|----------------|---------------|----------------|---|-----------------------------------------|
|               | Number of patients |               |                |   |                                         |
| Gender        |                |               |                |   |                                         |
| Men           | 438,845        | 406,017       | 32,828         |   | 1961                                   |
| Women         | 861 (1344)     | 714 (1174)    | 2675 (1883)    |   | <.001                                   |
| Age, y        |                |               |                |   |                                         |
| 50–64         | 39,726         | 35,638        | 28,740         |   | <.001                                   |
| 65–74         | 1068 (1563)    | 874 (1390)    | 2662 (1877)    |   | 1784                                   |
| ≥75           | 399,119        | 370,379       | 4088           |   |                                         |
|               | 840 (1319)     | 699 (1150)    | 2768 (1923)    |   | 2069                                   |
|               | 145,032        | 139,480       | 5562           |   |                                         |
|               | 699 (1087)     | 631 (998)     | 2415 (1669)    |   | <.001                                   |
|               | 179,634        | 167,793       | 11,841         |   | 1784                                   |
|               | 875 (1393)     | 753 (1270)    | 2605 (1834)    |   | 1851                                   |
|               | 114,179        | 98,744        | 15,435         |   |                                         |
|               | 1043 (1,526)   | 765 (1228)    | 2822 (1977)    |   | 2058                                   |

SD = standard deviation.

Table 3
Osteoporosis-related health care costs by fracture site.

| Fracture site | Number of patients | Hospitalization | Outpatient | Pharmacy | Total |
|---------------|--------------------|-----------------|------------|----------|-------|
| Hip           | 2788               | 5137 (1661)     | 93.61      | 210 (238) | 3.83  |
| Vertebral     | 22,640             | 1954 (1520)     | 82.02      | 277 (315) | 11.63 |
| Wrist         | 5508               | 1444 (1543)     | 70.01      | 474 (313) | 23.00 |
| Humerus       | 964                | 2279 (1901)     | 79.96      | 419 (418) | 14.69 |
| Multi fracture| 928                | 4333 (2316)     | 89.71      | 361 (322) | 7.47  |
| Fracture      | 32,828             | 2215 (1866)     | 82.81      | 311 (323) | 11.62 |
| Non-Fracture  | 406,017            | 336 (1140)      | 47.12      | 208 (249) | 29.10 |

SD = standard deviation.

in non-adherents was 1.04 times that in adherents. The proportion of the wrist and the humerus in non-adherents was 1.4 and 1.2 times, respectively, that in adherents. The proportion of multi-fractures was lowest but that in non-adherents was approximately 1.8 times that in adherents.

Table 2 describes the difference in osteoporosis-related health care costs between patients with fractures and those without fractures. Medical care costs per patient was $2,675 for those with fractures and $714 for those without fractures, with a difference of $1,961 (P < .001). The difference in mean medical care costs between fractures and non-fractures was $1,788 and $2,069 for men and women, respectively, with a greater difference for women (P < .001). The difference in mean medical care costs between fractures and non-fractures was $1,851 for 50 to 64 years, $1,851 for 65 to 74 years, and $2,058 for 75 years and older, with differences increasing with older age (P < .001).

Inpatient costs accounted for 82.8% of costs for patients with fractures and 47.12% of costs for patients without fractures. Medical care costs per patient was $2,675 for those with fractures and $714 for those without fractures, with a difference of $1,961 (P < .001). The difference in mean medical care costs between fractures and non-fractures was $1,788 and $2,069 for men and women, respectively, with a greater difference for women (P < .001). The difference in mean medical care costs between fractures and non-fractures was $1,851 for 50 to 64 years, $1,851 for 65 to 74 years, and $2,058 for 75 years and older, with differences increasing with older age (P < .001).

Table 2 presents the economic effects of fracture prevention through improving medication adherence among osteoporosis patients when other covariates were adjusted for. The estimated number of excess fractures in non-adherents was 2,342, consisting of 46 in the hip, 596 in vertebral, 1231 in the wrist, 131 in the humerus, and 338 in multiple fractures. We estimated that national health insurance expenses could be saved by $5,025,050 if all non-adherents become adherents.

4. Discussion

The study compared osteoporosis-related health care costs of osteoporosis between patients with fractures and those without fractures by using population-based health insurance claims data.
Table 4
Predictors of osteoporosis-related health care costs.

| Characteristic | Exponential estimate (Cost ratio) | Pr > $\chi^2$ |
|---------------|----------------------------------|--------------|
| Fracture site | Hip 6.8895 <.001 | Vertebral 3.0892 <.001 | Wrist 2.9350 <.001 | Humerus 3.7199 <.001 | Multiple fractures 3.4548 <.001 | None Reference |
| Age, y        | 50–64 1.2151 <.001 | 65–74 1.1900 <.001 | ≥75 1.1300 <.001 |
| Gender        | Men reference | Women 0.8360 <.001 |
| Area of residence | Metropolitan reference | Small to medium cities 1.0206 <.001 | Rural areas 1.1300 <.001 |
| Type of health coverage | Health insurance 0.8748 <.001 | Medical Aid Reference |
| Medical institution | General hospital 1.3406 <.001 | Hospital 1.0680 <.001 | Clinic/public medical center Reference |
| Fracture history | Yes 1.3051 <.001 | No Reference |
| Anti-osteoporosis drugs | Bisphosphonate 0.7535 <.001 | SERM 0.8720 <.001 | Calcitonin Reference |
| MPR           | <80% 1.3485 <.001 | Reference |
| CCI           | 0 1.1370 <.001 | 1 1.2100 <.001 | 3+ 1.3101 <.001 |

C2 = Charlson comorbidity index, MPR = medication possession ratio, SERM = selective estrogen receptor modulator.

Moreover, this study sought to identify the predictors of osteoporosis-related health care costs and to analyze the economic effects of improved medication adherence. We showed that there was a difference in the proportion of osteoporotic fractures according to medication adherence. Similarly, previous studies on the association between medication adherence of anti-osteoporosis drugs and fracture incidence showed a higher risk of fractures in non-adherents (MPR < 50%) than in adherents (MPR ≥ 80%).

Osteoporosis-related health care costs among patients with fractures were 3.8 times the costs among those without fractures. This was because health care costs for osteoporosis patients with fractures predominantly comprised of hospitalization cost among 3 components of costs that also included outpatient and pharmacy costs. This study also found predictor variables by using the GLM. Predictors of osteoporosis-related health care costs were fracture site, age, gender, area of residence, type of health coverage, medical institution, fracture history, anti-osteoporosis drugs, medication adherence, and CCI. Previous studies reported that medical care costs were higher for men than for women and increased with older age, higher CCI. Health care costs of osteoporosis patients with fracture were higher than those without fracture. Ha et al reported that from 2008 to 2011, health care costs per patient with osteoporotic fractures were 1.8 time costs per patient without fractures. Indeed, health care costs are much higher in hip fracture. When hip fracture occurred, health care costs increase three times in the United States. Mean health care costs per male patients with osteoporosis were 1.5 times higher than the costs per female patients in previous study. Health care costs for beneficiaries of medical aid were higher than those for beneficiaries of national health insurance. Medical aid patients might have low economic burden because of lower out-of-pocket money. Jung et al reported medical aid patients had received more pharmacotherapies than health insurer, and another study found out that mean health care costs of medical aid patients were higher than those of health insurer.

We showed that medication adherence was more strongly associated with increases in costs. These finding are similar to those of previous studies. However, better adherence may increase medical care costs due to treatment and prevention costs associated with osteoporosis medication but the occurrence of fractures can lead to greater health care costs. As a result, improved adherence can save osteoporosis-related health care costs. Our study estimated that if non-adherents become adherents, health care expenditure can be saved by $5 million. Similarly, Olsen et al estimated that non-adherents incurred excess costs of $ 2.5 million due to fractures, compared to adherents (MPR ≥ 80%). Sokol et al found that although pharmacy costs are related to increasing costs, improved medication adherents can reduce total health care costs among patients with some chronic diseases, diabetes, hypertension, hypercholesterolemia, and congestive heart failure.

Using national health insurance claims data, this study identified the disease burden of all patients who were diagnosed

Table 5
Economic effects of increased medication adherence among osteoporosis patients.

| Fracture site | Non-adherents (n=341,376) | Adherents (n=97,469) | Number of excess fractures in non-adherents | Osteoporosis treatment costs | Amount that can be saved |
|---------------|---------------------------|----------------------|--------------------------------------------|----------------------------|----------------------------|
| Hip           | 2179 0.64                 | 609 0.62             | 46                                         | 4882                       | 234,728                     |
| Vertebral     | 17,744 5.20               | 4896 5.02            | 596                                        | 1732                       | 1,032,452                   |
| Wrist         | 4558 1.34                 | 950 0.97             | 1231                                       | 1604                       | 1,973,895                   |
| Humerus       | 779 0.23                  | 185 0.19             | 131                                        | 2254                       | 295,460                     |
| Multiple fractures | 797 0.23              | 131 0.13             | 338                                        | 4431                       | 1,498,515                   |
| Total         | 26,057 7.63               | 6771 6.95            | 2,342                                      | 14,903                     | 5,025,050                   |

Adjusted for age, gender, area of residence, type of health coverage, medical institution, fracture history, osteoporosis medication, medication possession ratio (MPR), and Charlson comorbidity index (CCI).
with osteoporosis and treated in Korea. We further estimated osteoporosis-related health care costs that could be saved by increasing medication adherence. Although a number of studies investigated health care costs paid by Korean patients with fractures, a few went as far to estimate how much money could be saved by preventing fractures as this present study did. The findings of this study may inspire osteoporosis patients to initiate and maintain active medical treatment to prevent fractures.

Despite the strengths, however, the current study has various limitations. First, we may have overestimated the values of the MPR since they were based on the prescriptions but not whether patients actually took their prescribed medicines. Nevertheless, the MPR method is the best available tool to measure medication adherence using health insurance claim data. Second, this study included only direct medical costs from the payer’s perspective. We did not evaluate non-medical costs, including physical therapy, rehabilitation, orthotic treatments for fracture patients, herbal medicines, and caregiver costs, as well as indirect costs, such as work loss costs. This may have led to an underestimation of health care costs of osteoporosis patients. A previous study in Korea reported that social costs of osteoporotic fractures including out-of-pocket payment, long-term care cost, and non-medical costs are more than twice the total national health insurance payment due to osteoporotic fractures between 2007 and 2011. Third, the KNHICD contains electronic medical use records and prescription data for over 99% of the entire population but does not include non-reimbursable services such as medical checkups. For that reason, expensive non-reimbursable services might have been excluded from the analysis, underestimating health care costs. We also did not examine potential covariates such as family history of osteoporotic fractures, bone mineral density, and patient’s health behaviors (smoking and alcohol use). Lastly, we demonstrated that medication adherence lowered the occurrence of fractures by 1.3%, since we could not assess long term medication adherence. A previous study showed that long-term therapy of anti-osteoporosis drugs for more than 5 years reduced the chance of experiencing a fracture by 35%. A future study based on a longer study period may demonstrate larger savings of health care expenditures due to a greater difference in fracture probability according to medication adherence.

Despite these limitations, the findings of this study has policy implications on saving health care costs and improving quality of care of patients with osteoporosis. Improved osteoporosis medication adherence can prevent osteoporotic fractures and therefore reduce health care costs associated with osteoporotic fractures. Cost savings can be bigger if osteoporosis patients expand to the whole. Our findings highlight the need for self-care of patients, engagement of pharmacists, and education on the importance of improving medication adherence for the prevention of fractures to reduce overall health care burden.

In conclusion, this study identified the presence of fractures, age, and medication adherence as the factors affecting osteoporosis-related health care costs. Moreover, this study estimated that improved medication adherence could save nearly $5 million of osteoporosis-related health care costs annually. Persistent pharmacotherapy is recommended to prevent osteoporotic fractures and reduce health care costs in patients with osteoporosis.

Author contributions
Conceptualization: Hyemin Cho, Ji-Hye Byun, Sunmee Jang.
Data curation: Hyemin Cho, Ha Y. Kim, Young-Chan Ha, Tae-Young Kim, Young-Kyun Lee, Sunmee Jang.
Formal analysis: Hyemin Cho, Ji-Hye Byun.
Funding acquisition: Young-Chan Ha.
Investigation: Ha Y. Kim, Young-Chan Ha, Tae-Young Kim, Young-Kyun Lee, Sunmee Jang.
Methodology: Ha Y. Kim, Young-Chan Ha, Tae-Young Kim, Young-Kyun Lee, Sunmee Jang.
Project administration: Sunmee Jang.
Supervision: Young-Chan Ha, Sunmee Jang.
Writing – original draft: Hyemin Cho, Inmyung Song, Sunmee Jang.
Writing – review & editing: Hyemin Cho, Ji-hye Byun, Inmyung Song, Sunmee Jang.

References
[1] Dempster DW. Osteoporosis and the burden of osteoporosis-related fracture. Am J Manag Care 2011;17:564–9.
[2] Ha Y-C. Epidemiology of osteoporosis in Korea. J Korean Med Assoc 2016;59:836.
[3] Cauley JA. Public health impact of osteoporosis. J Gerontol A Biol Sci Med Sci 2013;68:1243–51.
[4] Lee YK, Yoon BH, Koo KH. Epidemiology of osteoporosis and osteoporotic fractures in South Korea. Endocrinol Metabol 2013;28:90–3.
[5] Choi HJ, Shin CS, Ha YC, et al. Burden of osteoporosis in adults in Korea: a national health insurance database study. J Bone Miner Metab 2012;30:54–8.
[6] Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761–7.
[7] Dennison E, Cooper C. epidemiology of osteoporotic fracture. Horm Res 2000;63:58–63.
[8] Lips P, van Schoor NM. Quality of life in patients with osteoporosis. Osteoporos Int 2005;16:447–55.
[9] Ha YC, Kim TY, Lee A, et al. Current trends and future projections of hip fracture in South Korea using nationwide claims data. Osteoporos Int 2016;27:2603–9.
[10] Lange A, Zeidler J, Beaum S. One-year disease-related health care costs of incident vertebral fractures in osteoporotic patients. Osteoporos Int 2014;25:2435–43.
[11] Chang CY, Tang CH, Chen KC, et al. The mortality and direct medical costs of osteoporotic fractures among postmenopausal women in Taiwan. Osteoporos Int 2016;27:665–76.
[12] Lotters FJ, van den Bergh JP, de Vries F, et al. Current and future incidence and costs of osteoporosis-related fractures in the Netherlands: combining claims data with BMD measurements. Calcif Tissue Int 2016;98:235–43.
[13] Bloijn J, Dragomir A, Fredette M, et al. Comparison of direct health care costs related to the pharmacological treatment of osteoporosis and to the management of osteoporotic fractures among compliant and noncompliant users of alendronate and risedronate: a population-based study. Osteoporos Int 2009;20:1571–81.
[14] Blume SW, Curtis JR. Medical costs of osteoporosis in the elderly Medicare population. Osteoporos Int 2011;22:1835–44.
[15] Corte FE, De Pouvourville G. Cost of non-persistence with oral bisphosphonates in post-menopausal osteoporosis treatment in France. BMC Health Serv Res 2011;11:151.
[16] Lee YHD, Lim YW, Lann KS. Economic cost of osteoporotic hip fractures in Singapore. Singapore Med J 2008;49:980–4.
[17] Leslie WD, Metge Cj, Arazana M, et al. Direct costs of fractures in Canada and trends 1996–2006: a population-based cost-of-illness analysis. J Bone Miner Res 2011;26:2419–29.
[18] Nojiri S, B urine RT, Flynn JA, et al. Osteoporosis and treatments in Japan: management for preventing subsequent fractures. J Bone Miner Metab 2013;31:367–80.
[19] Kim J, Lee E, Kim S, et al. Economic burden of osteoporotic fracture of the elderly in South Korea: a national survey. Value Health Reg Issues 2016;9:36–41.
[20] Kim HY, Ha YC, Kim TY, et al. Healthcare costs of osteoporotic fracture in Korea: information from the National Health Insurance Claims Database. 2008–2011. J Bone Metab 2017;24:125–33.

[21] Sharan Moser S, Yu J, Goldshein I, et al. Cost and consequences of nonadherence with oral bisphosphonate therapy: findings from a real-world data analysis. Ann Pharmacother 2016;50:262–9.

[22] Olsen KR, Hansen C, Abrahamsen B. Association between refill compliance to oral bisphosphonate treatment, incident fractures, and health care costs—an analysis using national health databases. Osteoporos Int 2013;24:2639–47.

[23] Ward MA, Xu Y, Viswanathan HN, et al. Association between osteoporosis treatment change and adherence, incident fracture, and total healthcare costs in a Medicare Advantage Prescription Drug plan. Osteoporos Int 2013;24:1195–206.

[24] Park C, Jang S, Lee A, et al. Incidence and mortality after proximal humerus fractures over 50 years of age in South Korea: national claim data from 2008 to 2012. J Bone Metab 2015;22:17–21.

[25] Shin S, Song H, Oh SK, et al. Effect of antihypertensive medication adherence on hospitalization for cardiovascular disease and mortality in hypertensive patients. Hypertens Res 2013;36:1090–5.

[26] Adachi JD, Lyles K, Boonen S, et al. Subtrochanteric fractures in bisphosphonate-naive patients: results from the HORIZON-recurrent fracture trial. Calcif Tissue Int 2011;89:427–33.

[27] Viswanathan HN, Curtis JR, Yu J, et al. Direct healthcare costs of osteoporosis-related fractures in managed care patients receiving pharmacological osteoporosis therapy. Appl Health Econ Health Policy 2012;10:163–73.

[28] Martin-Merino E, Huerta-Alvarez C, Pinto-Alhambra D, et al. Cessation rate of anti-osteoporotic treatments and risk factors in Spanish primary care settings: a population-based cohort analysis. Arch Osteoporos 2017;12:39.

[29] Kim HY, Jang EJ, Park B, et al. Development of a Korean Fracture Risk Score (KFRS) for predicting osteoporotic fracture risk: analysis of data from the Korean National Health Insurance Service. PloS One 2016;11:e0158918.

[30] Lakatos P, Toth F, Szekeres L, et al. Comparative statistical analysis of osteoporosis treatment based on Hungarian claims data and interpretation of the results in respect to cost-effectiveness. Osteoporos Int 2014;25:2077–87.

[31] Rolnick SJ, Pawloski PA, Hedblom BD, et al. Patient characteristics associated with medication adherence. Clin Med Res 2013;11:54–65.

[32] Jha AK, Aubert RE, Yao J, et al. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly $5 billion annually. Health Aff 2012;31:1836–46.

[33] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation 2009;119:3028–35.

[34] Jang S, Park C, Jang S, et al. Medical service utilization with osteoporosis. Endocrinol Metabol 2010;25:2362.

[35] Eisenberg DFP, Hilary , Gu T, et al. Cost and consequences of nonadherence with oral bisphosphonate treatment. J Manag Care Spec Pharm 2015;21:56–65.

[36] Dodd S, Bassi A, Rodger K, et al. a comparison of multivariable regression models to analyse cost data. J Eval Clin Pract 2005;12:76–86.

[37] Polgreen LA, Brooks JM. Estimating incremental costs with skew: a cautionary note. Appl Health Econ Health Policy 2012;10:319–29.

[38] Blough DK, Ramsey SD. Using generalized linear models to assess medical care costs. Health Serv Outcomes Res Methodol 2000;1:185–202.

[39] Halpern R, Becker L, Iqbal SL, et al. The association of adherence to osteoporosis therapies with fracture all-cause medical costs and all cause hospitalization: a retrospective claims analysis of female health plan enrollees with osteoporosis. J Manag Care Pharm 2011;17:25–39.

[40] Ha YC, Kim HY, Jang S, et al. Economic burden of osteoporosis in South Korea: claim data of the National Health Insurance Service from 2008 to 2011. Calcif Tissue Int 2017;101623–30.

[41] Hopkins RB, Tarride JE, Leslie WD, et al. Estimating the excess costs for patients with incident fractures, prevalent fractures, and nonfracture osteoporosis. Osteoporos Int 2013;24:581–93.

[42] Jung Y, Ko Y, Kim HY, et al. Gender differences in anti-osteoporosis drug treatment after osteoporotic fractures. J Bone Miner Metab 2018; [Epub ahead of print].

[43] Hazel-Fernandez L, Louder AM, Foster SA, et al. Association of teriparatide adherence and persistence with clinical and economic outcomes in Medicare Part D recipients: a retrospective cohort study. BMC Musculoskelet Disord 2013;14:53.

[44] Sokol MCM, Kimberly A, Verbrugge , et al. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care 2005;43:521–30.

[45] Kang HY, Kang DR, Jang YH, et al. Estimating the economic burden of osteoporotic vertebral fracture among elderly Korean women. J Prev Med Public Health 2008;287–94.

[46] Lim S, Koo BK, Lee EJ, et al. Incidence of hip fractures in Korea. J Bone Miner Metab 2008;26:400–5.

[47] Hong J-SK, Hee-Chung. Relationship between continuity of ambulatory care and medication adherence in adult patients with type 2 diabetes in Korea: a longitudinal analysis. Med care 2014;52:446–53.

[48] Tarride JE, Hopkins RB, Leslie WD, et al. The burden of illness of osteoporosis in Canada. Osteoporos Int 2012;23:2591–600.

[49] Borgstrom F, Johnell O, Kanis JA, et al. At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. Osteoporos Int 2006;17:1459–71.

[50] Kanis JA, Johnell O, Oden A, et al. Intervention thresholds for osteoporosis in men and women: a study based on data from Sweden. Osteoporos Int 2005;16:6–14.