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ORIGINAL ARTICLE

Cost-effectiveness of implementing guidelines for the treatment of glucocorticoid-induced osteoporosis in Japan

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Abstract

Summary A model-based cost-effectiveness analysis was performed to evaluate the cost-effectiveness of implementing the clinical guideline for the treatment for glucocorticoid-induced osteoporosis (GIO). The treatment indication for GIO in the current Japanese clinical guidelines is likely to be cost-effective except for the limited patients who are at low risk for fracture.

Introduction The purpose of this study was to evaluate the cost-effectiveness of implementing the clinical guideline for the treatment for glucocorticoid-induced osteoporosis (GIO) from the perspective of the Japanese healthcare system.

Methods A patient-level state transition model was developed to predict lifetime costs and quality-adjusted life years (QALYs) in postmenopausal Japanese women with osteopenia or osteoporosis using glucocorticoid (GC). An annual discount rate of 2% for both costs and QALYs was applied. The incremental cost-effectiveness ratio (ICER) of 5-year alendronate therapy compared with no therapy was estimated with different combinations of the risk factors such as starting age (45, 55, or 65), femoral neck BMD (% young adult mean (YAM) of 70%, 75%, or 80%), dose of GC (2.5, 5, or 10 mg per day), and the presence of previous fracture (yes or no).

Results For 55-year-old women using GC with a BMD of 75% of YAM, the ICER ranged from $10,958 to $ 29,727 per QALY. Scenario analyses indicated that the lower age, the lower BMD, the higher dose of GC, and the presence of previous fracture associated with lower ICER. The best-case scenario was 45-year-old women with a BMD of 70% of YAM, GC dose of 10 mg per day, and previous fracture, and resulted in healthcare cost-savings. The worst-case scenario was 65-year-old women with a BMD of 80% of YAM, GC dose of 2.5 mg per day, and no previous fracture, and resulted in the ICER of $66,791 per QALY. Sensitivity analyses in the worst-case scenario showed that the annual discount rate for costs and health benefit had the strong influence on the estimated ICER. Although the ICER was influenced by other parameters such as disutility due to vertebral fracture, efficacy of alendronate, and so on, the ICERs remained more than $50,000 per QALY.

Conclusions The cost-effectiveness of preventive alendronate therapy for postmenopausal women with osteopenia or osteoporosis using GC is sensitive to age, BMD, GC dose, and the presence of previous fracture. Our analysis suggested that the treatment indication for postmenopausal women with osteopenia or osteoporosis using GC in the current Japanese clinical guidelines is likely to be cost-effective except for the limited patients who are at low risk for fracture.

Keywords Cost-effectiveness analysis · Fracture prevention · Glucocorticoid-induced osteoporosis · Health economics

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Introduction

Glucocorticoid-induced osteoporosis (GIO) is the most common type of secondary osteoporosis. Glucocorticoid (GC) is typically used to treat rheumatoid arthritis, lupus, myositis, and polymyalgia rheumatic [1, 2]. It has been reported that about 30% to 50% of the patients receiving glucocorticoids therapy for long term had GIO [1, 2]. GIO patients are at very high risk of fractures through the decreasing of bone mass. Osteoporotic fractures such as hip fractures are associated with increased morbidity and mortality and impose a large

financial burden on healthcare systems. According to a nationwide survey of hip fractures in Japan, the total number of patients who experienced a hip fracture in 2012 was 175,700 (male 37,600, female 138,100), which represents an increase from 2007 (total 148,100, male 31,300, female 116,800) [3, 4]. Survival rates reported for patients who have experienced a hip fracture—81, 49, and 26% for 1, 5, and 10 years, respectively—are lower than rates for the general population [5]. Also, a health-related QOL score (utility value) of patients in the year following a hip fracture was reduced by 11.5% compared to the baseline [6]. Annual expenditure for medical care associated with bone density and bone structure, as well as fracture, in the population aged over 65 has been estimated to be 891.5 billion JPY in 2012 and 943.6 billion JPY in 2013 [7] and are expected to rise depending on the increase in the incidence of osteoporotic fractures.

Drug therapy is considered to be an effective measure against the burden incurred by osteoporotic fractures, and a wide variety of options are available today. Therefore, it is important to prevent early bone loss and to decrease in fracture risk as early as possible after the start of long-term GC therapy. In recent years, the Japanese Society for Bone and Mineral Research (JSBMR) has updated clinical guidelines on the management and treatment of GIO [8]. In this guideline, a committee for the revision of guideline developed a risk scoring algorithm to identify the optimal cutoff score for pharmacological intervention based on the Cox proportional analysis of three Japanese GIO cohorts ($n = 903$) [8]. The scoring algorithm consists of four items as follows; (1) Prior fragility fracture (No: 0 point, Yes: 7 point), (2) Age [years] (< 50 =: 0 point, 50 ≦ < 60: 2 point, and ≧ 65: 4 point), (3) GC dose [prednisolone equivalent mg/day] (< 5: 0 point, 5 ≦ < 7.5: 1 point, ≧ 7.5: 4 point), and (4) Lumber BMD [% of young adult mean (YAM)] (≧ 80: 0 point, 70 ≦ <80: 2 point, < 70: 4 point) [8]. The guideline recommends that patients using GC whose risk score based on the developed algorithm is more than 3 points should be treated with pharmaceuticals [8]. Although several guidelines for the management of GIO have been published during the last decade, it has been reported that the adherence to these guidelines is low, and a survey from Japan demonstrated that the level of adherence to guidelines in daily practice was only 23.3% [9, 10].

Implementing the guidelines on the management and treatment of GIO definitely reduces the risk of fracture and is anticipated to reduce the total treatment cost for osteoporotic fracture. However, there is the possibility of an increase in the total medical cost including medications. Recently, the cost-effectiveness of various drug therapies for osteoporosis has been studied in advanced countries and the results are having an influence on decision making in clinical practice as well as on healthcare policies. Kanis et al. performed a cost-effectiveness analysis of bisphosphonate therapy in GIO patients from the UK perspective and proposed an assessment algorithm for pharmacological intervention considering the presence of prior fracture, patient age, and BMD in terms of cost-effectiveness [11]. A previous study from the USA evaluating the cost-effectiveness of an intervention aimed at improving the management of GIO compared with current practice reported that multifaceted evidence implementation programs for the prevention of GIO was likely to be cost-effective only if it focuses on individuals with very high fracture risk and the proportion of prescriptions for generic bisphosphonates increases substantially [12]. In addition, Murphy et al. evaluated the cost-effectiveness of teriparatide as a first line treatment for GIO from the Swedish perspective and reported that teriparatide was cost-effective compared with no treatment in high-risk GIO patients [13].

In Japan, cost-effectiveness of bisphosphonate therapy in postmenopausal women with osteopenia or osteoporosis has been examined [14–17]. The results indicated that osteoporosis treatment should be considered only for a high-risk population on the basis of age, bone mineral density (BMD), and number of clinical risk factors [14–17]. However, to date, no economic evaluation of the drug therapy for postmenopausal women with GIO has been reported in Japan. There are epidemiological characteristics of a lower incidence rate of hip fracture [18, 19] and a higher incidence of vertebral fracture [20, 21] in Japanese compared to Western people. In addition, the Japanese healthcare system also differs from that of Europe and USA including drug prices, treatment fees, and the socially acceptable thresholds of the incremental cost-effectiveness ratio (ICER). For these reasons, direct application of the results of studies in Western countries to the Japanese population is problematic. Therefore, we assessed the cost-effectiveness of drug therapy based on the Japanese clinical guideline for the management and treatment for GIO from the perspective of the Japanese healthcare and nursing care system.

Methods

Model structure

A model-based cost-effectiveness analysis was performed to evaluate the cost-effectiveness of implementing guidelines for the treatment of GIO in postmenopausal women in Japan. Cohort-based Markov models have been frequently used for economic evaluation of osteoporotic interventions. However, this modeling approach is limited by the "memoryless" feature of the process, which is known as the Markov assumption. This assumption means that once a patient has moved from one state to another, the model will have "no memory" regarding where the patient came from. When parameters such as relative risk, mortality, cost, and

so on depend on prior events (ex: start of drug therapy, occurrence of fracture event, and so on), this "memory" should be reflected in the model. To overcome the "memoryless" feature of the Markov process, a patient-level state transition model was developed to estimate long-term costs and quality-adjusted life years (QALYs) associated with fracture prevention therapy by oral alendronate and no therapy (Fig. 1). The model consisted of ten health states: "No previous fracture," "post hip fracture," "post vertebral fracture," "post other fracture," "post hip and vertebral fracture," "post hip and other fracture," "post vertebral and hip fracture," "post hip, vertebral and other fracture," "bed ridden," and "death." In this model, we defined other fractures as proximal humeral fractures or wrist fractures. Additionally, we modeled clinical vertebral fractures and did not consider asymptomatic morphometric vertebral fractures. In the model simulation, hypothetical patients started with the state of "no previous fracture" or "post vert fracture" based on their background information (the presence of prior vertebral fracture). Patients faced different risks of fracture depending on age, femoral neck BMD, the dose of glucocorticoid, the presence of previous fracture, and the treatment received. The cycle length of the model was set to 1 year. During each cycle of the simulation, each patient experienced one of the following clinical events: "no event," "vertebral fracture," "hip fracture," "other fracture," "vertebral and hip fracture," "vertebral and other fracture," "hip and other fracture," or "vertebral, hip, and other fracture." After patients had suffered a fracture, they moved to the high-risk state and had an additional risk for subsequent fractures. We assumed that a certain proportion of patients with a hip fracture would move to the health state of "bedridden". The model was developed and analyzed using TreeAge Pro 2016 (TreeAge Software, Williamstown, MA, USA).

Target population

The modeled hypothetical cohort comprised postmenopausal Japanese women using GC. We examined different combinations of the risk factors such as starting age (45, 55, or 65), femoral neck BMD (%YAM of 70%, 75%, or 80%), dose of glucocorticoid (2.5, 5, or 10 mg per day), the presence of previous fracture (yes or no). The risk score based on the Japanese guidelines was calculated for each type of cohort [8]. In this model, the femoral neck BMD was calculated using the reference young adult mean of 0.790 g/cm^2 (SD = 0.09 g/cm^2) for Japanese women aged 20 to 29 as follows: BMD for 70% YAM = 0.790 × 0.7 = 0.553 g/cm^2 [22].

Transition probabilities

A transition probability (p) of a clinical event occurring over a time interval (t) was calculated according to the incidence rate (r), using the declining exponential approximation of life expectancy (DEALE) method with the following formula: $p = 1\text{-}\exp(-r \times t)$ [23]. Applying a series of methods proposed by De Laet and colleagues [24] to the epidemiological data from Japan, we developed equations for age and femoral neck BMD-specific fracture rates (Supplementary material S1). We first developed equations for age-dependent fracture rates for hip fracture, vertebral fracture, and other fractures by using data on postmenopausal Japanese women and curve fitting techniques [21, 25, 26]. The curve fitting functions were determined according to the Akaike information criterion (AIC) and clinical plausibility. An exponential curve was used to fit

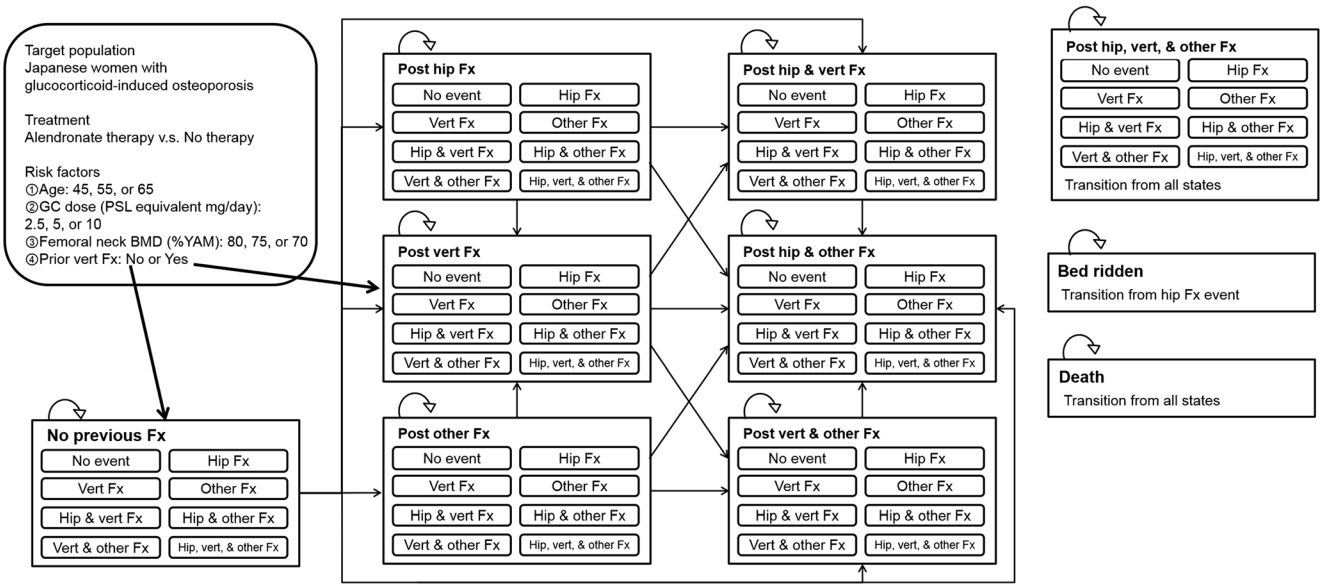

Fig. 1 Model structure. GC glucocorticoid, PSL prednisolone, BMD bone mineral density, YAM young adult mean, Vert vertebral, Fx fracture

the age-dependent fracture rate for hip fracture and vertebral fracture. A sigmoid curve was used to model the age-dependent fracture rate for other fractures. We then estimated age- and femoral neck BMD-specific fracture rates by combining the equations for age-dependent fracture rate, distribution of femoral neck BMD by age group, and relative risks (RRs) of fracture per 1 SD reduction in BMD (Supplementary material S2) [21, 24–27].

Incidence rates of subsequent fractures for those with a previous fracture were calculated by multiplying the age- and femoral neck BMD-specific fracture rates by the RR of subsequent fracture (Table 1) [28]. The proportion of clinical vertebral fractures among all vertebral fractures was assumed to be 30% for the base case (Table 1) [29].

The age-dependent mortality rate was obtained from the life table reported by the Ministry of Health, Labour, and Welfare in Japan [30]. Tsuboi et al. studied prospectively the change over 10 years in mortality after a hip fracture in 753 patients in Japan [5]. They compared the deaths observed in these patients with those expected in the general population, matched for age, gender, and calendar year at the time of fracture [5]. Also, they reported the mortality ratio by years after fracture occurrence [5]. We formulated the mortality ratio for 10 years after hip fracture by applying curve fitting techniques to the reported mortality ratio. (Supplementary material S 2) [5]. The mortality rate for patients who had experienced a hip fracture was calculated by multiplying the age-dependent mortality by the mortality ratio after hip fracture. The probability of becoming bedridden after hip fracture was derived from a published source in Japan [31]. In this study, curve-fitting analyses were performed with Stata 14 (StataCorp LP, Texas, USA).

Efficacy of drug therapy

The National Institute for Health and Care Excellence (NICE) in the UK has provided technology appraisal guidance on secondary prevention of osteoporotic fractures in postmenopausal women and recommended alendronate as a first-line treatment in terms of clinical effectiveness and cost-effectiveness [32]. Also, the current clinical guideline in Japan recommends alendronate or risedronate as first-line treatment in a patient with GIO [8]. Therefore, in this study, we assumed that patients in the treatment arm received 5 years of once-weekly alendronate therapy (35 mg per a week) with 5 years of offset time and modeled residual effects of alendronate, assuming a linear decline in efficacy over 5 years, after 5 years of treatment for the base case scenario [33]. We also assumed that patients received 5 years of alendronate therapy with 5 years of offset time again, if they experienced secondary or further fracture events after initial drug treatment of 5 years. We assumed that patients in the no-therapy arm did not receive drug therapy even if they had subsequent fractures. Incidence rates of fractures for those using alendronate therapy were calculated by multiplying the age- and femoral neck BMD-specific fracture rate by the RR of alendronate vs. placebo (Table 1). The RR of alendronate for hip, vertebral, and other fractures was derived from a published network meta-analysis estimating the comparative effectiveness of different drug therapies in reducing the risk of fragility fractures [34]. In this model, partial compliance with alendronate therapy was assumed by using a method previously reported [33]. Loss of efficacy due to adherence was assumed to 10% for the base case scenario and considered using the following formula: efficacy in patients with partial adherence = (1-[1-RR of fracture with alendronate] × [100%-10% reduction in efficacy] (Table 1). Additionally, adverse events associated with alendronate therapy were not considered because their impact on long-term costs and clinical benefits was relatively small.

Costs

We considered only direct costs for medication and nursing care from the perspective of the Japanese public healthcare and nursing care system. Table 1 summarizes input values for cost parameters in this model. All costs were estimated in Japanese yen and converted to US dollars with the currency exchange rate of 1$ = JPY120. The annual drug cost of alendronate was calculated according to a Japanese price list for drugs [35]. Annual medical costs for daily practice, including consulting, clinical testing, and radiography, were estimated on the basis of Japanese tariffs, assuming standard clinical practice [31, 36]. Patients in the treatment arm were assumed to have bimonthly consultations with their doctor, twice-yearly bone marker tests, and twice-yearly BMD measurements with dual-energy X-ray absorptiometry (DEXA) [31]. The drug cost of alendronate and medical cost were accumulated during drug treatment of 5 years. Medical costs due to a fracture event were obtained from published sources in Japan [37–39]. We converted the previously reported costs for hip fracture, vertebral fracture, and other fractures into the present values by using the price revision rate of the Japanese medical fee schedule. Because no studies have provided data on the costs of nursing care for bedridden patients, we used data for patients receiving level 5 nursing care under the nursing care insurance scheme in Japan (those who are unable to perform the activities of daily life without assistance) [40].

Utilities

Input values for utility parameters are shown in Table 1. The equation for age-dependent utility value, based on the EuroQOL-5Dimension-3Level (EQ-5D-3L) for event-free women, was developed by using a linear regression analysis based on data from the Japanese population [41]. The utilities for patients who experienced fracture events were calculated

Table 1 Parameter settings

Parameter	Value	Range	Reference
Relative risk of hip fracture			
With previous hip fracture	1.56	–	[28]
With previous vertebral and hip fracture	2.43 (= 1.56^2)	–	
With previous vertebral and other fracture	2.43 (= 1.56^2)	–	
With previous vertebral, hip, and other fracture	3.80 (= 1.56^3)	–	
Relative risk of vertebral fracture			
With previous hip fracture	1.74	–	[28]
With previous vertebral and hip fracture	3.03 (= 1.74^2)	–	
With previous vertebral and other fracture	3.03 (= 1.74^2)	–	
With previous vertebral, hip, and other fracture	5.27 (= 1.74^3)	–	
Relative risk of other fracture			
With previous hip fracture	1.74	–	[28]
With previous vertebral and hip fracture	3.03 (= 1.74^2)	–	
With previous vertebral and other fracture	3.03 (= 1.74^2)	–	
With previous vertebral, hip, and other fracture	5.27 (= 1.74^3)	–	
Relative risk of fracture with steroid treatment (per 1 mg/day increase)	1.04	1.02–1.05	[8]
Proportion of clinical vertebral fracture	0.30	0.25–0.35	[29]
Probability of bed ridden after hip fracture	0.136	± 30%	[30]
Efficacy of alendronate			
Relative risk of vertebral fracture	0.50	0.33–0.79	[31]
Relative risk of hip fracture	0.45	0.27–0.68	[31]
Relative risk of other fracture	0.78	0.66–0.92	[31]
Loss of efficacy due to partial adherence	10%	0%–20%	Assumption
Treatment period (years)	5	–	Assumption
Offset time (years)	5	0–5	Assumption
Annual drug cost of alendronate ($)	256.4	± 30%	[32]
Annual medical cost ($)	350.8	± 30%	[30, 33]
Annual drug cost of prednisone (per 1 mg) ($)	5.84	± 30%	[32]
Treatment costs of fracture per event ($)			
Hip fracture	18,056	± 30%	[34]
Vertebral fracture	6764	± 30%	[35]
Other fracture	4635	± 30%	[36]
Annual cost of nursing care ($)	26,250	± 30%	[37]
Age-dependent event-free utility	1.2388–0.0059 × Age	± 5%	[38]
Relative disutility due to hip fracture			
First year	× 0.775	± 10%	[6]
Subsequent years	× 0.855		[6]
Relative disutility due to vertebral fracture			
First year	× 0.848	± 10%	[6]
Subsequent years	× 0.950		[6]
Relative disutility due to other fracture			
First year	× 0.902	± 10%	[6]
Subsequent years	× 0.943		[6]
Utility for bed ridden	0.131	0.091–0.17	[39]
Annual discount rate	0.02	0–0.05	[40]

1$ = JPY120

by multiplying the event-free utility value by the relative disutility associated with various fracture events. The relative disutility associated with fractures for the first year and subsequent years was calculated on the basis of a prospective study in Japan [6]. Given the lack of data on utility values for bedridden patients, we used published data for patients provided with level 5 nursing care [42].

Cost-effectiveness analysis

For the base case analysis, a first-order Monte Carlo simulation (individual simulation), using 50,000 patients, was run to obtain the point estimate of lifetime expected costs and QALYs associated with alendronate therapy compared with no therapy based on a lifetime horizon. In fact, we assumed that the simulation was done until the patient is 100 years old. In this case, the substantial simulation periods for cohort patients aged 45, 55, and 65 will be 55, 45, and 35 years, respectively. An annual discount rate of 2% for both costs and QALYs was applied [43]. The incremental cost-effectiveness ratio (ICER) was estimated by the following formula: ICER = (Cost $_{\text{ALN therapy}}$-Cost $_{\text{no therapy}}$) ÷ (QALY $_{\text{ALN therapy}}$-QALY $_{\text{no therapy}}$). The willingness to pay for one additional QALY gained was set to $50,000. We ran the model with 54 types of hypothetical cohort who have different combinations of the risk factors such as starting age (45, 55, or 65), femoral neck BMD (%YAM of 70%, 75%, or 80%), dose of glucocorticoid (2.5, 5, or 10 mg per day), and the presence of previous fracture (yes or no). The risk score based on the Japanese guidelines for GIO was calculated for the 54 types of cohort [8]. The scoring algorithm consists of four items as follows; (1) Prior fragility fracture (No: 0 point, Yes: 7 point), (2) Age [years] (< 50 = : 0 point, 50 ≦ < 60: 2 point, and ≧ 65: 4 point), (3) GC dose [prednisolone equivalent mg/day] (< 5: 0 point, 5 ≦ < 7.5: 1 point, ≧ 7.5: 4 point), and (4) Lumber BMD [% of young adult mean (YAM)] (≧ 80: 0 point, 70 ≦ <80: 2 point,< 70: 4 point) [8]. Also, the relationship between the ICER and the risk score was analyzed by using ordinary linear regression model. Deterministic sensitivity analyses were performed to assess the influence of various key parameters on the worst case result. Assessed parameters and ranges are shown in Supplementary material S1 and Table 1. The plausible ranges for each parameter were determined based on reported values, such as 95% confidence intervals in published sources, or expert opinions.

Results

Base case results

The results of the cost-effectiveness of alendronate therapy for 55-year-old-women with a BMD of 75% of YAM are summarized in Table 2. Compared with no therapy, alendronate therapy for women using 2.5 mg/day of GC without a previous vertebral fracture (risk score 4) resulted in average additional lifetime costs of $3413 per patient and conferred an additional 0.115 QALYs, which resulted in an ICER of $29,727 per QALY gained based on a lifetime horizon. The ICER in women using 5 mg/day (risk score 5) and 10 mg/day (risk score 8) of GC without a previous vertebral fracture was $24,278 per QALY and $16,184 per QALY, respectively. For women with a previous vertebral fracture using 2.5 mg/day (risk score 11), 5 mg/day (risk score 12), and 10 mg/day of GC (risk score 15), the ICER was estimated to be $19,538 per QALY, $16,080 per QALY, and $10,958 per QALY, respectively.

Scenario analysis

The results of the cost-effectiveness of alendronate therapy for 54 types of hypothetical cohort who have different combinations of the risk factors such as starting age (45, 55, or 65), femoral neck BMD (%YAM of 70%, 75%, or 80%), dose of GC (2.5, 5, or 10 mg per day), and the presence of previous fracture (yes or no) were summarized in Fig. 2. The lower starting age, lower BMD, higher GC dose, and presence of previous vertebral fracture associated with an increase in the incremental QALYs. Also, the higher starting age, lower BMD, higher GC dose, and presence of previous vertebral fracture associated with a decrease in the incremental costs. In addition, the lower starting age, lower BMD, higher GC dose, and presence of previous vertebral fracture associated with a decrease in the ICER. In terms of cost-effectiveness, the worst scenario was 65-year-old-women who had no previous fracture with a BMD of 80% of YAM and 2.5 mg/day of GC, which resulted in the ICER of $66,791 per QALY. The best scenario was 45-year-old women who had a previous fracture with a BMD of 70% of YAM and 10 mg/day of GC, which resulted in the cost-saving compared with no therapy (− $1359 per a patient). The relationship between ICER and risk score was summarized by scatter plot as shown in Fig. 3. The regression analysis showed that the higher risk score associated with a decrease in the ICER. The ICER was more than $50,000 per QALY gained in the following scenarios; (1) ICER = $51,164 per QALY in patient aged 55 with no prior fracture, GC dose 2.5 mg/day, 80% of YAM [risk score 2], (2) ICER = $66,791 per QALY in patient aged 65 with no prior fracture, with GC dose 2.5 mg/day, 80% of YAM [risk score 4], and (3) ICER = $55,778 per QALY in patient aged 65 with no prior fracture, with GC dose 5 mg/day, 80% of YAM [risk score 5].

Table 2 Cost-effectiveness of alendronate therapy for 55-year-old women using GC with a BMD of 75% of YAM

Strategy	QALYs	Incremental QALYs	Cost (US$)	Incremental cost (US$)	ICER (US$ per QALY)
Without previous fracture, GC dose of 2.5 mg/day					
No therapy	19.518	–	9754	–	–
Alendronate therapy	19.632	0.115	13,167	3413	29,727
Without previous fracture, GC dose of 5 mg/day					
No therapy	19.455	–	11,114	–	–
Alendronate therapy	19.588	0.133	14,345	3231	24,278
Without previous fracture, GC dose of 10 mg/day					
No therapy	19.319	–	14,171	–	–
Alendronate therapy	19.486	0.167	16,877	2707	16,184
With previous fracture, GC dose of 2.5 mg/day					
No therapy	18.349	–	13,841	–	–
Alendronate therapy	18.502	0.153	16,831	2991	19,538
With previous fracture, GC dose of 5 mg/day					
No therapy	18.286	–	15,380	–	–
Alendronate therapy	18.457	0.172	18,139	2759	16,080
With previous fracture, GC dose of 10 mg/day					
No therapy	18.141	–	18,967	–	–
Alendronate therapy	18.347	0.206	21,221	2254	10,958

BMD, bone mineral density; *YAM*, young adult mean; *GC*, glucocorticoid; *QALY*, quality-adjusted life year; *ICER*, incremental cost-effectiveness ratio

Sensitivity analysis

The results of deterministic sensitivity analyses in the worst scenario (65-year-old women who had no previous fracture with a BMD of 80% of YAM and 2.5 mg/day of GC) were summarized by using a tornado diagram, as shown in Fig. 3. The annual discount rate for costs and health benefit had the strongest influence on the estimated ICER ($45,327 to $110,797 per QALY gained). Although the ICER was influenced by other parameters such as the utility reduction due to vertebral fracture ($51,508 to $95,573 per QALY gained), the RR of hip fracture by alendronate ($53,122 to $89,262 per QALY gained), the RR of vertebral fracture by alendronate ($55,971 to $89,173 per QALY gained) ,and so on, it remained more than $50,000 per QALY gained (Fig. 4).

Discussion

In this study, we estimated the cost-effectiveness of alendronate therapy relative to no therapy in patients with GIO from the perspective of the medical and nursing care system in Japan. Using a societal willingness to pay threshold of $50,000 per QALY gained, fracture prevention by alendronate therapy was cost-effective in 55-year-old women using GC with a BMD of 75% of YAM (ICER: $10,958 to $29,727 per QALY gained). We showed that lower age, lower BMD, higher dose of GC, and the presence of prior fracture were associated with a decrease in the ICER. Notably, alendronate therapy for secondary fracture prevention became cost-saving compared with no therapy in 45-year-old women using GC of 10 mg/day with a BMD of 70% of YAM (incremental cost was -$1359 per a patient). Our analysis showed that the treatment for postmenopausal Japanese women with GIO was likely to be cost-effective except for the limited patients who are at low risk for fracture. The current Japanese guideline recommends that patients using GC whose risk score based on the scoring algorithm is more than 3 point should be treated with pharmaceuticals [8]. However, our simulation indicated that drug therapy in patient aged 65 with no prior fracture, 80% of YAM and GC dose 2.5 or 5.0 mg/day [risk score 4 or 5] was less cost-effective (ICER = $55,778 or $66,791per QALY). The results of the deterministic sensitivity analysis in the worst scenario patients indicated that discount rate has a relatively strong impact on the ICER. In this study, we applied an annual discount rate of 2% for both

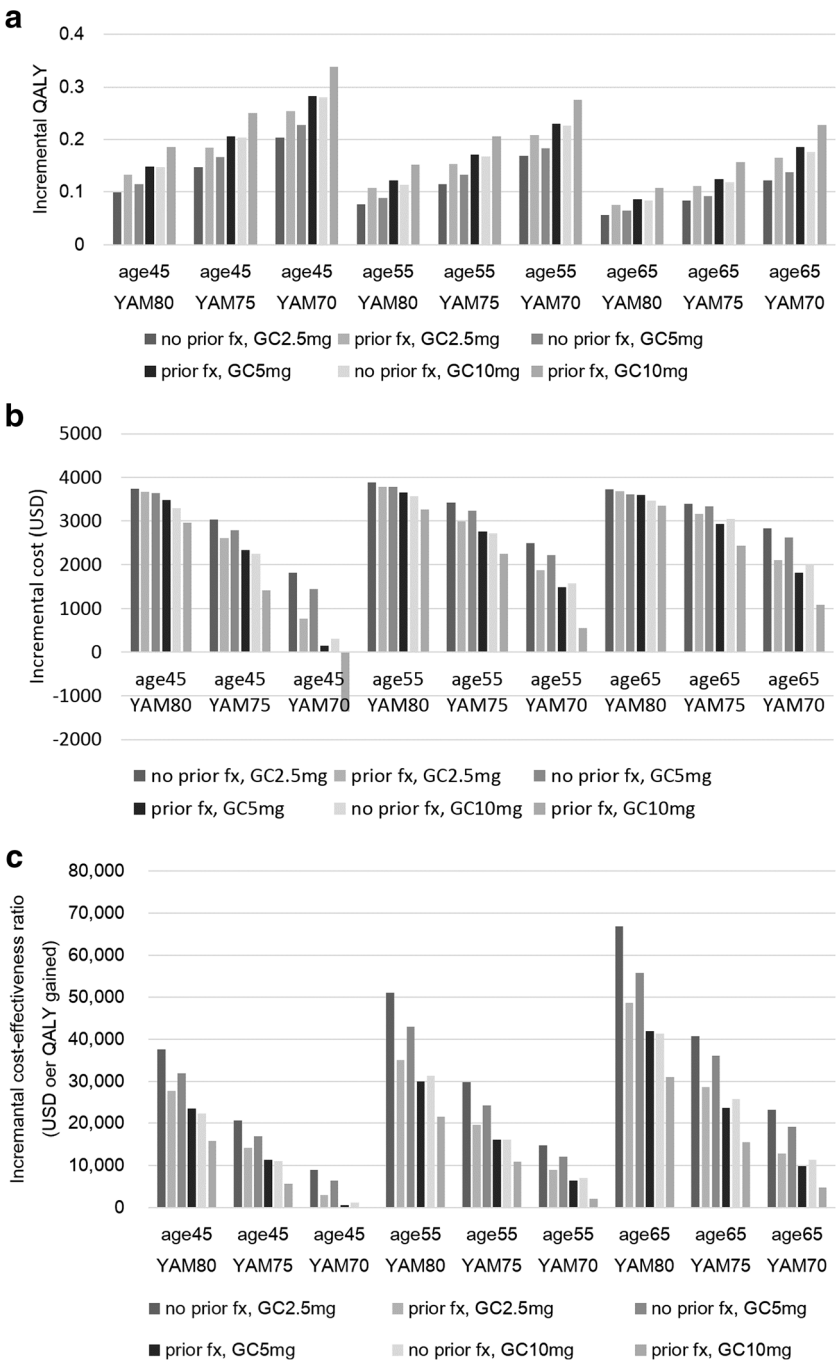

Fig. 2 Results of scenario analyses. **a** Incremental QALY, **b** incremental cost, **c** incremental cost-effectiveness ratio. QALY quality-adjusted life year

costs and QALYs, according to the guideline for economic evaluation of healthcare technologies in Japan [43]. However, if a decision maker were to use a higher value such as 5%, our results might change. Our results were robust to changes in other key input parameters, including variables that vary from country to country. These results suggested that the treatment indication for women with GIO and lower risk score based on the current Japanese clinical guidelines was unlikely to be cost-effective if society is willingness to pay $50,000 per additional QALY.

Previous economic evaluations have reported that pharmaceutical intervention reduced fracture rates and was cost-effective in patients with GIO [11, 13]. A study from the UK has estimated the ICER of bisphosphonate compared with no therapy in patients with GIO by age, T-score, and the presence of prior fracture [11]. It has been reported that the ICER ranged from £0 to £33,000 ($0 to $42,900: £1 = $1.3 was applied) per QALY or cost-saving to £12,000 ($0 to $15,600:£1 = $1.3 was applied) per QALY in patients

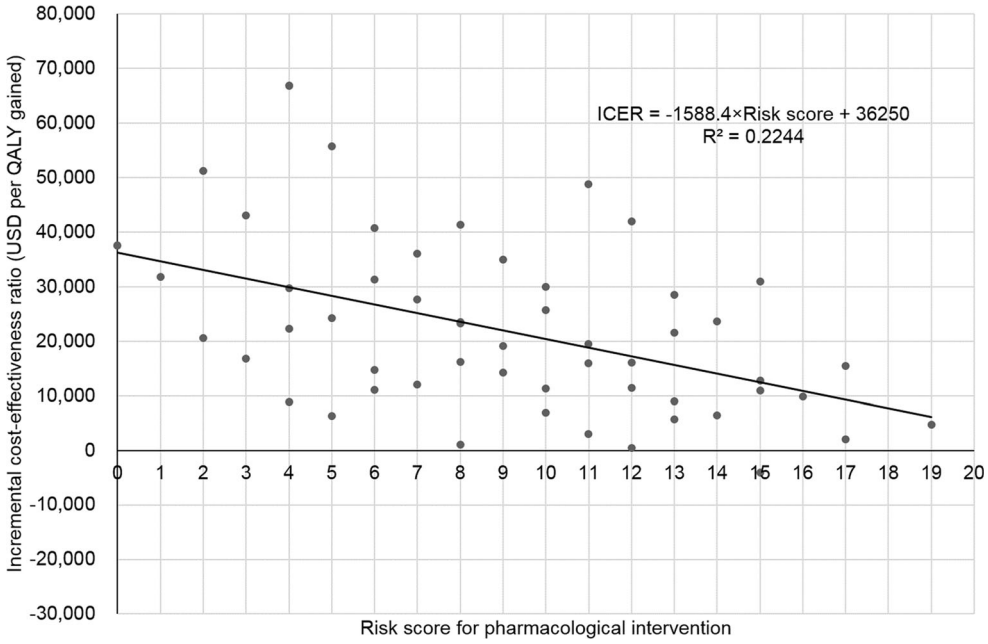

Fig. 3 Relationship between risk score and ICER

with T-score of − 2.5 who have no prior fracture or prior fracture, respectively [11].

In addition, a study from Sweden has reported that the ICER of teriparatide relative to no therapy in patients with GIO (T-score of − 2.5) ranged €3271 to €7330 per QALY ($3925 to $8796 per QALY:€1 = $1.2) [13]. In our analysis, alendronate therapy was cost-effective only in Japanese women with GIO except for the limited lower risk population. Although the present study differs from previous studies conducted in Western countries because of differences in

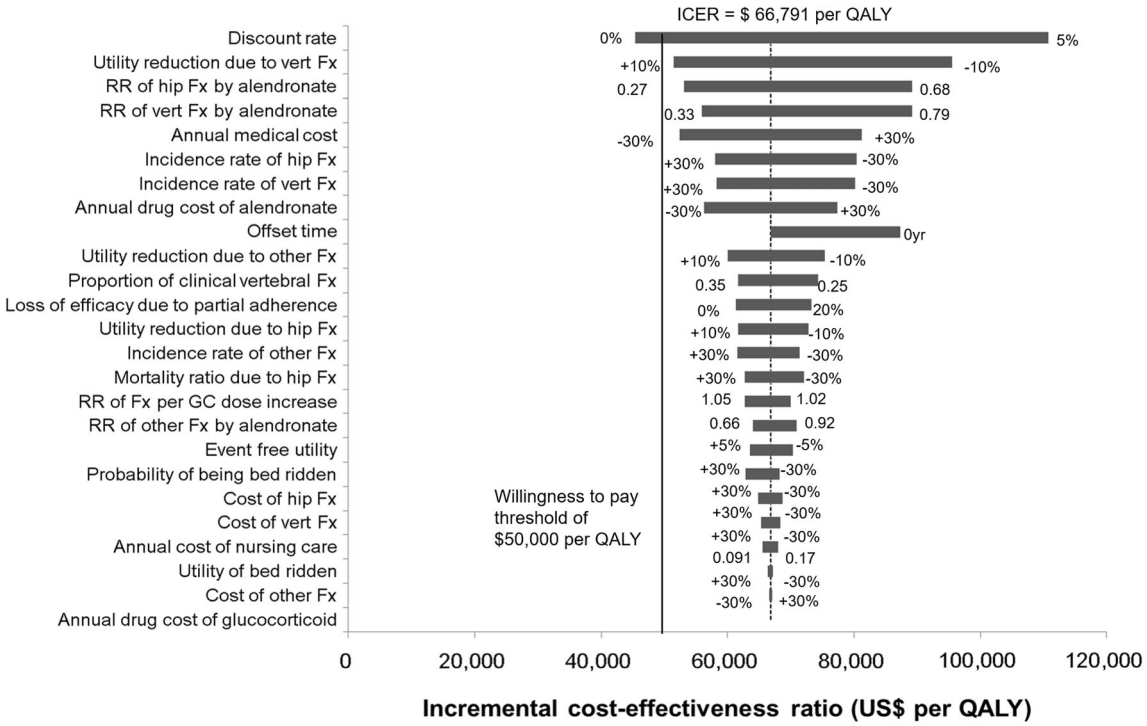

Fig. 4 Results of deterministic sensitivity analyses in the worst scenario. Sixty-five-year-old women who had no previous fracture with a BMD of 80% of YAM and 2.5 mg/day of GC. BMD bone mineral density, YAM young adult mean, GC glucocorticoid

healthcare systems, epidemiological characteristics, and parameter settings, our results are consistent with those observed in the previous studies [18–21].

The novelty of our present study was its clarification of the cost-effectiveness of bisphosphonate therapy in Japanese women with GIO who have different combinations of age, BMD and clinical risk factors. These findings support healthcare decisions such as the development of treatment guideline in Japan. Also, the application of our results should be considered, especially in other Asian countries, and may provide an important rationale for the development of treatment program in patients with GIO in terms of cost-effectiveness. Although the fracture risk assessment tool (FRAX) developed by the World Health Organization (WHO) is considered to be valid and reliable, its algorithm is not open to the public and was thus unavailable for our simulation model [44]. Therefore, we developed risk equations for age- and femoral neck BMD-specific fracture incidence rates by using epidemiological data from the Japanese population and combined these with the state transition model. In this study, major osteoporotic fractures such as hip fractures, clinical vertebral fractures, proximal humeral fractures, and wrist fractures were modeled. Most of the estimations for the model input parameters, such as costs, utilities, and transition probabilities, were derived from data unique to Japan. The validity of our simulation model was verified by comparing the predicted 10-year osteoporotic fracture probabilities in our model with those derived from the FRAX. The probabilities of hip fracture and major fracture in our model were similar to those of the FRAX [14–17]. These findings support the validity of our model in this economic evaluation.

Our study has several limitations. Firstly, our model may oversimplify the multiple fracture event. For example, we assumed that both patients with hip fracture history who experienced a vertebral fracture and those who experienced hip and vertebral fracture moved to the health state of "post vertebral and hip fracture" in the next cycle. Although the risk of having multiple fracture events was quite small, this assumption might oversimplify the prognosis for patients who experienced multiple fractures and influenced on the results. The structural uncertainty of the model should be examined by using the detail data on patients who experienced multiple fractures in the future study. Secondly, there were no data on the disutility due to multiple fractures in Japan. Therefore, we assumed that disutility due to osteoporotic fracture and used the multiplicative approach to estimate the disutility due to multiple fractures. Although the sensitivity analysis showed the influence of utility parameters on the results was limited, our approach might overestimate the disutility for multiple fractures. Further research was needed to the relation between the health-related QOL and multiple fractures. Finally, the cost-effectiveness of alendronate therapy in patients with GIO varies depending on the willingness to pay thresholds for each additional QALY gained. Although the willingness to pay thresholds of $50,000 per QALY and £20,000 to £30,000 per QALY have commonly been used as an acceptable level in the US and UK, these values vary among countries [45–47] has proposed a willingness to pay threshold of JPY6,350,000 to JPY6,700,000 ($52,917 to $55,833) per QALY gained, and the cost-effective intervention thresholds for osteopenia may vary depending on the acceptability level of the ICER.

In conclusion, the cost-effectiveness of preventive alendronate therapy for postmenopausal women with GIO is sensitive to age, BMD, GC dose, and the presence of previous fracture. Our analysis suggested that the treatment indication for postmenopausal women with osteopenia or osteoporosis using GC in the current Japanese clinical guidelines is likely to be cost-effective except for the limited patients who are at low risk for fracture. These findings should aid in healthcare decisions regarding the development of treatment programs in Japan.

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Compliance with ethical standards

Conflict of interest KM has received speaker honoraria, consulting fees, or reimbursement for attending meetings from Asahi Kasei Pharma Corp., Amgen Astellas BioPharma K.K., Astellas Pharma Europe Ltd., Sumitomo Dainippon Pharma Co., Ltd., and Takeda Pharmaceutical Co., Ltd.. HF has received speaker honoraria, consulting fees, or reimbursement for attending meetings from Astellas Pharma Ltd., Nippon Becton Dickinson Company, Ltd., MSD, Eli Lilly Japan, Abbott, and KYORIN Pharmaceutical Co., Ltd.

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