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Clinical Outcomes and Cost-Effectiveness of Osteoporosis Screening With Dual-Energy X-ray Absorptiometry

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Objective: This study aimed to evaluate the clinical outcomes and cost-effectiveness of dual-energy X-ray absorptiometry (DXA) for osteoporosis screening.

Materials and Methods: Eligible patients who had and had not undergone DXA screening were identified from among those aged 50 years or older at Kaohsiung Veterans General Hospital, Taiwan. Age, sex, screening year (index year), and Charlson comorbidity index of the DXA and non-DXA groups were matched using inverse probability of treatment weighting (IPTW) for propensity score analysis. For cost-effectiveness analysis, a societal perspective, 1-year cycle length, 20-year time horizon, and discount rate of 2% per year for both effectiveness and costs were adopted in the incremental cost-effectiveness (ICER) model.

Results: The outcome analysis included 10337 patients (female:male, 63.8%:36.2%) who were screened for osteoporosis in southern Taiwan between January 1, 2012, and December 31, 2021. The DXA group had significantly better outcomes than the non-DXA group in terms of fragility fractures (7.6% vs. 12.5%, $P < 0.001$) and mortality (0.6% vs. 4.3%, $P < 0.001$). The DXA screening strategy gained an ICER of US$ -2794 per quality-adjusted life year (QALY) relative to the non-DXA at the willingness-to-pay threshold of US$ 33004 (Taiwan's per capita gross domestic product). The ICER after stratifying by ages of 50–59, 60–69, 70–79, and ≥ 80 years were US$ -17815, US$ -26862, US$ -28981, and US$ -34816 per QALY, respectively.

Conclusion: Using DXA to screen adults aged 50 years or older for osteoporosis resulted in a reduced incidence of fragility fractures, lower mortality rate, and reduced total costs. Screening for osteoporosis is a cost-saving strategy and its effectiveness increases with age. However, caution is needed when generalizing these cost-effectiveness results to all older populations because the study population consisted mainly of women.

Keywords: Osteoporosis; Dual-energy X-ray absorptiometry (DXA); Screening; Cost-saving

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INTRODUCTION

International studies have applied different criteria and evaluated different screening methods for the cost-effectiveness of osteoporosis screening [1-7]. However, the prevalence of osteoporosis, incidence of fractures, demographics, and medical insurance systems in other countries differ from those in Taiwan; therefore, the results of international studies are not directly generalizable to Taiwan. Most previous relevant studies have focused on cost-effectiveness analysis of osteoporosis screening for older adults or patients with fragility fractures [3-8], and only a few studies have considered a relatively newer drug, such as denosumab, which often lacks real-world data or includes populations that are fracture naïve or younger than 65. Younger men have a lower incidence of osteoporosis-related fractures, which contributes to the perception of a reduced priority for screening in this population. Considering that fragility fractures can still occur in this demographic, we aimed to shed light on the potential impact of screening in this group and provide further insights to better inform clinicians' healthcare decisions. Therefore, this study aimed to investigate the incidence of fragility fractures, mortality rate, and cost-effectiveness of dual-energy X-ray absorptiometry (DXA) screening among people aged 50 years or older using propensity score (PS) analysis and the decision tree and Markov models.

MATERIALS AND METHODS

This study was reviewed and approved by the Institutional Review Board of the Kaohsiung Veterans General Hospital (KVGH) (KSVGH21-CT3-21 and KSVGH23-CT8-08). The study used anonymized data, waiving the need for informed consent.

Study Population

The study population consisted of patients aged 50 years or older who were identified from the de-identified electronic medical records of KVGH between January 1, 2012, and December 31, 2021. Patients were divided into two groups: the DXA group, which included individuals who underwent DXA screening, and the non-DXA group, which served as controls. The control group was later matched with the DXA group by age, sex, index year, and Charlson comorbidity index (CCI) using PS for between-group comparisons (see Statistical Analysis section). In the DXA group, patients with unavailable T-score records, which were used to define osteoporosis were excluded. Among both groups, those with missing values, who had sustained traumatic fractures or undergone revision of hip prosthesis (according to the International Classification of Diseases, Ninth [ICD-9-CM] and Tenth [ICD-10-CM] Revisions' diagnostic/procedure codes [ICD-9-CM: E810-E819, E881-E883, E884.1, 816.1, or 79.3X or the ICD-10-CM]), who had sustained fragility fractures before DXA (ICD-9-CM codes 820.X, 805.2–805.5, 806.2–806.5, 812. xx–814.xx, 79.15, 79.25, 79.35, 81.53, 81.62, 81.63, 81.64, 81.65, 81.66 or the ICD-10-CM) (Supplementary Table 1), and who used medications for osteoporosis (i.e., osteoporosis had been diagnosed prior to the start of the study) were excluded.

Clinical Outcomes

The clinical outcomes assessed in this study included fracture and mortality rates. The fracture rate was determined by comparing the proportion of individuals who experienced fractures in the DXA group with those in the non-DXA group. The mortality rate was calculated by comparing the proportion of individuals who died in the non-DXA and DXA groups.

Cost-effectiveness Analysis

The researchers constructed the Markov model used in this study based on domestic clinical experience and with reference to the relevant literature (Fig. 1) [9]. Our study combined Taiwan-specific data and relevant international literature to offer a comprehensive perspective on the screening and management of osteoporosis, hoping to balance specific domestic data with broader implications. The model classified the patient status into three categories: fracture, no fracture, and death. Based on domestic clinical experience, we set one cycle as one year, and the research time horizon was 20 years. The Markov model assumed three scenarios: the patient never had any fracture and did not sustain fractures, the patient sustained a fragility fracture and had a refracture, and the patient sustained a fragility fracture and later died. In each cycle, the status of the patient could be transferred directly to the death state; however, if the patient was transferred to the death stage, they would remain in this stage permanently and no further state transfers would occur.

Statistical Analysis

Before conducting the inferential statistical analysis,

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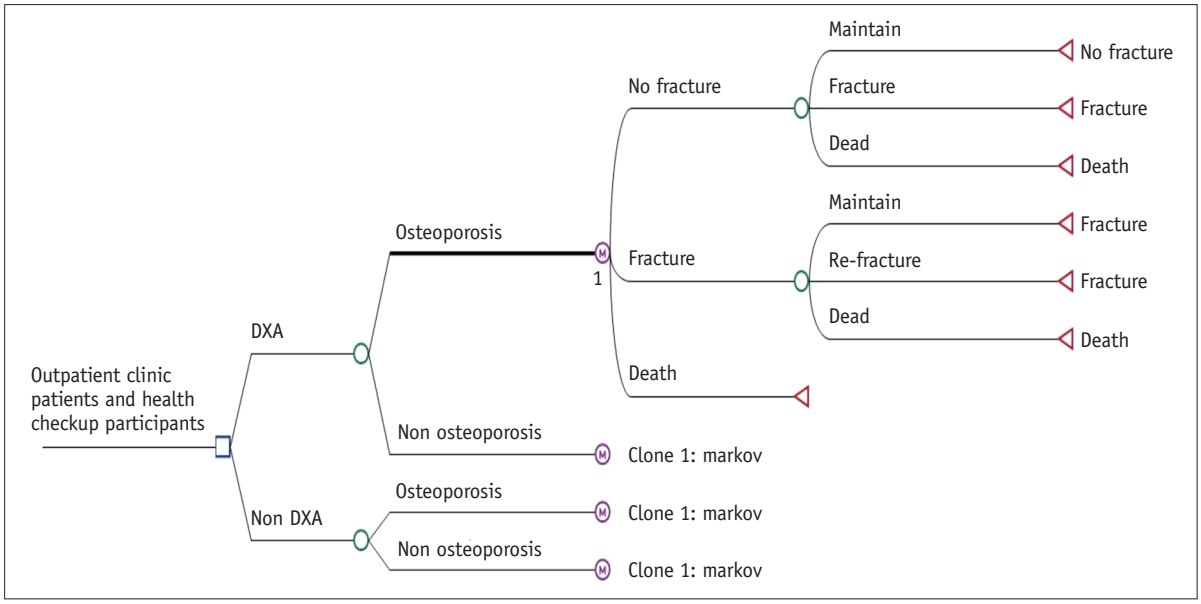

Fig. 1. Markov decision model for cost-utility analysis of the DXA and non-DXA groups for patients with osteoporosis aged ≥ 50 years.
DXA = dual-energy X-ray absorptiometry

we employed inverse probability of treatment weighting (IPTW) to mitigate selection bias by aligning the study characteristics. Weights were calculated by taking the inverse of PS, which denote the likelihood of receiving treatment based on the observed study characteristics. A logistic regression model was employed to compute the PS for each individual, using treatment groups as the dependent variable and baseline study characteristics (age, sex, index year, and CCI) as independent variables. According to established guidelines, a balanced distribution of study characteristics was verified in the weighted sample, with standardized differences below 10% [10]. The IPTW PS method assigned patients in the DXA group a weight of 1/(propensity score) and those in the non-DXA group a weight of 1/(1–propensity score) [11,12]. The IPTW method has found numerous applications in various diseases [13,14].

We built a Markov decision model by predetermining the utility value, transfer rate value, cost, and benefit of each state; simulating the patient's state transition during treatment; summing the results of each stage; and finally using the decision tree results to determine the most cost-effective option (Table 1). All the parameters of the Markov model, including the probabilities of events, costs, and utilities, were extracted from the KVGH database and previous studies [8,15-31]. The indirect societal costs were calculated as period x average man-hours x production cost x average participation rate x percentage of patients aged < 65 years old [32]. In addition, EuroQol five dimensions questionnaire (EQ-5D) scores were converted into utility values using the time trade-off formula of the Taiwanese coefficient [33]. Additionally, each cost structure was converted to its present value in 2021, according to Taiwan's consumer price index, and the cost and quality-adjusted life years (QALYs) in the decision-making model were discounted at a rate of 2.0%. Apart from considering the local conditions of Taiwan, the choice of discount rate is crucial, as higher rates tend to result in more conservative evaluations, reducing the impact of future benefits and potentially making interventions appear less cost-effective. Conversely, a lower discount rate, such as 2%, places increased emphasis on future outcomes and may lead to a more favorable assessment of long-term cost-effectiveness. Willingness-to-pay (WTP) was set at the average gross domestic product per capita in 2021 (US$ 33004).

A one-way deterministic sensitivity analysis was performed with values that were within two standard deviations from those of previous studies and clinical observations. A tornado diagram was used to visualize the results. Probabilistic sensitivity analysis was performed using the statistical properties of each parameter (continuous or categorical variables) to select the appropriate probability distribution.

Descriptive and PS analyses were performed using IBM SPSS version 23 (IBM Corp.). Cost-effectiveness acceptability (CEA) and sensitivity analyses were performed using TreeAge Pro Healthcare 2021 (https://www.treeage.com/software-downloads/treeage-pro-2021-r1-healthcare/). Statistical

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Table 1. Probabilities, costs, and utilities of clinical and outcome events in the transition model

Probability strategy	Group	Status	Value	Distribution	References
DXA	OP	Still no fracture	53.5%		Present study
		From no fracture to fracture	30.5%	9.0%–26.0%	Present study [15,16]
		From no fracture to death	16.0%	6.6%–28.0%	[16,17]
		Still fracture	60.0%		Present study
		From fracture to re-fracture	7.0%	3.5%–8.5%	[18,19]
		From fracture to death	33.0%	16.8%–44.9%	[20,21]
	No OP	Still no fracture	97.0%		Present study
		From no fracture to fracture	2.3%	2.1%–2.3%	Present study
		From no fracture to death	0.7%	7.3%–50.8%	[22,23]
		Still fracture	94.1%		
		From fracture to re-fracture	2.4%	1.3%–2.6%	[24]
		From fracture to death	3.5%	3.1%–4.6%	[24]
Non-DXA	OP	Still no fracture	53.5%		Present study
		From no fracture to fracture	30.5%	9.0%–26.0%	Present study [15,25]
		From no fracture to death	16.0%	6.6%–28.0%	[16,17]
		Still fracture	60.0%		Present study
		From fracture to re-fracture	7.0%	3.5%–8.5%	[18,19]
		From fracture to death	33.0%	16.8%–44.9%	[20,21]
	No OP	Still no fracture	97.0%		Present study
		From no fracture to fracture	2.3%	2.1%–2.3%	Present study
		From no fracture to death	0.7%	7.3%–50.8%	[22,23]
		Still fracture	94.1%		Present study
		From fracture to re-fracture	2.4%	1.3%–2.6%	[24]
		From fracture to death	3.5%	3.1%–4.6%	[24]

Cost strategy	Group	Status	Direct medical cost, US$	Direct non-medical cost, US$	Indirect societal cost, US$	Total costs, US$	References
DXA	OP	No fracture	328		223	551	Present study and [8,18]
		Fracture	343	3370	325	4038	
	No OP	No fracture	339		346	685	
		Fracture	303	3370	290	3963	
Non-DXA	OP	No fracture	313		182	495	Present study and [8,18]
		Fracture	460	3370	372	4202	
	No OP	No fracture	239		77	316	
		Fracture	809	3370	805	4984	

Utility strategy	Group	Status	Values	Distribution	References
DXA	OP	No fracture	0.76	0.66–0.82	[26]
		Fracture	0.73	0.48–0.98	[27]
	No OP	No fracture	0.91	0.77–1.00	[28]
		Fracture	0.56	0.51–0.60	[29]
Non-DXA	OP	No fracture	0.66	0.66–0.76	[26]
		Fracture	0.73	0.48–0.98	[27]
	No OP	No fracture	0.82	0.81–0.83	[28,30]
		Fracture	0.51	0.51–0.60	[31]

DXA = dual-energy X-ray absorptiometry, OP = osteoporosis

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significance was set at $\alpha = 0.05$.

RESULTS

Study Population Characteristics

Of the 10337 patients (female:male, 63.8%:36.2%) included in this study, 2673 (25.9%) underwent DXA and 7664 (74.1%) did not (Fig. 2). After IPTW matching, the standardized differences in all the covariables were < 10.0% (Table 2).

Clinical Outcomes

As shown in Table 3, the fracture rate in the DXA group was significantly lower than that in the non-DXA group (7.6%

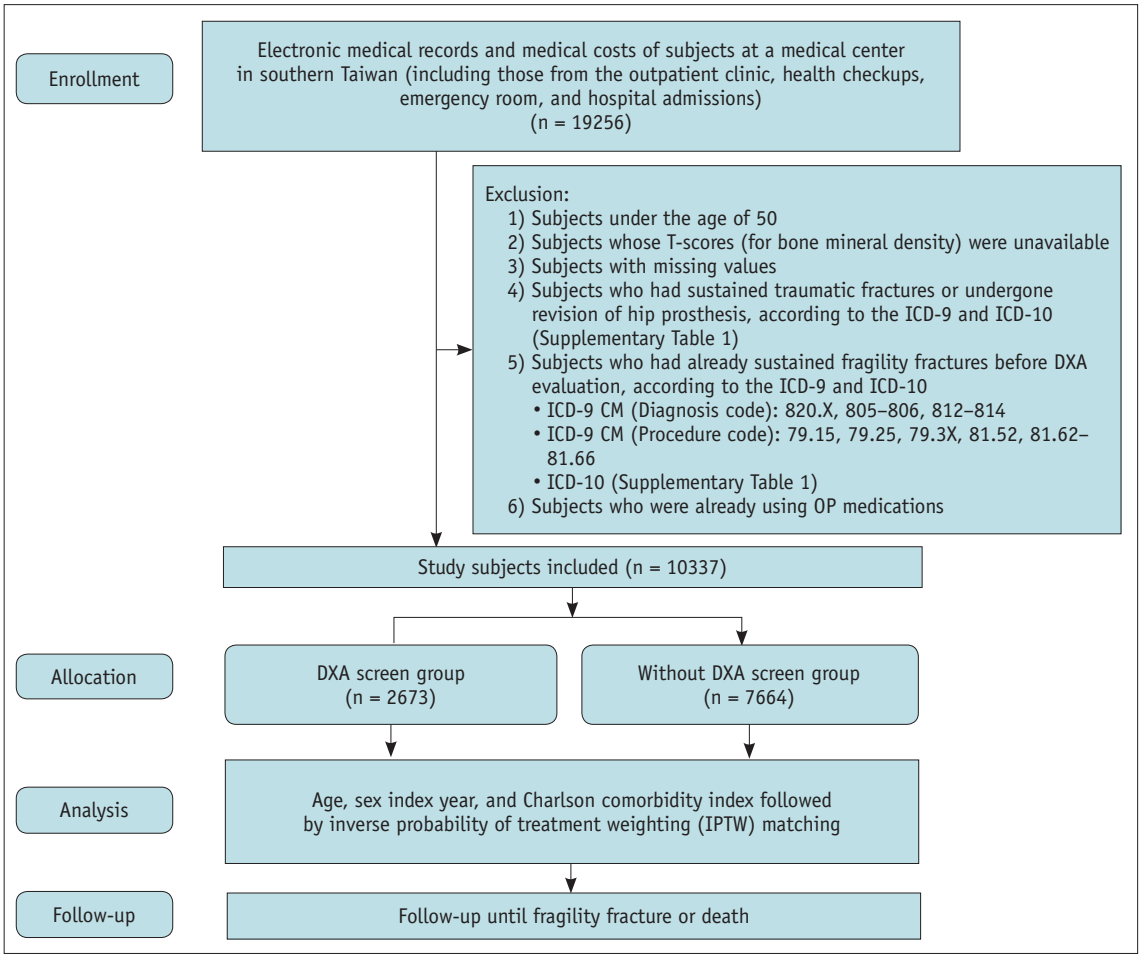

Fig. 2. Flowchart of data collection. DXA = dual-energy X-ray absorptiometry, ICD-9 CM = International Classification of Diseases, 9th revision, clinical modification, ICD-10 CM = International Classification of Diseases, 10th revision, clinical modification, OP = osteoporosis

Table 2. Descriptive statistics of study subjects before and after IPTW

Variables	Before IPTW				After IPTW			
	Total* (n = 10337)	DXA* (n = 2673)	Non-DXA* (n = 7664)	Standardized difference, %	Total*	DXA*	Non-DXA*	Standardized difference, %
Sex				1.3				-2.5
Male	3746 (36.2)	980 (36.7)	2766 (36.1)		36.1	35.5	36.7	
Female	6591 (63.8)	1693 (63.3)	4898 (63.9)		63.9	64.5	63.3	
Age, yr	70.39 ± 11.32	64.10 ± 9.52	72.58 ± 11.08	-82.1	70.10 ± 11.32	70.02 ± 11.15	70.18 ± 11.50	-1.4
Index, yr	11.13 ± 3.00	11.33 ± 2.39	11.06 ± 3.19	9.3	11.22 ± 2.81	11.29 ± 2.40	11.17 ± 3.17	4.1
CCI	1.91 ± 2.22	1.43 ± 1.81	2.08 ± 2.33	-31.2	1.95 ± 2.30	2.00 ± 2.37	1.91 ± 2.23	3.9

*Values are expressed as mean ± standard deviation or n (%).
IPTW = inverse probability of treatment weighting, DXA = dual-energy X-ray absorptiometry, CCI = Charlson comorbidity index

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vs. 12.5%, respectively) ($P < 0.001$). The mortality rate was significantly lower in the DXA group than in the non-DXA group (0.6% vs. 4.3%, respectively) ($P < 0.001$).

Cost-Utility Analysis

The constructed Markov decision-making model is shown in Figure 1. The optimal path selection for the decision analysis was analyzed using the rollback method, which was used to backtrack the respective total costs and treatment results caused by choosing different strategies. The results of the cost-effectiveness analyses for the DXA and non-DXA screening groups are shown in Table 4. Over the 20-year time horizon, the average total costs and QALYs gained in the DXA group were US$ 15254 and 9.592, respectively, whereas those in the non-DXA group were US$ 25427 and 5.946, respectively, with an incremental cost-effectiveness (ICER) of US$ -2794/QALYs. This shows that the addition of DXA screening in patients with osteoporosis is more cost-effective than non-DXA screening.

The cost-utility analyses of the DXA and non-DXA groups are shown in Supplementary Figure 1. The DXA group was non-dominant, whereas the non-DXA group was dominant. As presented in Supplementary Figure 2, as WTP increased, the net monetary benefit (NMB) of both the DXA and non-DXA groups increased; when WTP reached US$ 32052 (ICER), the NMB of the DXA group was higher than that of the non-DXA group. Additionally, the CEA curve for varying WTP values per QALY is shown in Supplementary Figure 3 for varying values of WTP per QALY. Based on the CEA curve, 100.0% of the patients in the DXA group were more cost-effective than those in the non-DXA group.

Sensitivity analysis revealed ICER after 1000 random samples using a scatter diagram (Fig. 3). All values were located in the fourth quadrant, which indicates that, compared with the non-DXA group, the marginal treatment effects (QALYs) tended to increase when the total marginal costs in the DXA group decreased. Supplementary Figure 4 shows that the most influential parameter was the QALYs gained by the patients without osteoporosis or fractures in the DXA group (0.63–1), followed by the probability of osteoporosis in the

Table 3. Fracture and mortality rates in the DXA and non-DXA group within 1 year

	Non-DXA group (n = 7664)	DXA group (n = 2673)	*P*
Fracture			< 0.001
No	6705 (87.5)	2471 (92.4)	
Yes	959 (12.5)	202 (7.6)	
Mortality			< 0.001
Alive	7333 (95.7)	2657 (99.4)	
Death	331 (4.3)	16 (0.6)	

Values are expressed as n (%).
DXA = dual-energy X-ray absorptiometry

Table 4. Cost-effectiveness analysis of the DXA and non-DXA groups by different age and sex

Group	Strategy	Cost, US$	Incremental cost, US$	QALYs	Incremental QALYs	ICER
1 year (per cycle)	DXA	833		0.856		
	Non-DXA	2457	1624	0.678	-0.178	-9111
20 years (time horizon)	DXA	15254		9.592		
	Non-DXA	25427	10174	5.946	-3.646	-2794
Age						
50–59 yr	DXA	1238		0.820		
	Non-DXA	2765	1527	0.735	-0.085	-17815
60–69 yr	DXA	1063		0.793		
	Non-DXA	2525	1462	0.739	-0.058	-26862
70–79 yr	DXA	961		0.752		
	Non-DXA	2387	1426	0.703	-0.049	-28981
≥ 80 yr	DXA	889		0.715		
	Non-DXA	2244	1355	0.677	-0.038	-34816
Sex						
Male	DXA	1093		0.818		
	Non-DXA	2708	1615	0.840	0.022	74761
Female	DXA	1083		0.752		
	Non-DXA	2499	1416	0.703	-0.049	-26736

DXA = dual-energy X-ray absorptiometry, QALYs = quality-adjusted life-years, ICER = incremental cost-effectiveness

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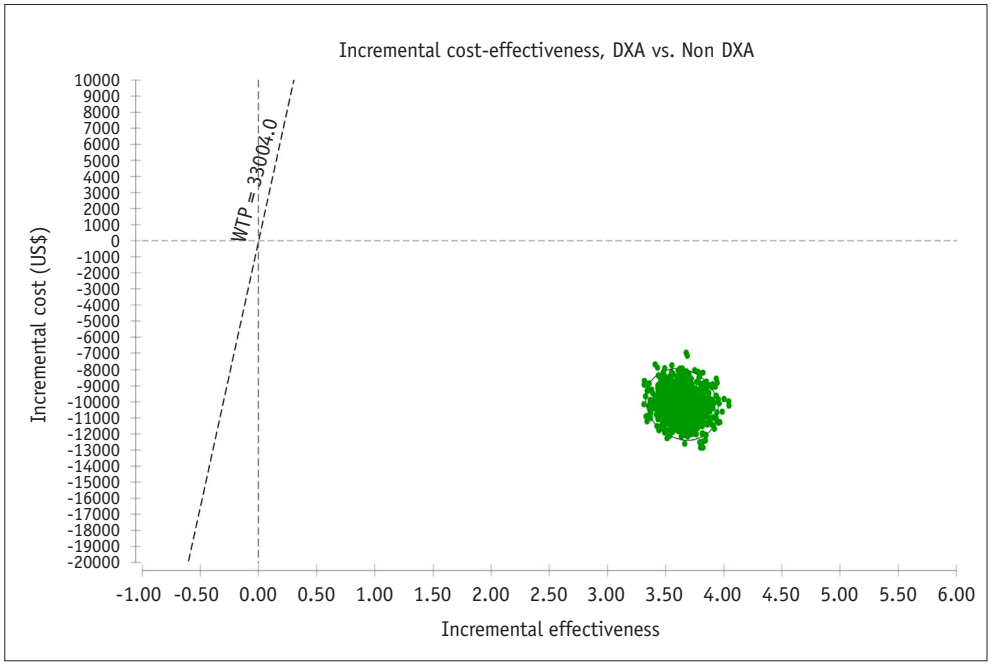

Fig. 3. Incremental cost-effectiveness scatter plot of the DXA and non-DXA groups for patients with osteoporosis aged ≥ 50 years. DXA = dual-energy X-ray absorptiometry, WTP = willingness-to-pay

non-DXA group (0.376–0.564), the probability of fragility fractures causing death in the non-DXA group (0.168–0.449), the medical costs of patients without osteoporosis and fractures in the non-DXA group (US$ 3987–US$ 5980), and the probability of osteoporosis in the DXA group (0.267–0.401).

CEA Stratified by Age and Sex

The prevalence of osteoporosis and fracture rate, cost, and utility values differed according to age and sex. Therefore, a subgroup cost-effectiveness analysis was performed based on age and sex (Table 4). Regardless of age, patients in the DXA group had lower average total costs than those in the non-DXA group and older patients had lower average total costs. The ICERs were negative regardless of age, and older patients had lower ICERs than younger patients. This indicates that screening for osteoporosis at an older age can reduce average total costs. Sex group analysis demonstrated that the QALYs of men were higher than those of women, regardless of the group. Regardless of sex, patients in the non-DXA group incurred higher average total costs than those in the DXA group. The QALYs of men in the DXA group were lower than those in the non-DXA group, and the ICER among men was US$ 74761/QALYs, indicating poor cost-effectiveness. The QALYs of women in the DXA group were higher than those of women in the non-DXA group, and the ICER was US$ -26736/QALYs, indicating that screening was cost-effective for women.

Economic Burdens

According to the annual report of the National Health Insurance Prescription and Detail Files published by the Ministry of Health and Welfare in Taiwan, in 2019, only 1.2% of the high-risk population underwent DXA using a designated payment code. Kung et al. [34] conducted questionnaire surveys of patients with fractures in China, Taiwan, Hong Kong, South Korea, Singapore, Malaysia, and Thailand and discovered that 28.2% of them were screened for osteoporosis before experiencing fractures. Based on the above information, the economic burdens of the DXA screening were US$ -182966466 and US$ -4299712762, respectively (Supplementary Table 2).

DISCUSSION

The DXA group showed better outcomes than the non-DXA group, with lower rates of fragility fractures and mortality. The DXA screening strategy was cost-effective, with an ICER of US$ -2794 per QALY, relative to the non-DXA strategy. Stratification of the results by age group revealed that the cost-effectiveness of screening increased with age. This study has several strengths. First, we used real-world data

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on osteoporosis-related costs and fracture probabilities. Few Taiwanese studies have included CEA levels in DXA screening for osteoporosis. Second, this study used the IPTW method, which reduced selection bias. Third, this study accounted for direct medical costs, direct nonmedical costs, indirect societal costs, cost-effectiveness, and clinical outcomes. Fourth, this study analyzed the economic burden of DXA screening.

In a 20-year timeframe, this study found that DXA screening resulted in lower fracture rates, reduced mortality, and decreased overall costs compared with no DXA screening. These findings are consistent with those of previous studies, including Turner et al. [7] and randomized trials involving older women [35]. Pisu et al. [30] and Ito et al. [4] found similar benefits of DXA in reducing fracture rates, whereas Ramachandran et al. [36] observed reduced mortality rates with DXA. However, some studies, like the one by Shepstone et al. [2], had different results, possibly due to variations in study design and the use of the Fracture Risk Assessment Tool (FRAX®) in identifying high-risk groups. Similarly, in the present study, the mortality rate was lower in the DXA group than in the non-DXA group.

The results of the present study also indicate that screening people aged 50 years or older for osteoporosis can reduce the total costs. These findings support those of Pisu et al. [30], who reported that using biomechanical computed tomography analysis or DXA to screen people for osteoporosis reduced total costs. Shepstone et al. [2] conducted a randomized controlled trial involving women aged 70–85 years from seven regional family medicine clinics in the United Kingdom and determined that patients who were screened saved an average of £ 286. This result supports that of the present study, in which screened patients saved an average of US$ 2794. Yoshimura et al. [5] conducted a study involving Japanese women aged 50 years or older and discovered that screening older people was cost-effective and that DXA could reduce the total medical costs of Japanese women aged 60 years or older. Similarly, Si et al. [26] discovered that screening individuals aged 65 years or older could reduce total medical costs.

Age group analysis demonstrated that screening older people resulted in reductions in total costs and was cost-effective. These findings support those of previous studies that used the Markov model and discovered that screening women aged 65 years or older for osteoporosis and treating them with bisphosphonates were highly cost-effective [3,6,22]. The ICERs of women aged 65 and 75 years were US$ 43000 and US$ 5600, respectively; screening women aged 85 years or older could reduce costs, and screening older people resulted in a greater total cost reduction [23]. Nayak et al. [6] discovered that DXA is cost-effective for American men aged 50 years or older. This finding conflicts with those of the present study, possibly because their study accounted for the interval between DXA and administration of the Osteoporosis Self-Assessment Tool (OST) and the benefits of repeated screening. In addition, they calculated the fracture rate under the assumption that the rate of adherence to alendronate treatment for five years was 50%, whereas the present study determined the fracture rates according to real data from medical records that contained information regarding the patients' use of alendronate and other drugs for treating osteoporosis. In their study, the fracture rate (37.0%) was higher than in the present study (7.6% and 12.5% in the DXA and non-DXA groups, respectively), suggesting that their study may have overestimated the benefits of screening. Schousboe et al. [3] demonstrated that for men aged 80 years or older or for men aged 65 years or older with a history of fractures, DXA followed by bisphosphonate treatment was cost-effective. This finding also conflicts with those of the present study, possibly because the present study did not compare the cost-effectiveness of screening in men of different age groups and excluded those with a history of fractures.

After screening for osteoporosis, it is crucial to provide treatment to the patients to effectively reduce the incidence of fractures. However, the proportion of patients who receive treatment after being diagnosed with osteoporosis is relatively low. A systematic literature review found that adherence to anti-osteoporosis medications is poor and suboptimal, ranging from 34.0% to 75.0% in the first year of treatment [25]. The inadequate treatment of osteoporosis can be attributed to patients and physicians. Therefore, future studies should consider incorporating medication use and adherence rates as analytical factors to effectively address the challenges of osteoporosis treatment.

This study has some limitations. First, this study did not evaluate the cost-effectiveness of using risk assessment questionnaires, such as the OST or FRAX®, before DXA, because using these questionnaires increases the burdens placed on clinical physicians. Second, the frequency of DXA use affected the research results and CEA levels; therefore, the analyses performed in this study should be repeated in a prospective study. Third, the results of our study indicate that screening women for osteoporosis is cost-effective,

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whereas screening men may not be as cost-effective, possibly because of the lower probability of fragility fractures in younger men. We performed a subgroup analysis based on age and sex; however, we lacked sufficient data for men and did not perform an age-stratified subgroup analysis for male participants. Nevertheless, the results offer substantial room for improvement in fracture prevention by focusing on individualized screening strategies that involve conducting comprehensive risk factor analyses for younger men rather than solely relying on age- or sex-based differentiation. Fourth, we could not determine whether the individuals in this study underwent DXA screening at external medical facilities. In future, it would be valuable to incorporate the National Health Insurance database to extend this research and perform relevant validations. Finally, this study did not account for rib fractures because the incidence of rib fractures is lower than that of other types of fractures, and the effect of rib fractures on the cost-effectiveness of osteoporosis screening is likely minimal.

In conclusion, using DXA to screen adults aged 50 years or older for osteoporosis resulted in a reduced incidence of fragility fractures, lower mortality rate, and reduced total costs. Screening for osteoporosis is a cost-saving strategy and its effectiveness increases with age. However, we should be cautious in generalizing these cost-effectiveness results of DXA screening to all older populations because our findings were obtained mainly in women.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.0555.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

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