AN OPTIMAL AND COST-EFFECTIVE APPROACH TO MANAGING OSTEOPOROSIS AND PREVENTING FRACTURES IN SINGAPORE

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I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

Tang-Ching Lau

ACKNOWLEDGEMENT OF AUTHORSHIP

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications

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GLOSSARY OF ABBREVIATIONS AND ACRONYMS

AAPC	Average Annual Percentage Change
AP	Asia-Pacific
AUC	Area Under ROC curve
BMD	Bone Mineral Density
BOD	Burden of Disease
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
COI	Cost-of-Illness
CP	Chronic Prostatitis
CPI	Consumer Price Index
CUA	Cost-Utility Analysis
CI	Confidence Interval
DALY	Disability Adjusted Life Years
DALE	Disability-Adjusted Life Expectancy
DFLE	Disability-Free Life Expectancy
DXA	Dual Energy X-ray Absorptiometry
EQ-5D	EuroQol
FCA	Friction Cost Approach
GDP	Gross Domestic Product
HALE	Health Life Expectancy
HCA	Human Capital Approach
HRQoL	Health-Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IOF	International Osteoporosis Foundation
IQR	Interquartile Range
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MID	Minimally Important Difference
MLR	Multiple Linear Regression
NIH	National Institutes of Health
OPTIMAL	Osteoporosis Patient Targeted and Integrated Management for Active Living
QoL	Quality of Life
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SD	Standard Deviation
SGD	Singapore Dollar
SF-6D	Short Form 6D
SF-36	Short Form 36
WTP	Willingness-to-Pay
YHL	Years of Healthy Life

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EXECUTIVE SUMMARY

In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. In the next 50 years, more than half of all hip fractures are projected to occur in Asia (1, 2). Osteoporosis is likely to increase as the population of Singapore is aging rapidly (3-5). In 1990, only 6% of the population in Singapore was above the age of 65, but by 2030, this figure is projected to rise to 25%(6). Osteoporotic fractures at the hip, wrist and spine are increasingly common. In Singaporean men and women above the age of 50 years, hip fracture incidence rates have risen 1.5-fold and 5-fold respectively since the 1960s (7). Our age-adjusted rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West. The rise in hip fracture incidence is consistent with secular trends seen in many other countries.

A previous study from Singapore reported a steady increase in age-adjusted hip fracture rates of around 1–1.5% per year in both men and women from 1991 to 1998. Based on these trends, we predicted a further 30–50% increase in hip fracture incidence rates over the ensuing 30 years in Singapore (7). This will result in a great financial burden to the healthcare system of Singapore. We therefore conducted a study to have a better understanding of the direct and indirect costs of osteoporotic fractures in Singapore. The findings were that hospitalization was associated with the highest cost borne by both the hospital and the patients, and informal care dominated indirect costs. With an aging population, the prevalence of osteoporosis-related fractures in Singapore will continue to grow in the years to come, generating what is expected to be a heavy burden on health budgets. Better knowledge of the financial consequences of fragility fractures could enable proactive and preventive measures to be undertaken, especially at sites of care with high cost drivers. This would also provide valuable information for health administrators in healthcare resource and budget allocation planning.

We then undertook a study to examine the incidence of hip fracture In Singapore from 2000 to 2017. We observed several important trends in the occurrence of hip fractures in this study. During the period 2000-2017, absolute numbers of hip fractures continued to increase, with a mean annual increase of 71 fractures per 100,000 and an Average Annual Percentage Change (AAPC) of 3.5% (95% CI: 3.3, 3.8). Nevertheless, the crude fracture rate per 100,000 declined in both men and women, indicating that the increase in absolute number of hip fractures was due to an increase in the numbers of women and men at risk for hip fracture. When crude rates per 100,000 were age-adjusted, fractures trends declined even more steeply, indicating the major contribution of the aging Singapore population to the increase in total number of fractures.

With the available information on patients' knowledge, attitude and practice, as well as the cost burden of fracture management in Singapore obtained from the studies as conducted in the thesis, we therefore undertook a fracture liaison service program (OPTIMAL) to prevent recurrent fractures from 2008 to 2016. The OPTIMAL program is a clinician champion-driven, case coordinator-run secondary prevention program for osteoporotic fractures. The program strives to narrow the prevalent care gap in osteoporosis care through a judicious combination of fracture case finding, appropriate assessment and evaluation, patient education on osteoporosis and risk factor management, education on nutrition, fall prevention and exercises for muscle strengthening, balance and coordination, in addition to the use of effective anti-osteoporosis pharmacological agents.

The most important finding of this study was the reduction in all sites fracture risk by 41% and hip fracture risk by 47.1% of patients enrolled into the OPTIMAL program when compared with non-enrolees after two years. The absolute risk reduction in hip fracture rate was 7.67% (15.58% in non-enrolees versus 7.93% in OPTIMAL enrolled patients). The absolute reduction in fracture risk was 9% at 5 years. The OPTIMAL program prevented 77 hip fractures for every 1000 participants and reduce mortality by 40% over five years. This led to significant gains of 228 QALYs per 1000 patients. Patients in the program incurred higher costs due to costs of the intervention, BMD test, and osteoporosis treatment, but preventing subsequent hip fractures also saved costs. Discounting costs and benefits at 5 % per year, the program cost $5,607 more and gained 0.228 QALYs per patient, with an incremental cost-effectiveness ratio (ICER) of $24,636 per QALY gained. These results compared favourably with other observational studies and randomised controlled trials of similar fracture liaison service program (8). Taking together with the reduction in fracture, this projected good return of investment would support the cost-effectiveness of implementing such program in Singapore.

Therefore, the overall results from the studies as presented in the thesis would indicate that with the aging population, there is a likelihood of increased osteoporosis-related fractures. This projected increase is expected to impose heavy financial burden to the health care system in Singapore. However, with a coordinated approach in managing osteoporosis as shown by the OPTIMAL program implemented in Singapore, it may be possible at least to damper the clinical and financial impact of osteoporosis-related fractures. The results from the studies in this thesis would also provide an example of tackling the problem of increased osteoporosis-related fractures faced by other countries, particularly in the Asia-Pacific region.

Chapter One: Introduction and Overview

1.1 Osteoporosis and fractures- an important public health Issue

The World Health Organisation defined osteoporosis as a ‘progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (9).

NIH definition of osteoporosis

National Institutes of Health (NIH), U.S.A. (2000) consensus conference modified this definition as follows: “a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of 2 main features: bone density and bone quality” (10). In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low bone density.

Fragility fracture

Clinically, a fragility fracture may be defined as one that occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma.

The definition of osteoporosis is centred on the level of *bone mass* measured as bone mineral density (BMD) in those without a fracture, or in the presence of a *fracture*. Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD (11). Using absorptiometric techniques, the risk of fracture increases approximately two-folds for each standard deviation decrease in BMD (12). The gradient of risk varies according to the measurement site and technique used (13, 14).

For diagnostic purposes, thresholds based on the number of standard deviations (SD) below the peak bone mass of young adults (or T-score) have been used to arbitrarily define various categories of bone mass (15) (see Table 1).

TABLE 1. WHO definitions based on BMD

BMD T-score (S.D.)	Definition
>-1	Normal
-1 to -2.5	Low bone mass (osteopaenia)
≤ -2.5	Osteoporosis
≤ -2.5 + fracture	Severe or established osteoporosis

Patients with established osteoporosis should be considered for treatment with drugs to reduce the risk of further fractures. The decision to treat would depend on the absolute fracture risk of the individual patients (16). The choice of therapy would depend on the relative anti-fracture efficacy of available drugs, non-skeletal benefits, contraindications, side effects, cost and convenience (14).

1.2 Falls

A fall is a sudden, unintentional change in position causing an individual to land at a lower level, on an object, the floor, or the ground, other than as a consequence of sudden onset of paralysis, epileptic seizure, or overwhelming external force.

Rates of morbidity and mortality from falls are higher among the elderly than among younger persons. Approximately 60 percent of persons who die from falls are 65 years old or older, and falls account for 87 percent of all fractures in older adults(17). The most important risk factors for falls and fall-related injuries among the elderly are a history of one or more prior falls, cognitive impairment, chronic illness, balance and gait impairment, a low body-mass index, female sex, general frailty (18), use of diuretics, use of psychotropic drugs (19), and hazards in the home (20-22). The prevention of falls in older adults has been most successful with the use of multimodal programs (21).

1.3 The socioeconomic burden of osteoporosis, falls and fracture

Using the WHO definition for osteoporosis (see Table 1), the approximate number of women having osteoporosis on hip BMD measurements has been estimated to be 4% of women between age 50-59 years, 8% of women between age 60-69 years, 25% of women between age 70-79 years and 48% of women above age 80 years(23). It is therefore estimated that there is currently about 40,000 female Singaporeans between the age of 50 and 80 who are suffering from osteoporosis.

The incidence of all osteoporotic fractures increases with age. The incidence of forearm fractures starts to increase shortly after the menopause until the age of 65 when it begins to plateau (24). The true incidence of vertebral fractures is difficult to assess, but in women, it rises after the menopause and continues to do so without reaching a plateau. The incidence of hip fracture increases more slowly with age until later life when it undergoes a steep exponential rise. At all ages, the incidence of fracture is higher in women than in men (24).

In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. In the next 50 years, more than half of all hip fractures are projected to occur in Asia (1, 2). Osteoporosis is likely to increase as the population of Singapore is aging rapidly (3-5). In 1990 only 6% of the population was above the age of 65, but by 2030, this figure is projected to rise to 25%(6). Osteoporotic fractures at the hip, wrist and spine are increasingly common. In Singapore men and women above the age of 50 years, hip fracture incidence rates have risen 1.5-fold and 5-fold respectively since the 1960s (7). Our age-adjusted rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West. The rise in hip fracture incidence is consistent with secular trends seen in many other countries.

An analysis of patients who sustained osteoporotic hip fractures in Singapore demonstrated a mortality of 20% at two years (15). Of the survivors, 20% became semi- or fully dependent, and 42% became less or non-ambulant. Only 8% were cared for by chronic health care facilities suggesting that the main social and economic burden was borne by the families of those affected. As nearly all hip fractures are surgically managed, there is a significant acute hospitalization and convalescent care cost which will only escalate further with increasing fracture numbers.

Vertebral fractures also cause significant complications including back pain, height loss, kyphosis and limitation of activity (25-28). There is also an association with increased mortality (29). Whereas hip fracture incidence rates in Asia remain lower than in the West, vertebral fracture prevalence in Asian populations appears to be similar to those in Caucasian populations (30). Women with severe vertebral deformities have a consistently higher risk of back pain and height loss. Hence, an accurate assessment of the risk of fractures associated with osteoporosis and of their impact on quality of life is essential if appropriate and cost-effective interventions are to be designed for different populations.

1.4 Economic cost of fractures

in Singapore, the direct costs of fractures are high: about S$8,000 to S$12,000 for hip fractures for the immediate hospital care (calculated at non subsidized rates in a restructured hospital) (31-33). There is no study so far that looks at the indirect cost of fractures. The numbers of hip fractures per year in Singapore are projected to increase from 1,200 in 1998 to 10,000 in 2050 because of the aging of the population; therefore, the total cost of these fractures will also increase substantially and pose a heavy financial burden to society.

Costs of vertebral fractures are variable, because the definition of a vertebral fracture differs between studies and because the costs depend on whether patients are hospitalized. It is difficult, therefore, to calculate the average cost of vertebral fracture. A reasonable estimate in Singapore is $1,200 per patient for a clinically symptomatic vertebral fracture on average. Likewise, there is currently no cost data on the direct or indirect cost of management of vertebral fractures in Singapore.

Therefore, the cost of managing fractures has become an important issue to patients, third-party payers, and governments alike. Today, and in the future, it is necessary to scientifically and systematically value the costs and consequences of management for osteoporosis and its associated fractures. In view of this, the application of pharmacoeconomic and outcomes principles in evaluating the management of osteoporosis and prevention of fractures would be a logical approach.

1.5 Pharmacoeconomics and Outcomes Research

During the past two decades, there is a gradual shift in the mindset of the clinical community as well as the healthcare administrators in assessing outcome of healthcare interventions globally. It is generally accepted nowadays that the outcomes of healthcare interventions should not be unidimensional as these will not give comprehensive and complete information on the impact of new interventions on patients' functioning and well-being. Therefore, outcome measurement must take into account economic considerations while recognizing that acceptable clinical and humanistic outcomes are also important objectives. It has been proposed that the evaluation of drug therapy and related services should include an assessment of economic, clinical, and humanistic outcomes (ECHO) model (34-36). Clinical outcomes are defined as medical events that occur as a result of disease or treatment. Economic outcomes are defined as direct, indirect, and intangible costs, compared with the consequences of medical treatment alternatives. Humanistic outcomes are defined as the consequences of disease or treatment on patient functional status, or quality of life. The true value of healthcare interventions, programs, and policy can be assessed only if all three dimensions of outcomes are measured and considered simultaneously. The application of pharmacoeconomic research and evaluation will be able to satisfy this requirement.

Practically speaking, pharmacoeconomic research identifies, measures, and compares the costs (i.e., resources consumed) and consequences (clinical, economic, and humanistic) of pharmaceutical products and services(35). Within this framework are included the research methods related to cost-minimization, cost-effectiveness, cost-benefit, cost-of-illness, cost-utility, and decision analysis, as well as quality-of-life and other humanistic assessments. Table 2 outlines different types of pharmacoeconomic methodologies, as well as their cost and outcomes measured (adapted from Bootman et al., 1999) (37). In essence, pharmacoeconomic analysis uses tools for examining the impact (desirable and undesirable) of alternative drug therapies and other medical interventions (37). Furthermore, pharmacoeconomics is not about determining the cheapest health care alternatives, but is about determining those alternatives that provide the best health care outcome per dollar spent.

Since the late 1990s, different models of care designed to prevent recurrent fractures after a fragility fracture have emerged (38). One such model is a fracture liaison service which includes coordinators to facilitate bone health assessment and evidence-based care (38, 39). Ganda et al. classified fracture liaison services by intensity, ranging from the most intensive model that identifies, assesses, and, as indicated, treats fragility fracture patients for osteoporosis within the fracture liaison service role to a less intensive model that only educates participants (40). In comparison, the more intensive models that included promoting adherence to therapies were cost-effective and those that focussed on educating participants alone had limited impact (40-44). However, there has not been a study on the cost effectiveness of the fracture liaison service in an Asian country, where healthcare financing has a substantial co-payment or out-of-pocket component (45).

In Singapore, the OPTIMAL program (Osteoporosis Patient Targeted and Integrated Management for Active Living) is a clinician champion-driven, case coordinator-run secondary prevention program for osteoporotic fractures. The program strives to narrow the prevalent care gap in osteoporosis care through a judicious combination of fracture case finding, appropriate assessment and evaluation, patient education on osteoporosis and risk factor management, education on nutrition, fall prevention and exercises for muscle strengthening, balance and coordination, in addition to the use of effective anti-osteoporosis pharmacological agents. The cost-utility of this program remained unknown. Decision analytic modelling can address this knowledge gap by providing an explicit framework that combines all available evidence to link osteoporosis treatment rates from a single-arm study to comparative cost and effectiveness. The results from the model will help inform clinical decision-making and health policy related to the best strategy in order to improve care for post-fracture patients.

Table 2. Pharmacoeconomic methodologies

Methodology	Measurement of outcome (health benefits)	Synthesis of cost and benefit
Cost-minimization	Assumed to be equivalent in comparative groups and can take any form (e.g. number of cases detected, reductions in cholesterol levels, years of life saved)	Additional costs of therapy A relative to B
Cost-effectiveness	Health benefits across therapies are measured in similar natural units (e.g. life-years gained, mm Hg blood pressure, mmol/L blood glucose)	Cost per life year gained, cost per life saved, cost per patient cured, etc.
Cost-utility	Health benefits across therapies are valued in similar units based on individual preferences	Cost per quality-adjusted life-year (QALY) or other utilities gained
Cost-benefit	Measured in similar or different units and are always valued in monetary units (e.g. amount willing to pay to prevent a death, amount willing to pay to reduce exposure to a hazard)	Net benefits = Benefits minus costs, benefit-cost ratio = benefits/ costs

1.6 Thesis Outline

In summary, the current thesis is organized in the following sequence to address the afore-mentioned research questions.

1. Chapter 1: an introduction to the scope of the problem of osteoporosis management in Singapore in terms of the burden of disease.
2. Chapter 2: a study of the gaps in knowledge, attitude and practice which act as barriers to effective primary prevention of osteoporosis in Singapore.
3. Chapter 3: a study on the incidence of hip fracture rates in Singapore from the year 2000 to 2017, with focus on temporal trends and ethnic differences
4. Chapter 4: cost of osteoporotic fracture in Singapore– To evaluate the direct and indirect cost of hip and vertebra fractures in hospitalised patients in Singapore.
5. Chapter 5: the effectiveness of a Fracture Liaison Service program in improving adherence and outcomes of patients with prior fragility fractures.
6. Chapter 6: health economic burden of Osteoporosis in Singapore.
7. Chapter 7: the cost-effectiveness of a fracture liaison service—a real-world evaluation after 5 years of OPTIMAL provision
8. Chapter 8. the last chapter of the thesis has concluded all the major findings of the above defined projects, contributions, limitations and the recommendation for future studies.

Chapter Two: Gaps in knowledge, attitude and practice in the community hinders effective primary prevention of osteoporosis in Singapore

ABSTRACT

Purpose: This study aimed to evaluate the awareness of osteoporosis, knowledge, attitude and preventive actions taken by both men and women aged 21 years and older who are attending a public sector primary care facility in Singapore. This study hoped to identify any gaps in knowledge, which could be addressed by health professionals in the planning of management and prevention of osteoporosis in the community.

Methods: We carried out survey of adult patients attending Sengkang Polyclinic, a public outpatient health facility in the suburb of Sengkang Town in Singapore during October 2008 to February 2009, were systemically selected (every fifth person) during registration and invited to answer an interviewer administered structured questionnaire on osteoporosis.

Results: A total of 1180 patients were approached and 650 agreed to participate in the survey (response rate 55.1%). Overall, four in every 5 patients had heard of osteoporosis. Amongst the respondents who were less than 50 years old, 77.4% of males and 84.1% of females had heard of osteoporosis. Amongst those who were between 50 and 65 years old, 71.4% of males and 84.9% of females had heard of osteoporosis. Of the group older than 65 years, 61.1% of males and 50.0% of females had heard of the condition. Older people were less likely to have heard of osteoporosis, especially women older than 65 years. They were the least inclined to exercise. Most people would go for screening and treatment. Even though the oldest people were more at risk for osteoporosis, they were generally the least inclined to take the appropriate health precautions.

Conclusion: The awareness of osteoporosis, identification of risk factors and knowledge of complications among middle-aged and elderly men and women in Singapore was fair. There was a gap of knowledge and lack of practice of good health habits, especially in the older people, which could be addressed by public health messages and health professionals in the prevention of osteoporosis. Addressing this knowledge gap can potentially improve patient compliance and encourage good health habits to reduce the disease burden of osteoporosis in Singapore.

Keywords: Osteoporosis, Knowledge, Attitude, Practice, Singapore, ethnic differences

2.1 Introduction

In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. In the next 50 years, more than half of all hip fractures are projected to occur in Asia (1, 2). Osteoporosis is likely to increase as the population of Singapore is aging rapidly (3-5). In 2010 only 6% of the population was above the age of 60, but by 2030, this figure is projected to rise to 25%(6). Osteoporotic fractures at the hip, wrist and spine are increasingly common. In Singapore men and women above the age of 50 years, hip fracture incidence rates have risen 1.5-folds and 5-folds respectively since the 1960s (7). Our age-adjusted fracture rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West. The rise in hip fracture incidence is consistent with secular trends seen in many other countries.

An analysis of patients who sustained osteoporotic hip fractures in Singapore demonstrated a mortality of 20% at two years (15). Of the survivors, 20% became semi- or fully dependent, and 42% became less or non-ambulant. Vertebral fractures also cause significant complications including back pain, height loss, kyphosis and limitation of activity (25-28). There is also an association with increased mortality (29). Whereas hip fracture incidence rates in Asia remain lower than in the West, vertebral fracture prevalence in Asian populations appears to be similar to those in Caucasian populations (30).

A population based survey study was done in Singapore in 2003 to determine the awareness, knowledge of risk factors, and attitudes toward osteoporosis in middle-aged and elderly women in Singapore (46). This study aimed to build on the previous study to evaluate the awareness of osteoporosis, knowledge, attitude and preventive actions taken by both men and women aged 21 years and older who are attending a public sector primary care facility in Singapore. The hypotheses were that men and the elderly had lower awareness of their risk of osteoporosis, less knowledge and less likelihood of taking steps to prevent osteoporosis compared to their female and younger counterparts. This study hoped to identify any gaps in knowledge, which could be addressed by health professionals in the planning of management and prevention of osteoporosis in the community.

2.2 Material and Methods

Study Population

Adult patients attending Sengkang Polyclinic, a public outpatient health facility in the suburb of Sengkang Town in Singapore during October 2008 to February 2009, were systemically selected (every fifth person) during registration and invited to answer an interviewer administered structured questionnaire on osteoporosis (see annex A). The questionnaire was developed by consensus agreement amongst the authors, with reference to a previous study conducted in Singapore (46). Patients who were younger than 21 years old, unable to understand or converse in English, Mandarin, Malay or Tamil were excluded. The SingHealth Institutional Review Board approval was obtained and patients gave a written consent before the interviews were conducted. The patients' demographic characteristics and questions pertaining to their understanding of prevention, diagnosis and treatment osteoporosis were asked. Reasons for inclination to go for screening and treatment were also solicited.

Data analysis

Descriptive analysis was initially conducted for the whole sample and the responses of the various stratified subgroups by age and gender were compared. The Student's t-test was used for continuous variables, and the chi-square test was applied for categorical variables using the statistical package STATA version 8.0. Key variables analyzed were age, gender, ethnic group, first-degree relatives with osteoporosis, smoking, alcohol consumption, intake of steroids, previous fractures, family history of fracture, practice of regular exercise, intake of calcium supplements and the knowledge about osteoporosis risk factors, prevention, and diagnosis.

2.3 Results

Demographics

A total of 1180 patients were approached and 650 agreed to participate in the survey (response rate 55.1%). Among the participants, 56% were females. The mean age for male participants was 41.9 years (SD 14.0) and the mean age for female participants was 43.5 years (SD 12.5). There were 74.6% Chinese, 14% Malays, 6.6% Indians and 4.6% others, similar to the ethnic composition in Singapore (refer table 1). The mean height of male participants was 167.8 m (SD12.6) and that for female participants was 156.9 m (SD 10.2). The mean weight of male participants was 71.4 kg (SD 13.8) and that for female participants was 59.3 kg (SD 12.1).

Knowledge about osteoporosis

Overall, four in every 5 patients had heard of osteoporosis. Amongst the respondents who were less than 50 years old, 77.4% of males and 84.1% of females had heard of osteoporosis. Amongst those who were between 50 and 65 years old, 71.4% of males and 84.9% of females had heard of osteoporosis. Of the group older than 65 years, 61.1% of males and 50.0% of females had heard of the condition. The details of the knowledge of the participants are summarised in table 2.

Practice of osteoporosis prevention

For the life style practice items, only 40.6% of patients engaged in exercise, of which jogging (27.6%) and brisk walking (20.6%) were the most commonly practiced. For this group who exercised, 70% was younger than 50 years old but there was no gender difference. Regarding practice frequency, 51% exercised 1-2 days a week while 25% exercised 5-7 days a week. Amongst those younger than 50 years, 52.8% of males and 66.7% of females did not exercise. For those between 50 and 65 years, 51.4% of males and 60.7% of females did not exercise. Lastly, for those older than 65 years old, 44.4% of males and 72.2% of females did not exercise.

Calcium supplementary products were consumed regularly by 29% of patients. For those younger than 50 years, 81.9% of males and 72.4%% of females did not consume calcium supplements. For those between 50 and 65 years, 70.0% of males and 42.4% of females did not take supplementary calcium. For those older than 65 years old, 83.3% of males and 44.4% of females did not take calcium supplements.

Attitude about osteoporosis screening and treatment

For health seeking behavior, 96% and 98.2% of patients would go for screening and treatment for osteoporosis, respectively. For those younger than 50 years old, 2.0% of males and 2.4% of females declined screening. For those between 50 and 65 years old, 1.4% of males and 7.1% of females would not go for screening. Amongst those older than 65 years, 5.6% of both sexes would not go for screening. For those younger than 50 years old, 1.0% of males and 0.4% of females declined treatment. For those between 50 and 65 years, only 2.0% of females would not go for treatment; all males would go for treatment. For those older than 65 years, 5.6% of both sexes declined treatment. It appeared that those who would go for screening and treatment belonged to the same cohort of younger patients and more of them were females.

The more commonly cited reasons for those willing to go for screening of osteoporosis were “prevention of complications from osteoporosis” (36.7%), “concern for good health” (13.8%) and “recognize role for early screening” (13.3%). Similarly for those willing to going for treatment of osteoporosis, “prevention of complications from osteoporosis” (28.5%), “want early cure” (19.3%) and “concern for good health” (11.3%) were cited.

Table 1: Awareness of osteoporosis by age groups, gender and ethnicity

	Number	% heard of osteoporosis (n=520)	% who have not heard of osteoporosis (n= 130)	P value (Chi^2 test, 2 sided)
Age < 50 ≥ 50	 205 (31.5%) 445 (68.5%)	 155 (75.6%) 360 (80.9%)	 50 (24.4%) 85 (19.1%)	 0.145
Gender Male Female	 287 (44.2%) 363 (55.8%)	 214 (74.6%) 301 (82.9%)	 73 (25.4%) 62 (17.1%)	 0.011
Ethnicity Chinese Malay Indian Others	 485 (74.6%) 92 (14.0%) 43 (6.6%) 30 (4.6%)	 399 (82.1%) 64 (70.3%) 29 (67.4%) 23 (76.7%)	 87 (17.9%) 27 (29.7%) 14 (32.6%) 7 (23.3%)	 0.014
Total	650	515	135	

Table 2: Knowledge with regard to osteoporosis

Question	Answers	Participants with correct answers
Do you think osteoporosis can occur in both men and women?	Yes	76.0%
How is osteoporosis detected?	Bone mineral density screening	10.0%
Which of the following can occur in osteoporosis	Bent spine, fracture, becomes shorter	66.7%
Which of the following can effectively prevent osteoporosis	Take calcium-rich foods	76.5%
	Falls prevention	64.5
	Taking Vitamin D rich food	61.6%
	Avoiding excessive alcohol	61.1%
	Taking medication	54.0%

2.4 Discussion

The study assessed the knowledge, attitude and practice of osteoporosis and its prevention amongst a randomly selected population above 21 years old in a community health clinic.

A fairly high proportion of the respondents had heard of osteoporosis (80%). Interestingly, more women had heard of osteoporosis compared to man (Table 1). This might be due to the fact that most educational efforts in osteoporosis prevention targeted the female gender predominantly. However, this trend was reverse when we compared the above 65-year-old group, when only 50% of women compared with 61% of men had heard of osteoporosis.

This was a community health clinic based study with an average participation rate (55.1%), and information on knowledge, attitude and practice regarding osteoporosis was obtained from interviews conducted by trained interviewers. The population was rather heterogeneous with a mixture of men, premenopausal and postmenopausal women. Our survey was fairly generalizable and the age distribution of our study population and the Singapore population were similar.

A study of 72 Japanese-American women in San Francisco (aged 55 years and older) showed that 79% of the first-generation Japanese and 97% of second-generation Japanese had heard of osteoporosis (47) . In a study of 145 Canadian adults (average age 76 years) attending a seniors' program, 89% had heard of osteoporosis (48). It would appear that awareness of osteoporosis in Singapore men and women above 50 years of age was lower than in adults in the United States and Canada. There were limitations, however, in the comparison of results from different studies as the age range, nature of selection of the population, and menopausal status may be different. Compared with a population based health survey of Saw et al done in 2001 (46), when only 30% of the women above 65 year old had heard of osteoporosis, the current survey showed a improvement to 50%. Nevertheless, this was still very low and would be an area of concern, as this age group would be at the highest risk of osteoporosis and fractures. The explanation for the phenomenon could be that many of these women above 65 years old were less educated, and therefore the current media of education in print might not be accessible for them.

Knowledge of the preventive aspects and fracture complication of osteoporosis was fairly adequate, these were comparable to the previous study by Saw et al (46). With regard to attitude towards screening and treatment of osteoporosis, majority of the respondents were keen to be screened and treated if required. However, only one in ten respondents were aware of the DXA BMD test being the diagnostic test for the condition. Only one in two were aware of effective medications to prevent fractures. These would be potential barriers to the effective management of osteoporosis in the community when awareness of diagnosis and treatment was relatively low.

In terms of practice, although most respondents could appreciate the benefit of exercise in the prevention of osteoporosis, only 40% engaged in exercise actively. With advancing age, the group that engaged in exercise regularly was even less with only 30% of women above 65 years old being active in any form of exercise. This would again be of great concern as this would be the high-risk group for osteoporosis and fractures.

An understanding of the characteristics of women with poor knowledge of osteoporosis may help us design more appropriate public health education programs.

Educational intervention programs may be targeted at older women with less formal education, especially those who do not practice osteoprotective behavior such as regular exercise. Nationwide strategies such as the mass media in the local dialect, Malay or Tamil that target an older audience may be preferred to educational efforts such as talks in voluntary organizations. Increased public education may lead to preventive behaviors and possibly a decreased incidence of osteoporosis.

2.5 Conclusion

In conclusion, the awareness of osteoporosis, identification of risk factors and knowledge of complications among middle-aged and elderly men and women in Singapore was fair. Older people were less likely to have heard of osteoporosis, especially women older than 65 years. They were the least inclined to exercise. Most people would go for screening and treatment. Even though the oldest people were more at risk for osteoporosis, they were generally the least inclined to take the appropriate health precautions. There was a gap of knowledge and lack of practice of good health habits, especially in the older people, which could be addressed by public health messages and health professionals in the prevention of osteoporosis. Addressing this knowledge gap can potentially improve patient compliance and encourage good health habits to reduce the disease burden of osteoporosis in Singapore.

Annex A

Section 1: Participant's particulars

1. Age ________ years
2. Sex: M / F
3. For women: menopausal: Yes/ No
4. Do you have any first-degree relative with osteoporosis?
5. Race _________
6. Occupation: __________________ (Full-time or part-time) / Not working
7. Current smoking: Yes / No
8. Drink alcohol 3 or more units a day: Yes/ No
9. Oral steroids? Yes/ No
10. Rheumatoid arthritis: Yes/ No
11. Previous fracture? Yes / No

    Site: Hip, spine, wrist, femur, humerus, others _________
12. Parent fracture hip: Yes/ No
13. Height _________ cm
14. Weight __________ kg

Section 2: Practice, Knowledge, and Attitude

Practice

15. Regular exercises: Yes/ No

a. what ______________

b. How often _______________

16. I take calcium products including supplements regularly? Yes/ No

Knowledge

17. Have you heard of a condition where your bones are soft or brittle and break easily or osteoporosis? Yes / No

18. Do you think osteoporosis can occur in both men and women? Yes/ No

19. How is osteoporosis detected? (do not prompt)

a. clinical examination alone

b. X-ray

c. Bone mineral density screening

d. Blood tests

e. I do not know

20. Which of the following can occur in osteoporosis (answer Y or N as I read out):

a. Bent spine: Yes/ No

b. Fracture: Yes / No

c. Risk of falls : Yes/ No

d. Becomes shorter as he gets older: Yes/ No

21. Which of the following can effectively prevent osteoporosis (answer Y or N as I read out):

a. Weight-bearing exercise like walking - Yes/ No
b. Take calcium-rich foods - Yes/ No
c. Take vitamin –D rich foods - Yes/ No
d. Stop smoking - Yes/ No
e. Don't drink excessive alcohol? - Yes / No
f. Special medications - Yes/ No
g. Take care to prevent falls at home or outside - Yes/ No

Attitude

22. If you are at risk for osteoporosis, will you go for screening? Yes/ No

If yes, why?

____

____

____

23. If you have osteoporosis, would you want to see a doctor for treatment?

Yes / No

If yes, why?

____

____

____

END

Annex B

Investigators' Information Sheet

Risk factors

For the clinical risk factors a yes or no response is asked for. If the field is left blank, then a "no" response is assumed. See also notes on risk factors.
The risk factors used are the following:

Age	The model accepts ages between 40 and 90 years. If ages below or above are entered, the programme will compute probabilities at 40 and 90 year, respectively.
Sex	Male or female. Enter as appropriate.
Weight	This should be entered in kg.
Height	This should be entered in cm.
Previous fracture	A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture. Enter yes or no (see also notes on risk factors).
Parent fractured hip	This enquires for a history of hip fracture in the patient's mother or father. Enter yes or no.
Current smoking	Enter yes or no depending on whether the patient currently smokes tobacco (see also notes on risk factors).
Glucocorticoids	Enter yes if the patient is exposed to oral glucocorticoids or has been exposed to oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids) (see also notes on risk factors).
Rheumatoid arthritis	Enter yes where the patient has a confirmed diagnosis of rheumatoid arthritis. Otherwise enter no (see also notes on risk factors).
Secondary osteoporosis	Enter yes if the patient has a disorder strongly associated with osteoporosis. These include type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease.
Alcohol 3 or more units/day	Enter yes if the patient takes 3 or more units of alcohol daily. A unit of alcohol varies slightly in different countries from 8-10g of alcohol. This is equivalent to a standard glass of beer (285ml), a single measure of spirits (30ml), a medium-sized glass of wine (120ml), or 1 measure of an aperitif (60ml) (see also notes on risk factors).
Bone mineral density (BMD)	BMD of the femoral neck is entered either as a T-score or as a Z-score. In patients without a BMD test, the field should be left blank (see also notes on risk factors).

Notes on risk factors

Previous fracture
A special situation pertains to a prior history of vertebral fracture. A fracture detected as a radiographic observation alone (a morphometric vertebral fracture) counts as a previous fracture. A prior clinical vertebral fracture from which the patient suffers consequences, is an especially strong risk factor. The probability of fracture computed may therefore be underestimated. Fracture probability is also underestimated with multiple fractures.

Smoking, alcohol, glucocorticoids
These risk factors appear to have a dose-dependent effect, i.e. the higher the exposure, the greater the risk. This is not taken into account and the computations assume average exposure. Clinical judgment should be used for low or high exposures.

Rheumatoid arthritis (RA)
RA is a risk factor for fracture. However, osteoarthritis is, if anything, protective. For this reason reliance should not be placed on a patient's report of 'arthritis' unless there is clinical or laboratory evidence to support the diagnosis.

Bone mineral density (BMD)
The site and reference technology is DXA at the femoral neck. T-scores are based on the NHANES reference values for women aged 20-29 years. The same absolute values are used in men. Although the model is constructed for BMD at the femoral neck, the total hip site is thought to predict fracture equivalently in women.

Q3: Menopausal: no menstruation for past 12 months (with no obvious cause) or at 51 years old (if not having menstruation due to absent uterus) [2]

Q4: First-degree relative: Parents, brother, sister or children. [3]

Q15: Regular exercise: Weight-bearing exercise, including resistance training to improve muscle mass, strength and balance, performed at least 3 times per week. [4]

Q16 & 21b. Calcium (food) products: [5]

See attached calcium chart

Q21c. Vitamin D-rich foods: [6]

There are only a few food sources of vitamin D. Good sources of vitamin D are fortified foods and beverages like milk, soy drinks, and margarine. Fish, liver, and egg yolk are the only foods that naturally contain vitamin D.

Food Sources of Vitamin D	Serving	Vitamin D (IU)
Milk	1 cup	100
Fortified rice or soy beverage	1 cup	80
Fortified orange juice	½ cup	45

Fortified margarine	2 tsp	51
Egg yolk	1	25
Herring or trout, cooked	75 g	156
Mackerel, cooked	75 g	80
Salmon, Atlantic, cooked	75 g	225
Salmon, canned or cooked*	75 g	608
Sardines, Atlantic, canned	75 g	70
Sardines, Pacific, canned	75 g	360
Tuna, canned, light or white	75 g	41
Tuna, canned, yellowfin (albacore, ahi)	75 g	105
Tuna, skipjack, cooked	75 g	381
Tuna, bluefin, cooked	75 g	690

* includes Chinook, Coho, Humpback (pink), Sockeye

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Chapter 3: Hip fractures in Singapore: Ethnic differences and temporal trends in the new millennium

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ABSTRACT

Purpose: A previous study published in 2001 predicted a 30–50% increase in hip fracture incidence rates over the ensuing 30 years in Singapore. To test that prediction, we examined the incidence of hip fracture in Singapore from 2000 to 2017.

Methods: We carried out a population-based study of hip fractures among Singapore residents aged ≥50 years from 2000 to 2017. National medical insurance claims data were used to identify admissions with a primary discharge diagnosis of hip fracture. Age-standardized rates, based on the age distribution of the Singapore population of 2000 and age specific rates, were analysed separately by sex and ethnicity (Chinese, Malay, and Indian).

Results: Over the 18-year study period, 36,082 first hip fractures were recorded among Singapore residents. Total hip fracture admissions increased from 1487 to 2729 fractures/year in the years 2000 to 2017 by an average annual percentage change (AAPC) of 3.5% (95%CI; 3.3, 3.8). Despite these increases in absolute numbers, age-adjusted fracture rates per 100,000 population declined, with an average annual percentage change (AAPC) of -1.6% (95%CI; -1.9, -1.4) for women and -0.9 (95%CI; -1.3, -0.4) for men. Chinese women have 1.4- and 1.9-fold higher rates than Malay and Indian women: 264 (95%CI; 260, 267) vs 185 (95%CI; 176, 193) and 141 (95%CI; 132, 150) per 100,000, respectively. Despite their higher fracture rates, Chinese women were the only ethnic group exhibiting declines in age-standardized fracture rates, with an AAPC of -1.9% (95%CI;-2.2, -1.6).

Conclusion: Ethnic differences in hip fracture rates were congruent with lower obesity prevalence in Chinese women, and may also be related to vitamin D deficiency in Malay women. Current demographic changes leading to increases in the older population will lead to a rise in total number of hip fractures' This will, require budgetary planning and new preventive strategies.

Abstract Word count: 244

Mini abstract: Despite an increase in absolute numbers, the age-standardized incidence of hip fractures in Singapore has declined in the period 2000 to 2017. Amongst the three major ethnic groups, Chinese women had the highest fracture rates, but were the only group to show a temporal decline.

Keywords: Hip fracture rates, Singapore, ethnic differences

3.1 Introduction

Hip fractures result in increased morbidity, disability and mortality risks amongst the elderly, and imposes a significant economic burden for acute and long-term care. Previous studies have reported increasing incidence in some countries, while others have found a decline trends, some after an initial rise (49-51). It is unknown whether such differences are driven by different data sources and methods, differences in healthcare provision or ethnic and racial differences.

Studying hip fracture trends amongst Singapore's multi-ethnic population of Chinese, Malays and Indians provide a comparison of hip fracture incidence across Asian ethnic groups. Globally, over 2.6 billion people belong to these three ethnic groups (52). With a low total fertility rate (1.16 births per woman in 2017) and increasing life expectancy (average lifespan of 83.1 years in 2017), Singapore has a rapidly aging population and is likely to face the financial and healthcare burden of numbers of hip fractures. A previous study from Singapore reported a steady increase in age-adjusted hip fracture rates of around 1–1.5% per year in both men and women from 1991 to 1998. Based on these trends, the authors predicted a further 30–50% increase in hip fracture incidence rates over the ensuing 30 years in Singapore (7). To test that prediction, we examined the incidence of hip fracture In Singapore from 2000 to 2017.

3.2 Material and Methods

We carried out a population-based study of hip fractures among Singapore residents from 2000 to 2017. Data on hip fractures were obtained from the Singapore Ministry of Health Central Claims Processing System which covers all hospitalisations in public and private acute hospitals in Singapore. Inpatient admissions of Singapore residents with a discharge diagnosis of fracture involving the neck or the intracapsular, upper epiphyseal, subcapital, cervical, trochanteric or subtrochanteric areas were retrieved using the following diagnostic codes from the International Classification of Disease, Tenth revision, Australian version (ICD-10-AM): S7200, S7201-S7211, S722-S723 for the period 2012-2017; and from ICD-9-CM (Australian version): 820, 820.1-820.3, 820.8, 820.9 for the period 2000-2011. To focus on osteoporotic fractures, we restricted the study to men and women ≥50 years at the time of admission.

Singapore's resident population is composed of 75.0% Chinese, 13.7% Malays and 8.7% Indians in 2007 [6]. In Singapore, an individual's race is determined at birth,self-reported by his or her father's race To calculate the age-specific incidence rates, demographic data were obtained from Department of Statistics of the Singapore resident population by sex, five-year age-group and race (53).

Identification of hip fracture cases (Fig. 1)

A total of 41,544 hospitalizations with a primary diagnosis of hip fracture for the period 2000-2017 were identified. To ensure that only first episodes of hip fracture were captured, fractures that occurred during the preceding 5 years (1995-1999) were excluded. In addition, 2,335 hospitalizations of persons <50 years of age and 2,528 non-residents were excluded. Of the remaining 36,108 first episodes within the study period, 26 were excluded because data on gender were missing. After these exclusions, 36,082 subjects with first hip fractures were analysed.

Statistical analysis

Age-standardised incidence rates were calculated based on the age distribution of the Singapore population in 2000, and rates were analyzed separately in the two sexes and the three ethnic groups. Fracture rates are expressed per 100,000, with 95% confidence intervals (CI) estimated using Stata v13 software. Age- and sex-specific hip fracture incidence rates were calculated by dividing the respective hip fracture episodes by the corresponding populations. The average change in fracture rate per 100,000 per year was estimated using regression coefficients in linear regression model, with incidence rate as the dependent variable and year as the independent variable. For comparisons with other cohorts globally, the annual percentage change (AAPC) and 95% CI were also calculated using the exponential method, based on linear regression of the natural logarithm of incidence rates with the year as independent variable, exponentiating to obtain the regression coefficient and its 95% CI [exp(coefficient) - 1].

Ethics

This study was conducted using anonymised data de-identified by the Ministry of Health, and approved by the Domain Specific Review Board (DSRB) of National Healthcare Group

3.3 Results

Over the 18-year study period (2000 to 2017), 36,082 first hip fractures were recorded among Singapore residents (Fig. 1). During the same period, the population of Singapore increased from 4.0 to 5.6 million, with the median age increasing from 34.0 to 41.3 years (53). Singaporean women had a 2-fold higher age-adjusted rate of hip fractures than men (252 [95% CI, 249, 255] vs 124 [95% CI; 122, 126] per 100,000).

The absolute number of hip fracture admissions to Singapore hospitals increased from 1487 to 2729 fractures/year in the years 2000 to 2017, an average of 71.7 (95% CI: 64.9, 78.5) additional fractures per 100,000 per year. This represents an average annual percentage change (AAPC) of 3.5% (95%CI: 3.3, 3.8). As shown in Figure 2 (upper panel), this absolute increase was observed in both women [average increase 46.3 (95%CI: 41.0, 51.6) fractures/year; AAPC 3.3% (95%CI: 3.0, 3.6)] and men [average increase 25.4 (95% CI: 22.6, 28.1) fractures/year; AAPC 4.1% (95%CI: 3.7, 4.4)].

Owing to increases in the Singapore population, however, these increases in absolute numbers were not reflected in hip fracture rates per 100,000 population, which declined by -1.6 (95% CI; -2.2, -0.9) per 100,000 per year [AAPC -0.7 (95% CI; -1.1, -0.4)]. As shown in the middle panel of Figure 2, this decline was observed both in women [–2.6 (95%CI; -3.6, -1.6)] per 100,000 per year; AAPC -0.9% (95%CI; -1.3, -0.6)] and men [-0.3 (95%CI; -0.9, -0.1) per 100,000 per year; AAPC -0.3% (95%CI: -0.7, -0.1).

B age-adjusted fractures rates declined to an even greater extent than the overall rates: -2.7 (95%CI; -3.2, -2.2) per 100,000 per year; AAPC -1.4%(95% CI; -1.6, -1.1). As shown in the lower panel of Figure 2, that decline was observed both in women [-4.3 (95%CI; -5.0, -3.5) per 100,000 per year; AAPC -1.6% (95%CI; -1.9, -1.4)] and men [-1.1 (95%CI; -1.7,-0.5) per 100,000 per year; AAPC -0.9% (95%CI; -1.3, -0.4)].

Because of their higher rates, the remainder of the analysis was restricted to women, among whom marked ethnic differences were observed. Chinese women had 1.4- and 1.9-fold higher rates than Malay and Indian women respectively: 264 (95% CI; 260,

267) vs 185 (95% CI; 176, 193) and 141 (95% CI; 132, 150) per 100,000 per year (Table 1). As shown in Figure 3, Chinese women had a steady decline in age-adjusted annual hip fracture rates, from 303 (95% CI; 295, 311) per 100,000 in 2000-2005 to 239 (95% CI; 234, 244) per 100,000 in 2011-2017, representing a 21% decline over the 3 time periods (5-7 years each), an annual decrease of -5.3 (95%CI; -6.0, -4.5) per 100,000, AAPC -1.9% (95%CI; -2.2, -1.6). As shown in Figure 4 and Supplementary Table 1, this decline was most evident in Chinese women ≥85 years: -62.2 (95%CI; -75.6, -48.7) fractures/100,000/year; AAPC -2.5% (95%CI: -3.1, -2.0). Significant declines were also observed among the 80-84, 75-79, 70-74 year groups, decreasing by -27.6 (95%CI: -36.4, -18.8) fractures/100,000/year, AAPC -2.1%(95%CI; -2.7, -1.4); -11.1 (95%CI; -16.3, -5.9) fractures/100,000/year, AAPC -1.5% (95%CI; -2.2, -0.7) and -6.4(95%CI; -9.1, -3.7) fractures/100,000/year, AAPC -1.7% (95%CI; -2.5,-1.0) respectively. In contrast, no significant changes in hip fracture rates were observed in Malay or Indian women with 0.7 (95%CI; -1.6, 3.1) fractures/100,000/year, AAPC 0.4% (95%CI; -0.9, 1.8); and -0.4 (95%CI; -2.4, 1.6) fractures/100,000/year, AAPC -0.3%(95%CI; -1.8, 1.0) respectively (Fig. 3)

3.4 Discussion

We observed several important trends in the occurrence of hip fractures in Singapore. During the period 2000-2017, absolute numbers of hip fractures continued to increase, with a mean annual increase of 71 fractures per 100,000 and an AAPC of 3.5% (95% CI, 3.3, 3.8). Nevertheless, the crude fracture rate per 100,000 declined in both men and a woman, indicating that the increase in absolute number of hip fractures was due to an increase in the numbers of women and men at risk for hip fracture. When crude rates per 100,000 were age-adjusted, fractures trends declined even more steeply, indicating the contribution of the aging Singapore population to the increase in total number of fractures. Marked ethnic differences were observed, with Chinese women having 1.4- and 1.9-fold higher fracture rates than Malay and Indian women, respectively. However Chinese women had a steady decline in their age-standardized fracture rates during the 17-year study period, a trend limited to women ≥70 years. In contrast, no decline was observed among women of Malay or Indian ethnicity.

An earlier Singapore study from 1958 to 1998 reported a 3-fold increase in age- and sex-adjusted hip fracture rates among residents aged ≥50 years [5]. In contrast, we observed a reversal of the trend in Singaporean women, limited to those of Chinese ethnicity, with an age-adjusted AAPC of -1.6%. This decline is consistent with those reported from Chinese populations in Hong Kong (54) and Taiwan (55), and from economically advanced populations in Sweden (56), France (57); Denmark, Switzerland, and Canada (58); and the United States 2018 (51, 59). Such declines are not universal, however. In Tangshan, a city in Northern China with a population similar to Singapore's, increases of 85% and 306% were observed in hip fracture incidence in men and women, respectively, from 1994 to 2010 (60). In Beijing, hip fractures rates increased 58% in women and 49% in men comparing the periods 1990-1992 and 2002-2006 (61). In Spain, an annual decline of 2.2 % was reported for women 65–74 years of age but a 0.6% annual increase was observed for those over 85 years (62). In Singapore, the median length of stay in hospital for hip fractures undergoing surgery is 12 days (63). As in other rapidly ageing Asian societies (64), the absolute increase in number of fractures (due to ageing and increase of the Singapore population) ensures that the heavy burden for inpatient care of hip fractures will continue to rise.

Consistent with a previous survey (7), we found that hip fractures were highest in Chinese women. Nevertheless, Chinese women were the only ethnic group with a significant decline in hip fracture rates. The reasons for these ethnic-specific features of hip fracture epidemiology are unclear. One key risk factor for hip fracture is low bone mineral density leading to osteoporosis. As such we consulted recent population trends in known risk factors of low bone mineral density, including body weight, smoking, alcohol consumption, physical activity, and diabetes (51, 65). National trends in the prevalence of these risk factors are summarized in Table 2 (66). Although the prevalence of obesity (BMI >30.0 kg/m^2) in all races increased from 6.3% (95% CI; 5.6, 6.7) in 1998 to 10.8% (95% CI; 9.8, 11.8) in 2010, obesity prevalence among the Chinese was 2- to 5- fold lower than for Indians or Malays (Table 2). Low body fat is associated with lower bone mineral density (67), and obesity protects against hip fractures. A low prevalence of obesity may contribute to the higher rates of hip fractures observed in Chinese. Interestingly, differences in obesity rates narrowed from 3.1-fold and 4.5-fold higher in 1998, to 2.1-fold and 3.0-fold higher in Chinese vs Indians and Malays, respectively, in 2010, congruent with the convergence in hip fracture rates shown in Figure 3. Despite having the highest obesity rates, however, Malay women have higher fracture rates than Indian women, who in turn have intermediate obesity rates, but the lowest fracture rates, among the three ethnic groups. These data suggest that although lower obesity rates may contribute to the higher fracture rates in Chinese women, it does not entirely account for the differences across ethnicities.

Vitamin D deficiency is associated with increased muscle weakness, higher bone turnover and risk of falls and hip fractures in older adults (68). In Singapore, vitamin D deficiency (≤20 ng/ml of 25(OH) vitamin D) has been reported to be present in about 18% of patients referred to an osteoporosis clinic (69), and up to 57% in patients hospitalised for hip fractures (70). Intriguingly, hypovitaminosis D is significantly higher in those of Malay ethnic origin, being present in 90.5% in Malay patients with hip fracture compared to 55% of Chinese and 61.1% Indians (71). Low Vitamin D may have contributed to the higher hip fracture rates observed in Malay compared to Indian women. These differences are thought to be related to the cover all dressing style, such as long sleeves and head dress for Muslim-Malay females. Whether vitamin D deficiency contributes to the increase risk of hip fracture in Malay women compared to Indians requires further evaluation.

Malays have the highest smoking rates among the three ethnic groups, whereas alcohol consumption is low in all three ethnic groups (Table 2) Among the ethnic groups, no major change has been observed in the proportion of women who exercise regularly, or in the prevalence of diabetes. The contribution of smoking and other factors to ethnic differences in fracture rates should be explored in future studies. Amongst Singaporeans, greater genetic heterogeneity has been observed between Indians and Chinese, than between Chinese and Malays subjects (72). Chinese women have been reported to have significantly longer hip axis length compared to either Malay or Indian women which may contribute to lower hip fracture rates. (73). Whether ethnic specific genetic variants contribute to differences in hip geometry (74) and other loci associated with bone mineral density and risk of fracture (75) are worthy of future study.

Although having the highest fracture rates, Chinese women were the only ethnic group to show a temporal decline. It is relevant to note that several factors may be associated with this decline. Since an early study revealed that a large fraction (42%) of Chinese women were not aware of the relationship of osteoporosis to hip fractures (46) various initiatives to increase awareness have been implemented. A Singapore Ministry of Health clinical practise guideline (70) and editorials in local medical journals (76) (77) [26-27] have been published. The Singapore Health Promotion Board and Osteoporosis Society of Singapore held public forums with extensive press coverage to emphasize the scale of the problem (78). The OPTIMAL secondary fracture prevention program, which is clinician champion-driven and case manager-run, was established in public hospitals in Singapore in 2008 (79). Anti-osteoporosis drugs such as bisphosphonates are increasingly prescribed and consumed, as costs have fallen with the introduction of generic medications (80). Currently, more than half of Singapore hospitals have implemented fracture liaison services (63), resulting in good compliance with osteoporosis medications. Intriguingly, a recent U.S. study reported a reversal in the last few years of the earlier age-adjusted declines in hip fracture incidence (59). Factors postulated to contribute to this reversal include a decline in DXA measurement (due to changes in health funding), as well as a reduction in bisphosphonate therapy for osteoporosis due to fear of rare adverse effects, such as atypical femoral fractures and osteonecrosis of the jaw (81). Whether awareness of these adverse events will lead to similar reductions in bisphosphonate use in Singapore, with subsequent flattening of declining fracture trends, should be examined in future studies.

Our study has a number of strengths. We used a large database that includes all Singaporean residents so our results should be generalizable to Singapore. We included a large number of subjects over an 18-year period and studied both women and men and three ethnic groups of women. However, our study has several limitations. Some degree of misclassification of diagnoses and coding errors is likely when using administrative databases. In addition, age-specific analyses of temporal trends for Malay and Indian women had limited statistical power due to their smaller populations and lower rates of hip fractures.

Despite declining age- and population-adjusted fracture rates, absolute numbers of hip fractures increased on average 3.5% per year in Singapore. This increase was partly contributed by the population growth of those over 70 years, especially those aged ≥85 years. Globally, the number of people aged 80 years or over is growing even faster than the number of older persons overall. Projections indicate that the number of people aged 80 or over worldwide will increase more than threefold between 2017 and 2050, rising from 137 million to 425 million (82). Our study predicts a mean increase of 70 hip fractures annually per 100,000 population and this needs to be factored into hospital and health manpower and expenditure planning.

LEGENDS TO FIGURES

Figure 1: Case selection, identification and exclusions.

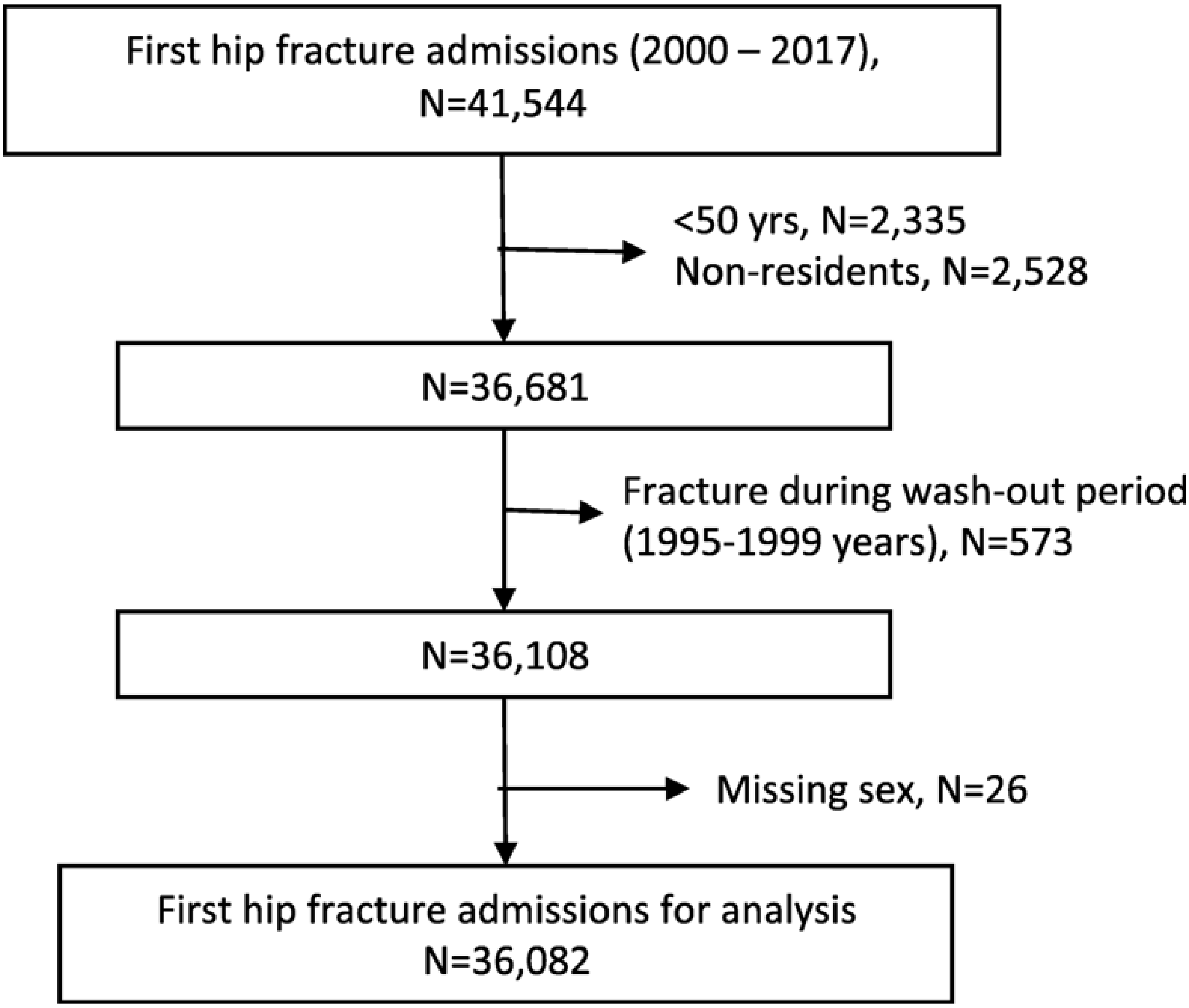

Figure 2: Temporal trends in hip fractures in Singapore, 2000 to 2017. Upper panel: Crude annual numbers of hip fractures. Middle panel: crude incidence rates per 100,000 population. Lowest panel: Age-adjusted incidence rates per 100,000 population. Age weightage was adjusted to the year 2000 population.

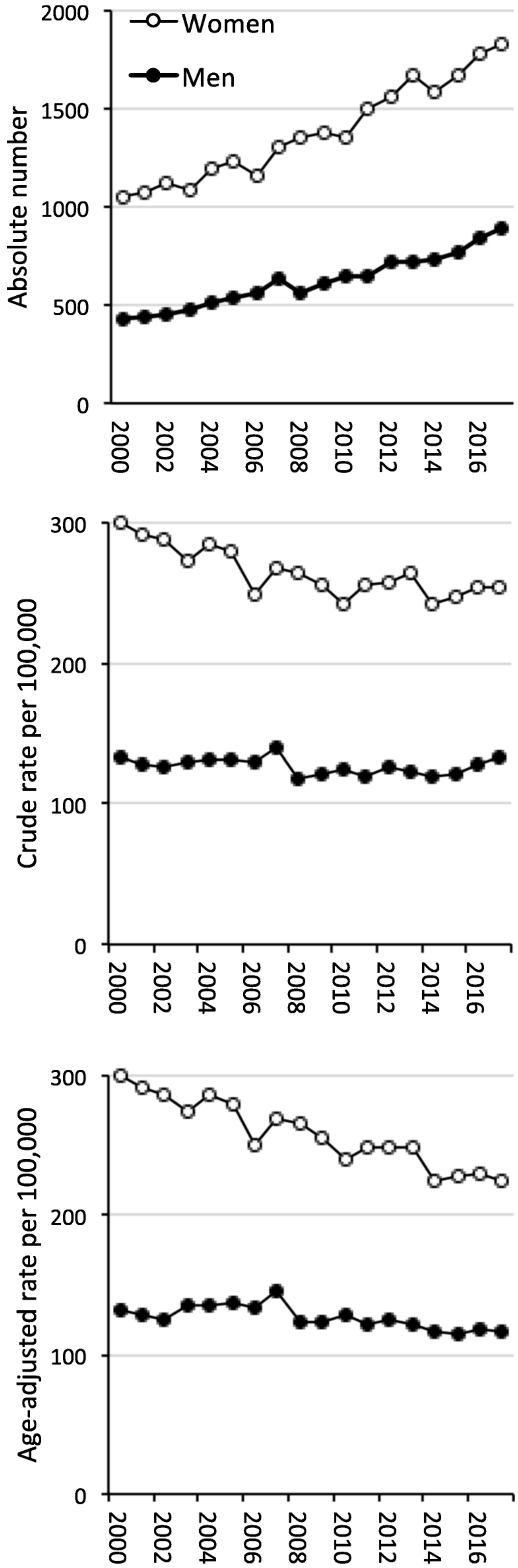

Figure 3: Hip fracture incidence trends in Singapore women, stratified by ethnicity. Data shown are mean age-adjusted rates per 100,000 for the periods indicated. Dotted lines are 95% CI. Based on data in Supplementary

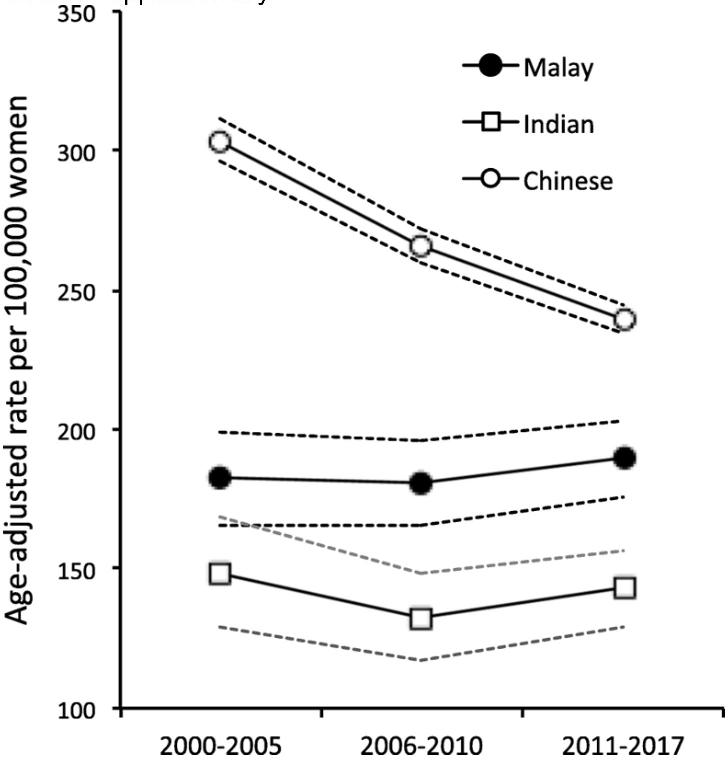

Table.

Figure 4: Temporal trends in age-specific hip fracture incidence rates per 100,000 Chinese women (2000-2017).

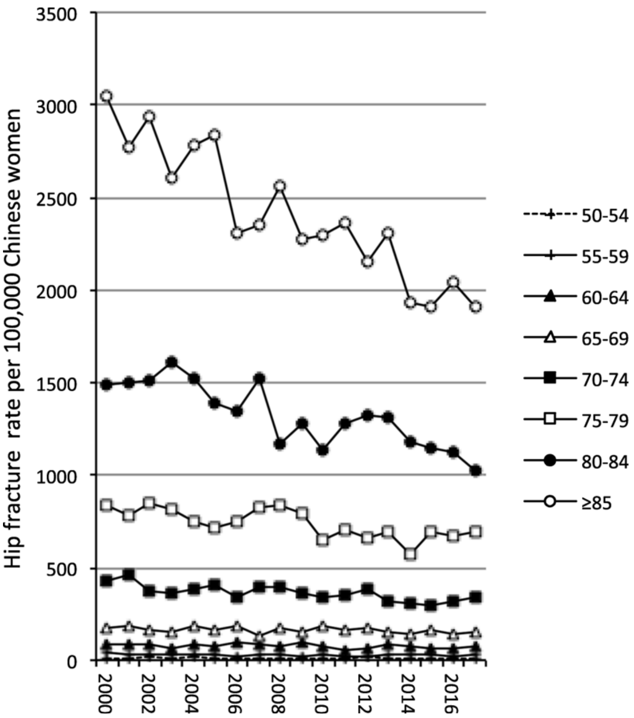

Table 1: Age-specific hip fracture rates per 100,000 women by ethnicity (2000-2017).

	Chinese			**Malay**			**Indian**		
Age	**Mean**	**95% CI**		**Mean**	**95% CI**		**Mean**	**95% CI**	
50-54	11	9,	13	9	6,	12	8	3,	14
55-59	29	27,	32	24	16,	31	22	15,	29
60-64	76	71,	82	68	52,	85	77	54,	99
65-69	163	154,	172	173	143,	204	164	133,	194
70-74	365	343,	386	396	342,	450	346	302,	391
75-79	738	698,	777	722	643,	800	632	536,	729
80-84	1326	1240,	1411	1235	1077,	1394	1216	1030,	1403
≥85	2409	2231,	2588	1699	1423,	1975	1825	1486,	2165
≥50*	**264**	**260,**	**267**	**185**	**176,**	**193**	**141**	**132,**	**150**

* age-standardised to Singapore 2000 population

TABLE 2: Prevalence of risk factors for hip fracture risk factors obtained for Singapore residents (men and women) aged 18-69 years from National Health Surveys 1998, 2004, and 2010 expressed as percentage (95% CI) of residents in that ethnic group. National health surveys use a consistent methodology based on stratified random sampling of over 4,000 subjects/survey. The ethnic composition of each survey was 30% Chinese, 30% Indians and 30% Malays. Minority groups (Malays and Indians) were oversampled to ensure reliable prevalence estimates.

	1998	**2004**	**2010**
Obesity (BMI>30kg/m^2)			
All races	6.3 (5.6,7.0)	6.8(6.0,7.5)	10.8(9.8,11.8)
Chinese	4.0(3.4,4.6)	4.2(3.5,4.9)	7.9(6.5,9.3)
Malay	18.0(14.9,21.1)	20.0(16.6,23.5)	24.0(21.9,26.1)
Indian	12.6(9.1,16.1)	13.2(9.5,16.8)	16.9(14.3,19.5)
Daily smoking			
All races	15.1(14.1,16.1)	12.3(11.3,13.4)	14.3(13.2,15.4)
Chinese	13.8(12.7,14.9)	11.5(10.4,12.6)	12.8(11.1,14.5)
Malay	22.1(18.7,25.4)	17.7(14.4,21.0)	26.5(24.3,28.7)
Indian	16.3(12.5,20.2)	11.8(8.3,15.30	10.1(8.0,12.2)
Regular alcohol consumption			
All races	2.8(2.4,3.3)	3.3(2.8,3.9)	2.6(2.1,3.1)
Chinese	3.192.6,3.7)	3.7(3.0,4.3)	2.9(2.0,3.8)
Malay	0.6(0.0,1.2)	0.7(0.0,1.4)	0.6(0.2,1.0)
Indian	3.3(1.4,5.1)	3.5(1.5,5.5)	3.3(2.1,4.5)
Regular exercise			
All races	17.7(16.7,18.8)	16.9(15.8,18.1)	19.0(17.7,20.3)
Chinese	16.9(15.7,18.1)	16.6(15.3,17.9)	19.2(17.3,21.3)
Malay	18.4(15.3,21.5)	18.0(14.7,21.3)	15.3(13.3,16.9)
Indian	24.3(19.8,28.8)	17.0(12.9,21.0)	21.7(18.8,24.6)
Diabetes			
All races	11.3(10.4,12.2)	9.0(8.1,9.9)	11.3(10.3,12.3)
Chinese	10.0(9.0,10.9)	7.5(6.6,8.5)	9.7(8.2,11.2)
Malay	15.8(12.9,18.7)	13.2(10.2,16.1)	16.6(14.7,18.5)
Indian	20.2(16.0,24.4)	18.1(13.9,22.2)	17.2(14.6,19.8)

Conflict Of Interest:
Eu-Leong YONG, Ganga Ganesan, Michael S. Kramer, Susan Logan, Tang Ching Lau, Jane A. Cauley, and Kelvin B. Tan declare that they have no conflict of interest.

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Chapter Four: Cost of Osteoporotic Fractures in Singapore

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Abstract

Purpose: To estimate the 3-month direct and indirect costs associated with osteoporotic fractures from both the hospital's and patient's perspectives in Singapore and to compare the cost between acute and prevalent osteoporotic fractures.

Methods: Resource use and expenditure data were collected using interviewer-administered questionnaires at baseline and at a 3-month follow-up between July 2013 and January 2014. Estimated osteoporotic fracture–related costs included hospitalizations, accident and emergency room visits, out- patient physician visits, laboratory tests, medications, transportation, health care and community services, special equipment and home/ car modifications, and productivity loss.

Results: A total of 67 patients agreed to participate, giving a response rate of 64.4%. The mean (median) 3-month direct medical cost from the hospital's perspective was found to be SGD 3,886.90 (SGD 413.10), of which 74.2% was accounted for by inpatient services, 25.2% by outpatient services, and 0.6% by accident and emergency services. Moreover, considerable variation (SD 1⁄4 SGD 2,615.40) was observed in the costs of outpatient rehabilitation services. Findings were similar when the patient's perspective was taken. The total costs, with both direct and indirect costs included, were SGD 11,438.70 (acute) and SGD 1,015.40 (prevalent), of which 34.7% and 8.0%, respectively, were accounted for by inpatient services.

Conclusions: Hospitalization was associated with the highest cost borne by both the hospital and the patient, and informal care dominated indirect costs. Better knowledge of the financial consequences of fragility fractures could enable proactive and preventive measures to be undertaken, especially at sites of care with high cost drivers.

Keywords: cost analysis, cost of disease, cost of illness, economic burden, osteoporosis, osteoporotic fracture.

4.1 Introduction

Osteoporosis is a bone condition closely related to advancing age that is characterized by reduced bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures (9, 83, 84). It is considered to be a serious public health concern, with an estimated 200 million people worldwide suffering from this disease (85). Osteoporosis-related fractures are associated with a high degree of morbidity and mortality (86). The average risk that a person older than 50 years will experience osteoporotic fracture has been estimated at 40% to 50% for women and at 13% to 22% for men (87). In 2000, 9 million osteoporotic fractures occurred worldwide, including 1.6 million hip fractures, 1.7 million forearm fractures, and 1.4 million clinical vertebral fractures (49, 88). In Singapore, hip fracture incidence rates have risen 1.5-fold for men and 5-fold for women since the 1960s. In addition, the age-adjusted hip fracture rate among women older than 50 years is about 402 per 100,000 females, and this rate is now among the highest in Asia (7, 89, 90).

An osteoporotic fracture is a chronic condition and is one of the most common causes of disability, incurring substantial costs in many regions of the world. The annual costs of all osteoporotic fractures have been estimated to be US $20 billion in the United States (91), €30 billion in the European Union (92), and A$1.8 billion in Australia (93). In addition, a study conducted in Singapore in 2001 estimated the mean hospitalization cost for patients with hip fractures treated surgically to be SGD 10,515 (32).

By 2050, the percentage of the population aged 60 years and older in Singapore is projected to increase to 38% (82). With this aging population, the number of hip fractures per year is projected to increase from 1300 in 1998 to 9000 by 2050 (89). Despite the large number of people affected by osteoporosis, no previous study in Singapore has compared the costs of acute osteoporotic fractures to those with prevalent ones or examined their indirect costs. It is the right time to estimate various costs of osteoporotic fractures to help decision makers to develop interventions that may potentially result in financial savings.

The aim of the present study was to identify the total direct and indirect costs of osteoporotic fractures in Singapore from both the hospital's and the patient's perspectives and also compare the costs between acute and prevalent osteoporotic fractures.

4.2 Material and Methods

Study Design

This study adopted a prevalence-based approach and a bottom- up method to estimate different cost components. The prevalence approach can yield more precise estimates because it ascertains the current economic burden of a disease rather than projected ones (94). The perspective of the National University Hospital (NUH) and that of the patients were taken in this study. This study was approved by the National Healthcare Group Domain-Specific Review Board.

Data Collection

A prospective observational study of patients with osteoporotic fractures was conducted from late July 2013 to January 2014 at the NUH, which is a 997-bed public tertiary hospital that served more than 670,000 outpatients and 59,000 inpatients in 2010 (95).

Data regarding resource use were collected using interviewer- administered questionnaires at baseline (i.e., the date of interview) and at a 3-month follow-up to minimize recall bias. The interviews were conducted at the Department of Orthopaedics of the NUH. The questionnaires used for data collection were adapted from existing instruments developed by the collaborating NUH rheumatologist and the author of a previous cost-of- illness (COI) study conducted in Singapore. Either the English or the Chinese version of the questionnaire was administered, depending on the patient's preference. At baseline, patients' demographic characteristics, clinical characteristics, and resources used for that particular visit were obtained. Patients were then asked, for the next 3 months, to take note week by week of all fracture-related physician visits, receipts, or bills they had. At the 3-month follow-up, the resource use since the last visit was collected. If a face-to-face interview was not feasible at the follow-up, a telephone interview was conducted instead. In circumstances in which the patient was unable to respond to the questions accurately, the questionnaires were given to a “proxy responder” (i.e., a person in close contact with the patient).

Patient Selection

To be included in the study, patients were required to have a bone mineral density scan or relevant x-ray examinations to ensure that their fractures were low-trauma (i.e., sustained from standing height or less). In addition, the patients needed to fulfil the following criteria: 1) they were older than 50 years; 2) they had a fragility fracture of the vertebral column, hip, humerus, wrist, or other bone (excluding the skull and bones distal to the ankles and wrists); and 3) they were able to ambulate with or without aid before fall (i.e., not wheelchair- or bed-bound). Eligible patients were identified at their visits to the Department of Orthopaedics (inpatient ward and outpatient specialist clinics), the Accident and Emergency (A&E) Department, or other relevant clinics. This was an institutional review board–approved study and written informed consent was obtained from each patient.

After a fracture occurs, there is an acute incident phase and a prevalent fracture phase. Patients were categorized as being in the acute phase if the fracture first occurred 4 weeks or less before the interview, whereas patients who had had their present fracture for more than 1 year were considered prevalent. Patients with a pathological fracture due to metastasis or those seeking care for multiple fractures at the same visit were excluded. Patients with apparent cognitive impairment that could prevent them from answering the questions accurately were also excluded.

Estimation of Direct Medical Costs

Singapore provides all its citizens with health care coverage, and the amount of coverage is determined by patient age, citizenship, income, and disability. The three tiers of coverage are govern- ment subsidies, Medisave, and MediShield. The government subsidies tier covers up to 80% of a patient’s bill in an acute public hospital and up to 50% in specialist clinics. Medisave is a compulsory medical savings account for individuals, from which citizens can make co-payments for their treatments, whereas MediShield is a basic health insurance plan (96).

Direct medical cost was classified as one of three types of service: inpatient hospitalization, A&E services, and ambulatory outpatient care, the last of which included physician visits, laboratory tests, rehabilitations, and medications. The total costs were estimated using the total out of pocket charges paid by the patients and the government subsidies, which are the total medical charges before any deductions that result from general government subsidies.

Costs of inpatient care and A&E services were estimated by the total charge, which was determined by the length of stay and the resources used. A&E visits that resulted in hospitalization were included as a part of the inpatient costs. In outpatient care cost calculation, physician visits included visits to primary care clinics (polyclinics) and specialist outpatient clinics (hospitals), whereas laboratory tests included x-rays, magnetic resonance imaging, bone mineral density, and blood tests. Rehabilitation costs that required admission to the community hospital were also included in the cost estimation. A standardized rate obtained from the pharmacy was used as the unit price of osteoporosis- related prescription medications (Table 1). Medication costs were estimated by multiplying the number of medications prescribed by the unit price of each medication. The expenditures on non-prescription medications such as vitamins or supplements were estimated on the basis of the receipts provided by the patients.

Estimation of Direct Nonmedical Costs

Direct nonmedical costs consisted of costs for transportation, health care, and community services as well as special equipment and home/car modifications. Health care and community services included, but were not limited to, massage therapy, acupuncture, traditional Chinese medicine, meal delivery, domestic helpers, and community private nursing. Special equipment and home/car modifications included bathroom equipment (commode and handlebars), bedroom room equipment (rope ladder and mattress), crutches, wheelchairs, home modifications (steps alteration and ramps), and car modifications (seat alteration and steering devices).

Table 1 – Osteoporosis-related prescription medications.

Drug	Brand name
Alendronate	Fosamax 10 mg®
	Fosamax 70 mg®
Denosumab	Prolia 60 mg®
Risedronate	Actonel 35 mg®
Strontium ranelate	Protelos 2 g®
Teriparatide	Forteo 20 mcg®
Zoledronate	Aclasta 5 mg®
	Zometa 5 mg®
Calcitonin (nasal spray)	Calcitonin Novartis Nasal Spray®
Calcium carbonate (450 mg) + vitamin D (200 IU)	Nonspecific
Vitamin D_3 (1,000/5,000 IU)	Lynae®
Ergocalciferol (1.25 mg) + vitamin D (50,000 IU)	Nonspecific

IU, international unit.

Table 2 – Sociodemographic and clinical characteristics of patients with osteoporotic fractures, 2013.

Characteristic	n (%)* or mean ± SD					
	Overall (N = 67)		Acute (n = 16)		Prevalent (n = 51)	
Individual-level variables						
Age (y)	73.7 ± 10.8		71.3 ± 10.5		74.5 ± 10.9	
Sex						
Female	60	(89.6)	14	(87.5)	46	(90.2)
Male	7	(10.4)	2	(12.5)	5	(9.8)
Race						
Chinese	59	(88.1)	14	(87.5)	45	(88.2)
Indian	4	(6.0)	1	(6.3)	3	(5.9)
Malay	3	(4.5)	1	(6.3)	2	(3.9)
Others	1	(1.5)	0	(0.0)	1	(2.0)
Marital status						
Married	40	(59.7)	11	(68.8)	29	(56.9)
Widow	24	(35.8)	4	(25.0)	20	(39.2)
Single	3	(4.5)	1	(6.3)	2	(3.9)
Highest level of education						
No school	26	(38.8)	6	(37.5)	20	(39.2)
Primary	18	(26.9)	3	(18.8)	15	(29.4)
Secondary	14	(20.9)	3	(18.8)	11	(21.6)
Junior college/polytechnic	4	(6.0)	2	(12.5)	2	(3.9)
University	5	(7.5)	2	(12.5)	3	(5.9)
Monthly household income (SGD)						
No income	12	(17.9)	4	(25.0)	8	(15.7)
<1000	4	(6.0)	1	(6.3)	3	(5.9)
1000–2999	23	(34.3)	7	(43.8)	16	(31.4)
3000–4999	10	(14.9)	0	(0.0)	10	(19.6)
>5000	18	(26.9)	4	(25.0)	14	(27.5)
Smoking status						
Nonsmoker	64	(95.5)	15	(93.8)	49	(96.1)
Smoker	3	(4.5)	1	(6.3)	2	(3.9)
Employment status						
Retired	47	(70.1)	7	(43.8)	40	(78.4)
Employed	6	(9.0)	2	(12.5)	4	(7.8)
Unemployed	1	(1.5)	1	(6.3)	0	(0.0)
Other	13	(19.4)	6	(37.5)	7	(13.7)
Current living arrangement						
Live with spouse/children/relatives	62	(92.5)	15	(93.8)	47	(92.2)
Live alone	2	(3.0)	1	(6.3)	1	(2.0)
Other	3	(4.5)	0	(0.0)	3	(5.9)
Primary caregiver						
Spouse/partner	23	(34.3)	7	(43.8)	16	(31.4)
Daughter/son	20	(29.9)	6	(37.5)	14	(27.5)
Other	24	(35.8)	3	(18.8)	21	(41.2)
Receive money from Medifund						
No	64	(95.5)	15	(93.8)	2	(3.9)
Yes	3	(4.5)	1	(6.3)	49	(96.1)
Plan to use government schemes†						
No	52	(77.6)	2	(12.5)	50	(98.0)
Yes	15	(22.4)	14	(87.5)	1	(2.0)
Plan to use private health insurance						
No	59	(88.1)	10	(62.5)	49	(96.1)
Yes	8	(11.9)	6	(37.5)	2	(3.9)
Receive health insurance from employer						
No	65	(97.0)	14	(87.5)	51	(100.0)
Yes	2	(3.0)	2	(12.5)	0	(0.0)
Fracture-related variables						
First fracture						
No	8	(11.9)	0	(0.0)	8	(15.7)
Yes	59	(88.1)	16	(100.0)	43	(84.3)
Duration of fracture (y)	2.7 ± 2.6		0.3 ± 0.2		3.4 ± 2.6	

continued on next page

Table 2 – *continued*

Characteristic	n (%)[*] or mean ± SD					
	Overall (N = 67)		Acute (n = 16)		Prevalent (n = 51)	
Fracture type						
Vertebral column (spine)	29	(43.3)	3	(18.8)	26	(51.0)
Hip	23	(34.3)	8	(50.0)	15	(29.4)
Humerus	6	(9.0)	1	(6.3)	5	(9.8)
Wrist	2	(3.0)	0	(0.0)	2	(3.9)
Other[‡]	7	(10.4)	4	(25.0)	3	(5.9)

[*] Percentages may not add up to 100% because of rounding.
[†] Includes Medisave, Medifund, Medishield, or Eldershield.
[‡] Includes patella, elbow, tibia, and pelvis.

Direct nonmedical costs were not eligible for government subsidies and were estimated by the total charge shown on the receipts provided by the patient. Transportation costs via personal vehicle were calculated by multiplying the distance travelled by the unit cost of petrol (SGD 0.45/km) (97), whereas the costs of taking mass rapid transit, bus, or taxi were estimated using a Web-based calculator (98). In addition, the cost for hiring a domestic helper was estimated by using a conservative rate of 50% of the helper's monthly salary assuming that the helper would not spend 100% of his or her time caring for the patient.

Estimation of Indirect Costs

Indirect costs were estimated using the human capital approach instead of the friction-cost method because the former is grounded in neoclassical economic theory, whereas the latter is not (99). Moreover, Singapore's unemployment rate in 2013 remained low, and it is only in the case of labor market imperfections or periods of high unemployment that the friction-cost approach should be considered (92). Productivity loss due to absence from work and costs of informal (unpaid) care provided by family members and/or other persons were included in the indirect cost estimation. Working patients were asked about their current occupation and to estimate the number of days and/or hours of productivity that were lost because of their fracture. As individual hourly wage rates were not available, monthly occupational wages obtained from the Ministry of Manpower (100) were used to derive hourly earnings with the assumption that a full-time worker is employed 5 days per week, 8 hours per day. Absenteeism was thus calculated by multiplying the number of hours of absence from work with the hourly rates. The occupation "housekeeper" was used to estimate the hourly earnings of patients or caregivers who were retired or homemakers. Patients were asked about the occupation of their primary caregiver and to estimate the hours of care provided by them. For caregivers who were employed, the occupational wages from the Ministry of Manpower were used and multiplied by the number of hours spent on caring for the patient.

Statistical Analysis

Descriptive statistics (frequency, percentage, mean, median, SD, and 90th percentile) were used to present costs and patients' demographic characteristics. Before-subsidy charges were used for cost estimation when the hospital's perspective was taken and only direct medical costs were included. For the patient's perspective, after-subsidy charges were used for cost estimation, which included direct medical costs, direct nonmedical costs, and indirect costs. In the cost estimation, only osteoporotic fracture– related costs were included. All costs were reported in 2013 Singapore dollars. The statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL).

4.3 Results

Patients' Characteristics

A total of 104 eligible patients were approached and 67 (16 acute; 51 prevalent) agreed to participate in this study, giving a response rate of 64.4%. The sociodemographic profile of the patients is presented in Table 2. Most of the patients were female (89.6%), Chinese (88.1%), married (59.7%), non-smokers (95.5%), retired (70.1%), and living with their spouse, children, or relatives (92.5%). The mean age was 73.7 10.8 years and the mean duration of fracture was 2.7 2.6 years. Approximately one-third of the patients did not attend school (38.8%) and had a monthly household income between SGD 1,000 and SGD 2,999 (34.3%). The number of patients who had a spouse (34.3%) serving as their primary caregiver was similar to the number who had other help such as a domestic helper (35.8%). The most common fractures were those of the vertebral column (43.3%) and hip (34.3%), and 88.1% of the patients were experiencing their first fracture.

Costs of Osteoporotic Fractures

Taking the hospital's perspective, the mean (median) direct medical cost of osteoporotic fractures was found to be SGD 3,886.90 (SGD 413.10) (US $1.00 1⁄4 SGD 1.30 as of December 2013) (101), of which SGD 2,884.00 was for inpatient services, SGD 979.60 for outpatient services, and SGD 23.40 for A&E services (Table 3). The main cost driver was inpatient costs (74.2%), whereas A&E services (0.6%) contributed to only a small portion of the total costs. Moreover, considerable variation (SD 1⁄4 SGD 2,615.40) was observed in the costs of outpatient rehabilitation services. The findings were similar from the patient's perspective, with inpatient services (57.9%) being the main cost driver and the costs of rehabilitation services significantly varied (SD 1⁄4 SGD 2,211.40). Overall, the costs from the patient's perspective were lower than those from the hospital's perspective because of government subsidies.

The mean total costs (including direct and indirect costs) were SGD 11,438.70 (acute) and SGD 1,015.40 (prevalent), of which 34.7% and 8.0%, respectively, were accounted for by inpatient services. The costs across all service types were consistently higher in acute patients than in prevalent patients except for in the categories of outpatient medications and health care and community services. Compared with the acute patients, the prevalent group spent a higher proportion of the total costs on outpatient services as well as on health care and community services. It is noteworthy that great variation was present in outpatient rehabilitation and informal care costs in the acute group (Table 4).

Table 3 – Direct medical costs incurred by the hospital and patient at different sites of care (n = 67).

Site of care	Hospital*	Patient†
Inpatient		
Mean ± SD	2,884.0 ± 6,650.0	1,010.2 ± 2,405.7
Median	0.0	0.0
90th percentile	13,621.1	4,292.3
Percentage of total cost (%)‡	74.2	57.9
Accident and emergency		
Mean ± SD	23.4 ± 89.1	13.4 ± 53.4
Median	0.0	0.0
90th percentile	0.0	0.0
Percentage of total cost (%)‡	0.6	0.8
Outpatient		
Mean ± SD	979.6 ± 2,656.1	721.6 ± 2,258.3
Median	344.0	226.1
90th percentile	1,477.2	1,018.9
Percentage of total cost (%)‡	25.2	41.3
Outpatient physician visits		
Mean ± SD	263.4 ± 288.0	138.5 ± 152.6
Median	208.1	112.4
90th percentile	533.4	332.3
Percentage of total outpatient cost (%)‡	26.9	19.2
Outpatient laboratory tests		
Mean ± SD	19.6 ± 117.1	10.1 ± 62.9
Median	0.0	0.0
90th percentile	0.0	0.0
Percentage of total outpatient cost (%)‡	2.0	1.4
Outpatient rehabilitations		
Mean ± SD	532.3 ± 2,615.4	389.2 ± 2,211.4
Median	0.0	0.0
90th percentile	56.7	27.3
Percentage of total outpatient cost (%)‡	54.3	53.9
Outpatient medications		
Mean ± SD	164.3 ± 267.4	149.7 ± 241.4
Median	65.9	68.0
90th percentile	774.8	700.0
Percentage of total outpatient cost (%)‡	16.8	20.7
Total cost		
Mean ± SD	3,886.9 ± 8,463.5	1,745.2 ± 4,043.9
Median	413.1	265.0
90th percentile	14,258.4	4,670.1

* Before government subsidy charges.
† After government subsidy charges.
‡ Percentages may not add up to 100% because of rounding.

4.4 Discussion

This prevalence-based COI study is the first one in Singapore, and one of the few in Asia, that compares the costs of acute and prevalent osteoporosis-related fractures. Furthermore, both direct and indirect costs of these fractures were examined in this study.

Taking the hospital's perspective, the direct medical cost per patient over a 3-month time period estimated in this study was SGD 3,886.90 (US $2,876.30, with SGD 1 1⁄4 US $0.74), and this figure appears to be similar to those reported in other Asian countries. A study in China reported an estimate of approximately ¥15,736.90 (US $2,360.50, with ¥1 1⁄4 US $0.15) (102) per patient, whereas in Taiwan it costs

NT$100,000.00 (US $3,000.00, with NT $1 1⁄4 US $0.03) for the management of osteoporotic fractures (103). Nevertheless, when taking the patient's perspective, the cost per patient estimate was greatly reduced by more than half to SGD 1,745.20 (US $1,291.40, with SGD 1 1⁄4 US $0.74). This difference is mainly due to having up to 80% inpatient subsidies depending on the patient's financial status (104-106). Notably, direct medical costs of fractures reported in the American (107, 108) and European continents (109-111) were much higher than those estimated in this study. Nevertheless, caution is required when making these comparisons because of the differences in the length of period over which the costs were calculated and the types of costs examined among the studies.

Despite the difference in total costs estimated between the hospital's and patient's perspectives, inpatient costs remained the main cost contributor, which is consistent with findings in other osteoporotic fracture COI studies (107, 108, 112-114). Understanding the factors influencing inpatient costs is therefore important. High inpatient costs are usually strongly correlated to length of stay, with a longer length of stay resulting in higher costs (115, 116). Nevertheless, though perhaps not intuitive, the health consequences of shortened hospital stays may in fact be positive if coupled with adequate rehabilitation services after discharge. One study (117) reported significant cost savings when patients had early discharge from the hospital followed by community-based rehabilitation, which allows for faster retraining of physical independence and other activities of daily living. As such, attempts to expedite early discharge from hospital to a community-based rehabilitation setting may help reduce overall costs.

The cost of osteoporosis-related fractures within the first 4 weeks of occurrence is concerning, with health care resource consumption in acute patients being significantly higher than in prevalent patients. Complications and comorbidities were also more likely to occur within the first few weeks after a fracture, which result in higher health care costs in the acute phase than in the prevalent phase (118). In contrast, direct nonmedical costs were found to be comparable between acute and prevalent groups, with health care and community services being the greatest generator of costs. Nevertheless, domestic helpers were employed by most of the prevalent patients, whereas caregivers such as family members were the main source of assistance in the acute group. As expected, transport costs and the expenditures on special equipment and home/car modifications were noticeably higher in the acute group. Immediately after a fracture occurred, private or public ambulances were usually used as the main mode of transportation, which were more costly than public transport or a personal vehicle. Furthermore, as acute patients had no previous fracture, they needed to spend money on special aids, such wheelchairs or walkers, in addition to making home modifications, such as the installation of ramps and handlebars. Currently, Singapore's government provides up to 90% subsidy for assistive devices that aids mobility with the aim of enabling independent living (106). Examples include walking aids, wheelchairs, shower chairs, and so forth. In addition, an Enhancement for Active Seniors program has also been rolled out to subsidize improvement items such as ramps and handlebars for families with an elderly between the ages of 60 and 64 years (119). The helpfulness and utilization of these initiatives in patients with osteoporosis-related fractures, particularly those in an acute phase, need to be further investigated.

In this study, indirect costs were also examined. Overall, the estimated cost of absenteeism was low because few patients were younger than 65 years and working. Nevertheless, informal care was the most significant cost contributor when the fracture was recent; most caregivers for acute patients were the patient's spouse, who had mostly been retired, but many were the patient's children, who had to give up their remunerated work. In Singapore, eldercare leave, which is a benefit that allows employees to take time off from work to take care of elderly parents or family members, has been offered in certain companies, but has yet to be legislated (120). Given the aging population and the informal care needs of elderly patients with diseases such as osteoporotic fracture, decision makers should consider strengthening the practice of eldercare leave and also developing new care options to better support working families caring for seniors.

Table 4 – Direct and indirect costs incurred by the patient according to patient type.

Cost	Acute (n = 16)	Prevalent (n = 51)
	Direct medical costs	
Inpatient		
Length of stay (d)	10.1 ± 7.4	0.3 ± 1.4
Mean ± SD	3,972.3 ± 3,543.7	80.9 ± 428.3
Median	3,684.3	0.0
90th percentile	9,025.7	0.0
Percentage of total cost (%)*	34.7	8.0
Accident and emergency		
Mean ± SD	38.9 ± 81.9	5.4 ± 38.5
Median	0.0	0.0
90th percentile	174.0	0.0
Percentage of total cost (%)*	0.3	0.5
Outpatient		
Mean ± SD	1,922.9 ± 4,430.7	377.8 ± 514.5
Median	446.7	214.4
90th percentile	9,096.5	999.5
Percentage of total cost (%)*	16.8	37.2
Outpatient physician visits		
Mean ± SD	212.1 ± 115.1	115.4 ± 156.5
Median	194.5	56.2
90th percentile	387.1	209.2
Percentage of total outpatient cost (%)*	11.0	30.5
Outpatient laboratory tests		
Mean ± SD	31.4 ± 125.6	3.4 ± 17.5
Median	0.0	0.0
90th percentile	150.7	0.0
Percentage of total outpatient cost (%)*	1.6	0.9
Outpatient rehabilitations		
Mean ± SD	1,541.4 ± 4,421.5	27.8 ± 179.9
Median	0.0	0.0
90th percentile	8,257.4	0.0
Percentage of total outpatient cost (%)*	80.2	7.4
Outpatient medications†		
Mean ± SD	138.0 ± 236.1	231.2 ± 414.9
Median	54.7	104.1
90th percentile	503.4	783.4
Percentage of total outpatient cost (%)*	7.2	61.2
Total direct medical costs		
Mean ± SD	5,934.1 ± 6,779.7	464.0 ± 687.7
Median	4,286.2	216.1
90th percentile	21,553.3	1,034.5
	Direct nonmedical costs	
Transport		
Mean ± SD	121.9 ± 128.1	28.1 ± 29.4
Median	74.9	16.5
90th percentile	367.3	66.4
Percentage of total cost (%)*	1.1	2.8
Other health care and community services		
Mean ± SD	157.8 ± 334.1	372.4 ± 438.4
Median	0.0	0.0
90th percentile	850.5	975.0
Percentage of total cost (%)*	1.4	36.7
Special equipment and home/car modifications		
Mean ± SD	376.6 ± 685.6	19.9 ± 68.3
Median	67.0	0.0
90th percentile	1,929.7	54.9
Percentage of total cost (%)*	3.3	2.0
Total direct nonmedical costs		
Mean ± SD	656.3 ± 958.0	420.4 ± 444.1
Median	214.7	81.9
90th percentile	2,629.6	1,066.7

continued on next page

Table 4 – continued

Cost	Acute (n = 16)	Prevalent (n = 51)
	Indirect costs	
Absenteeism		
Hours of productivity loss	76.7 ± 134.3	1.8 ± 4.5
Mean ± SD	609.8 ± 1,062.6	24.0 ± 91.3
Median	161.0	0.0
90th percentile	3,069.9	62.6
Percentage of total cost (%)*	5.3	2.4
Informal care		
Hours of informal care	237.5 ± 313.5	4.7 ± 5.2
Mean ± SD	4,238.5 ± 11,919.0	107.0 ± 291.8
Median	858.9	50.0
90th percentile	18,109.5	232.2
Percentage of total cost (%)*	37.1	10.5
Total indirect costs		
Mean ± SD	4,848.2 ± 11,778.2	131.0 ± 298.8
Median	1,581.0	61.6
90th percentile	18,109.5	235.4
Total cost		
Mean ± SD	11,438.7 ± 14,320.1	1,015.4 ± 1,018.4
Median	5,721.4	839.0
90th percentile	37,642.8	1,775.2

* Percentages may not add up to 100% because of rounding.
† Includes prescription and nonprescription medications.

Contrary to the common opinion that indirect costs far exceed direct costs (121, 122), the findings in this study were less decisive, as were reported in two other osteoporotic fracture–related COI studies, in which direct costs were found to be higher than indirect costs (123). The adequate method for indirect cost estimation has been subject to considerable debate (124, 125); therefore, caution is warranted when comparing results among studies that used different methodologies. For example, the present study's cost estimates are considerably lower than those obtained by three previous studies of fractures conducted in Singapore (31-33). Chen et al. (33) estimated an average cost of SGD 9,347.50, whereas Wong et al. (31) and Lee et al. (32) reported costs of SGD 7,367.00 and SGD 10,515.00, respectively. It should, however, be noted that these studies had a different length of period for cost estimation and focused on the costs of hip fractures.

This study is not without limitations. First, selection bias may have been present because patients were selected from a single tertiary hospital, and the response rate (64.4%) was less than satisfactory. As such, the study findings may be generalizable only to those patients, particularly female patients with prevalent osteoporotic fractures, who seek care at a public hospital. Second, although costs were highly dependent on fracture types, we were unable to estimate the costs by fracture type because of the small sample size in our study. As such, the cost estimates could be generalizable only to patients groups with a similar mixture of fracture types. Third, although strategies, such as giving multiple reminders, were used to attempt to collect complete cost data from patients, the data collected may still be incomplete or inaccurate because of forgetfulness and/or carelessness. Along with the short period of data collection, these challenges may have resulted in an underestimation of the total costs.

4.5 Conclusions

This study provides a better understanding of the direct and indirect costs of osteoporotic fractures in Singapore. Hospitalization was associated with the highest cost borne by both the hospital and the patients, and informal care dominated indirect costs. With an aging population, the prevalence of osteoporosis- related fractures in Singapore will continue to grow in the years to come, generating what is expected to be a heavy burden on health budgets. Better knowledge of the financial consequences of fragility fractures could enable proactive and preventive measures to be undertaken, especially at sites of care with high cost drivers.

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Chapter Five: The effectiveness of a fracture liaison service program in improving outcomes of patients with prior fragility fractures

ABSTRACT

Purpose: This study aimed to evaluate the effectiveness of a fracture liaison service called OPTIMAL in Singapore.

Methods: Osteoporosis Patient Targeted and Integrated Management for Active Living (OPTIMAL) is a fracture liaison service program, funded by Singapore Ministry of Health. It was set up in the six public restructured hospitals in 2008 and later expanded to include the 18 polyclinics in Singapore. The aim of the program was to provide optimal assessment and treatment of osteoporosis to patients identified as having high risk of fragility fractures. OPTIMAL assumed responsibility for fracture case finding, for performing and assessing diagnostic laboratory tests and axial DXA, for providing falls prevention recommendations and exercise prescription, and for making specific treatment recommendations for the secondary prevention of osteoporotic fractures. The program supported six follow-up encounters for the patient with the case manager over a period of 2 years. During these follow-ups, the case manager answered questions, reinforced the importance of compliance to exercise and medications, and recorded any falls or fractures that might have happened in the interim period.

Results: A total of 21,233 patients were screened over the 8-year period. Among these, 8,116 patients were enrolled into the program, whilst the other 13,288 either did not fulfil recruitment criteria or did not provide consent. OPTIMAL enrolees tended to be younger, female, Chinese and had more recent or old fractures. OPTIMAL patients had a hazard ratio of 0.550 of fracture when compared with non-enrolees. Those who were of older age, of male gender, Malay ethnicity and higher Charlson comorbidity index (CCI) had higher odds of fracture after screening. In patients who developed fractures after screening, OPTIMAL enrolled patients had reduced mortality hazard rates of 40% controlling for age, gender, ethnicity and CCI.

Conclusion: The most important finding of this study is the reduction in all sites fracture risk by 41.0%, hip fracture risk by 47.1% and mortality hazard by 40% of patients enrolled into the OPTIMAL program when compared with non-enrolees after five years. The mortality our data and audit provide the first compelling evidence from an Asian country of the potential effectiveness of a secondary fracture prevention program. The lessons learned during the last 5 years would enable us to implement a revised and more effective program in the near future.

Keywords: Osteoporosis, Hip Fracture, Fracture Liaison Service, Singapore

5.1 Introduction

In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. In the next 50 years, more than half of all hip fractures are projected to occur in Asia(126). Osteoporosis is likely to increase as the population of Singapore is aging rapidly (127). In 2010 only 6% of the population was above the age of 60, but by 2030, this figure is projected to rise to 25% (6). Indeed, osteoporotic fractures at the hip, wrist and spine are increasingly observed clinically. In Singaporean men and women above the age of 50 years, hip fracture incidence rates have risen 1.5-fold and 5-fold respectively since the 1960s (7). Our age-adjusted rates among women over the age of 50 years are currently among the highest in Asia, and approaching those of the West. The rise in hip fracture incidence is consistent with secular trends seen in many other countries.

An analysis of patients who sustained osteoporotic hip fractures in Singapore demonstrated a mortality of 20% to 25% at two years (15, 128, 129). Of the survivors, 20% became semi- or fully dependent, and 42% became less or non-ambulant(130). Similarly, vertebral fractures also cause significant complications including back pain, height loss, kyphosis and limitation of activity (25). In addition, there is an association with increased mortality (29). Whereas hip fracture incidence rates in Asia remain lower than in the West, vertebral fracture prevalence in Asian populations appears to be similar to those in Caucasian populations (30).

In the past two decades, fracture liaison service (FLS) has been showed to reduce the burden of hip fractures by identifying patients who have previous fragility fractures, investigating for secondary causes of osteoporosis and risk factors for fracture, initiating lifestyle behavioural changes and osteoporosis medications, and monitoring for adherence to these interventions(44, 131-134). This study aimed to evaluate the effectiveness of a fracture liaison service called OPTIMAL (Osteoporosis Patient Targeted and Integrated Management for Active Living) in Singapore (figure 1).

5.2 Material and Methods:

Program Description

Osteoporosis Patient Targeted and Integrated Management for Active Living (OPTIMAL) (135) is a secondary fracture prevention program, funded by Singapore Ministry of Health. It was set up in the six public restructured hospitals in 2008 and later expanded to include the 18 polyclinics in Singapore. The aim of the program was to provide optimal assessment and treatment of osteoporosis to patients identified as having high risk of fragility fractures. OPTIMAL assumed responsibility for fracture case finding, for performing and assessing diagnostic laboratory tests and axial DXA, for providing falls prevention recommendations and exercise prescription, and for making specific treatment recommendations for the secondary prevention of osteoporotic fractures.

At the time of implementation of OPTIMAL, certain general standards of care in accordance with evidence-based national guidelines were decided upon after several consensus meetings among the various clinician champions. However, individual champions implemented the program in their hospitals in a way that would work best at their respective institutions. In most hospitals, it was set up as a multidisciplinary effort between the Department of Endocrinology, Emergency Medicine, Orthopedics, Rheumatology, and Geriatrics. In a few hospitals, Obstetrics and Gynecology, Internal Medicine, Family Medicine, and Physical Medicine and Rehabilitation were also involved. The set up was contextualised to include the departments that treated the majority of patients with osteoporosis and osteoporotic fractures.

The program was organised in such a way that a case manager specific to the program would be informed each time that a physician from any of the above departments identified patients aged 50 years or older with a low trauma fracture. Patients who had high Fracture Risk Assessment tool (FRAX) score (8) (all sites fracture rate greater than 20%, and hip fracture rate greater than 3% over ten years) but no prior fracture could also be enrolled. The case managers, who were specially trained nurses, assessed both inpatients and outpatients referred to the service. Fracture case records from the emergency department were also screened on a weekly to biweekly basis to identify patients with low trauma fractures that were seen in the department. Suitable patients were then contacted and invited to participate in the program. Patients with skull and facial fractures and those with fractures distal to the wrist and ankle were not recruited into the program, as most of these fractures are unlikely to be osteoporosis-related. Patients should also agree to be followed up for at least 2 years. There were no other exclusion criteria imposed.

Recommendations were made to the referring physicians to request, in all their patients who have consented to be in the program, to perform laboratory work-up which included a full blood count, bone profile including calcium, phosphate, alkaline phosphatase and vitamin D levels, thyroid function tests (TSH and free thyroxine) and serum creatinine. Dual Energy X ray Absorptiometry (DXA) Bone Mineral Density (BMD) at the hip and the lumbar spine (L1–L4) in the patients was measured using the Hologic Discovery series of BMD machines (Hologic, Waltham, MA, USA). Male and female local reference databases were used to calculate the T-score in men and women, respectively. Though treatment could be initiated without a DXA BMD testing in patients with previous fractures, recommendations were also made for performing a baseline DXA BMD of the hip and spine in all patients and to repeat the BMD at the end of 2 years to facilitate monitoring of BMD change if any.

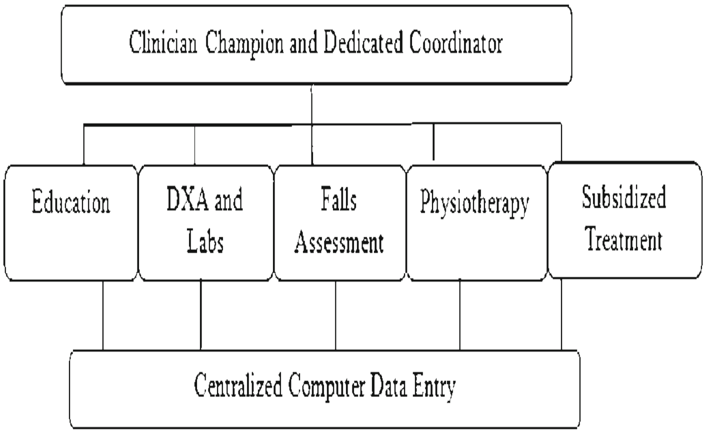
Education about osteoporosis and reduction of falls and fracture risk was provided individually to patients. All patients without contraindication to anti-osteoporosis medications were provided treatment recommendations and counselling about risks and benefits of medications. The medications include all the commonly prescribed medicines in Singapore for osteoporosis, namely the oral bisphosphonates—alendronate and risedronate, the intravenous bisphosphonate—zoledronic acid, strontium ranelate, raloxifene, and subcutaneous teriparatide.

Falls risk assessment was performed on all patients recruited into the program and this assessment was done through a thorough history taking, medication review, vision screening, and a timed up and go test (136) that measures basic mobility skills through a sequence of functional manoeuvres used in everyday life. These helped to determine whether an in-depth mobility assessment and early intervention, such as prescription of a walking aid, home visit, or physiotherapy, were necessary. Patients not wheel chair-bound were encouraged to enrol in one of the three exercise programs as part of the holistic management for osteoporosis, especially those who were sedentary before enrolment. The first is the OTAGO—a group strength and balance retraining program designed to prevent falls in older people living in the community (137). The second was individual physiotherapy exercise sessions especially for patients with physical limitations requiring a more tailored approach. The third was a community-based exercise (e.g., tai chi) whereby patients embark on an exercise program at their nearby community center or neighbourhood. The ultimate choice on which exercise program to enrol was left to the discretion of the physiotherapist and patient. OTAGO was conducted through six 1-hour sessions over 6 weeks, followed by recommendations to the patients to continue with either further individual physiotherapists or to continue the exercises that have been taught, at their home or community gym for the next 2 years. Patients who have been assessed, educated, and started on appropriate therapy were also offered the option to continue their follow-up in primary care at the polyclinics instead of at the clinics in the hospital.

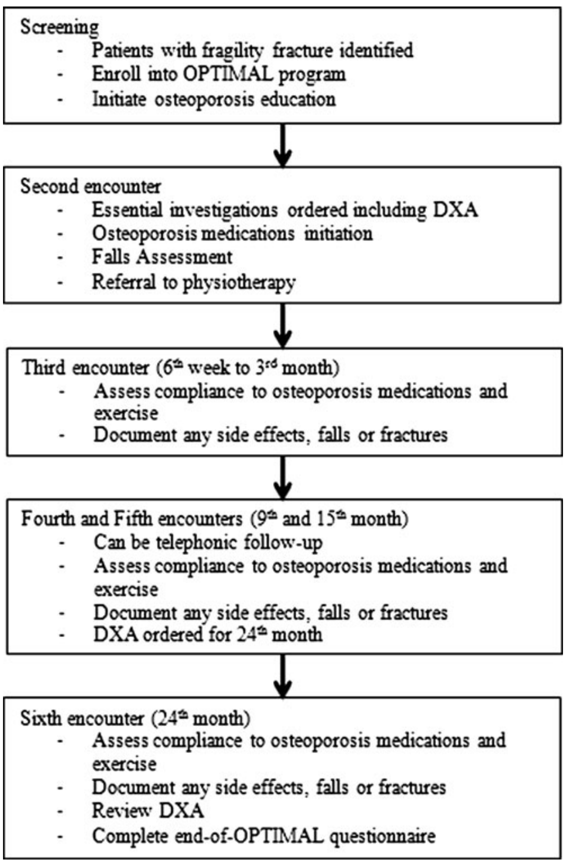
The program supported six follow-up encounters (at least three were face-to-face and the remaining either telephonic or face-to-face) for the patient with the case manager over a period of 2 years (flow chart 1). During these follow-ups, the case manager answered questions, reinforced the importance of compliance to exercise and medications, and recorded any falls or fractures that might have happened in the interim period.

OPTIMAL maintains a centralized computerized data- base (CCRD) for the entry of all data including demographic details, past medical and surgical including fracture and falls history, risk factors for osteoporosis, current medication use, dietary calcium intake, DXA results and interpretation, lifestyle and treatment recommendations, and arrangements for follow-up. A separate data form was also entered into the centralized database at the end of the 2-year follow-up to include information on medication and exercise compliance, falls or fractures that have occurred in the intervening period since recruitment, and DXA BMD results if done at 2 years. For further details of the program in one of the hospitals, please refer to the publications by Chandran et al (79, 138, 139).

Figure 1: Conceptual Model of OPTIMAL program



Flow chart 1: Enrollment and follow up process for patients in the OPTIMAL program



Data analysis

Analysis of outcome for patients who completed 2 years of follow-up by the program from 2008 to 2016 was done using data collected during the process of screening, recruitment, and follow-up of patients in the OPTIMAL program. The analysis was conducted in July 2018. Approval to conduct this study was obtained from the Centralized Institutional Review Board of National Healthcare Group and the study conformed to the provisions of the World Medical Association Declaration of Helsinki. Data from the program was supplemented with utilisation data from Ministry of Health Singapore administrative databases. The details of the data types and sources are listed in Table 1.

Table 1. Data items and data sources

Data items	Description	Source
Screening date	Date of screening/enrolment	OPTIMAL dataset
Enrolment status	Enrolled yes/no	OPTIMAL
Reason for not enrolling	Standardised list	OPTIMAL
Demographics	Gender, Race, Age	OPTIMAL, MOH admin
Past medical history	Chronic diseases	MOH admin
Past history of fracture	Fracture, type, year	OPTIMAL, MOH admin
Medications	Current meds (names) before enrolment; after enrolment;	OPTIMAL After screening (only for enrolled)
Fracture risk score	FRAX score – major fracture, hip fracture (4.7K, mostly from OPTIMAL patients	OPTIMAL
Fractures	Fracture, type, year	OPTIMAL (only enrolled) , MOH admin
Mortality	Date of death	MOH admin
Hospital utilisation	Admissions, LOS, ED visits, SOC visits costs	MOH admin
Primary care visits	Polyclinic and General Practioner visits, costs	MOH admin

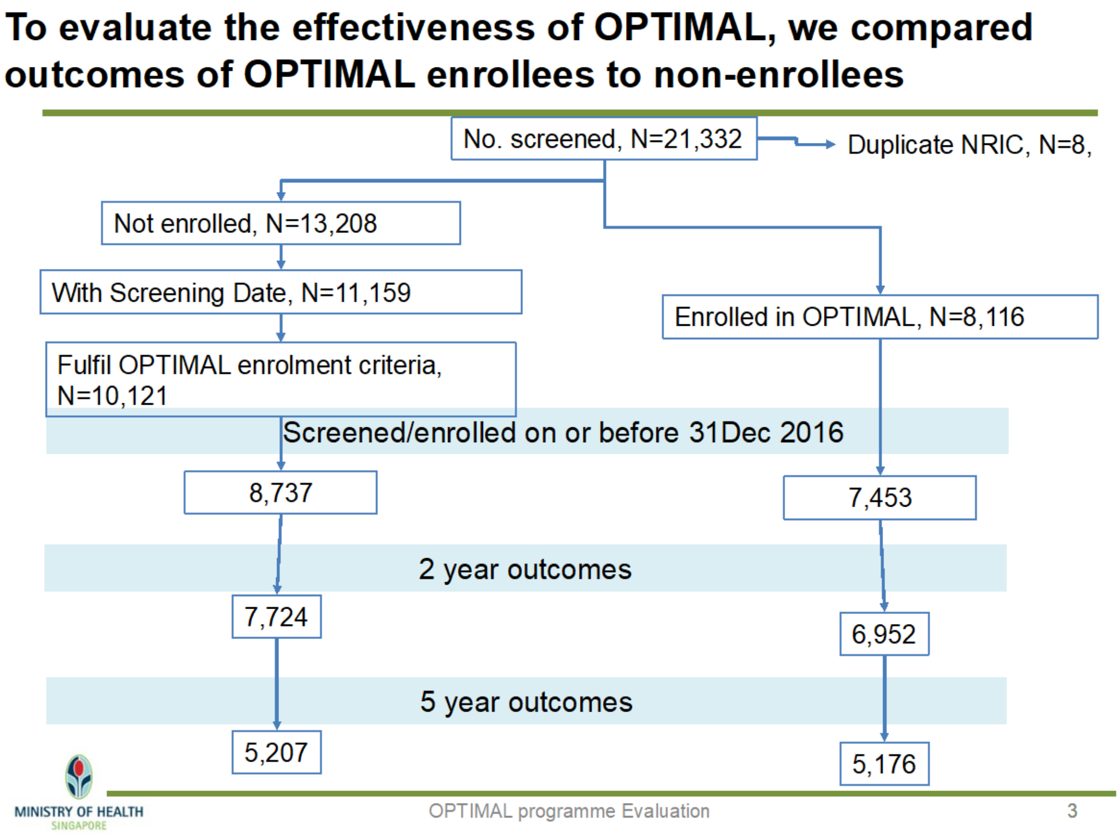
Descriptive analysis was initially conducted for the whole sample and the responses of the various stratified subgroups by age and gender were compared. The student's t-test was applied for continuous variable, and logistic regression, Cox proportional hazards regression analysis and the chi-square test was applied for categorical variables using the statistical package STATA version 14.0 (StataCorp LLC,Texas, USA). Key variables analyzed were age, gender, ethnic group, first-degree relatives with osteoporosis, smoking, alcohol, intake of steroids, previous fractures, family history of fracture, practice of regular exercise, intake of calcium supplements and the knowledge items. The main outcome variable was the presence of new fractures after screening and enrolment into the program.

5.3 Results

A total of 21,233 patients were screened by the care managers over the 8-year period. Among these, 8,116 patients were enrolled into the program, whilst the other 13,288 either did not fulfil recruitment criteria or did not provide consent. The most common reasons for their refusal to participate in the program were: 1) osteoporosis is not important condition to be managed, 2) no time to come for follow up appointment, and 3) no one to bring patient for follow up appointment. Amongst those who were not enrolled, 10,121 patients fulfilled OPTIMAL enrolment criteria, of whom 8,737 were enrolled on or before 31st Dec 2016. 7,724 patients had 2 years outcome data and 5,207 patients had 5 years outcome data by 31st Dec 2017.

Amongst patients who were enrolled in the program, 6,952 had 2 years outcome data and 5,176 had 5 years outcome data. Figure 2 shows the flow chart for the two comparison groups- the enrolees versus the non-enrolees

Figure 2. Recruitment flow chart of OPTIMAL enrolees versus non-enrolees



The demographic characteristics, certain pertinent risk factors, and baseline fracture rates of the patients are summarized in Table 2. Compared with non-enrolees, OPTIMAL patients were younger, with fewer comorbidities such as diabetes mellitus, and also more recent (fracture less than 1 year ago) and old fractures (fracture more than 1 year ago). 77% of OPTIMAL patients were on osteoporosis medications after enrolment into the program. As expected, the post screening fracture rates were higher amongst non-enrolees (19%) vs enrolees (14%). The details of fracture outcomes would be discussed further below.

Table 2. Comparison of demographics and characteristics of OPTIMAL enrolees versus non-enrolees

		CONTROL	OPTIMAL
	n	10,121	8,116
Age, mean years		76.8	74.3
Male, %		22%	14%
Race, %			
	Chinese	84%	90%
	Malay	8%	5%
	Indian	5%	3%
	Others	2%	1%
Housing Type, %			
	1/2 room/studio	8%	7%
	3 room HDB	27%	28%
	4 room HDB	30%	29%
	5 room HDB/EC	20%	20%
	Condo	4%	6%
	Landed property	6%	6%
CHAS card type, %			
	Blue	40%	43%
	Orange	9%	9%
	None	51%	47%

		CONTROL	OPTIMAL	
	n	10,121	8,116	p value
Comorbidities				
	Tot_CCI_Score	2.3	1.7	<0.001
	CDnum	3.5	3.1	<0.001
	Diabetes, %	41%	33%	<0.001
Osteoporosis medications, %				
	Before screening	2%	42%	<0.001
	After screening	1%	77%	<0.001
Fragility fractures at baseline, %				
	Recent fractures (<12 mon	53%	66%	<0.001
	Old fractures(>=12 months	18%	32%	<0.001
Post screening fractures, %				
	Any fragility fracture	19%	14%	<0.001
	Hip fracture	14%	9%	<0.001
	Spine fracture	3%	4%	0.067
	Upper limb fracture	1%	1%	0.409

OPTIMAL enrolees, tended to be younger, of female gender, Chinese ethnicity and had more prior fractures (Table 3). Sicker patients (with higher Charlson comordity index) were less likely to enrol in the program, perhaps due to the perception that they would have less gain from the intervention or they have greater difficulties in adhering to medication and follow-up due to mobility restrictions. Indians and Malay patients were less likely to enrol in the program, as there might be cultural differences that rendered them to regard osteoporosis as an unimportant condition for treatment. There was no socioeconomic differences between the two groups of patients, based on their Community Health Assistance Scheme (CHAS) card status (140) (blue status is for individuals with household monthly income per person below S$1100, orange status is between S$1100 to S$1800).

Table 3. Demographics and characteristics that predict enrolment into OPTIMAL Program

Enrolment in OPTIMAL	Odds Rati	Std. Err.	z	P>z	[95% Conf	Interval]
Age	**0.97**	0.002	-16.84	**<0.001**	**0.967**	**0.973**
Male	**0.61**	0.027	-11	**<0.001**	**0.562**	**0.669**
CCI	**0.90**	0.006	-14.58	**<0.001**	**0.888**	**0.914**
Diabetes	0.94	0.038	-1.66	0.097	0.86	1.01
Old fracture	**2.65**	0.109	23.77	<0.001	2.445	2.872
Recent fracture	**2.24**	0.084	21.59	<0.001	2.084	2.413
CHAS card type: None as reference						
Orange	0.98	0.059	-0.4	0.691	0.87	1.10
Blue	1.06	0.038	1.77	0.077	0.99	1.14
Race: Chinese as reference						
Indian	**0.67**	0.058	-4.58	**<0.001**	**0.568**	**0.797**
Malay	**0.66**	0.046	-5.91	**<0.001**	**0.578**	**0.759**
Others	**0.74**	0.092	-2.45	**0.014**	**0.579**	**0.941**
_cons	5.73	0.803	12.44	<0.001	4.35	7.54

Community Health Assistance Scheme (CHAS) card- a government issued medical subsidy card for patients from lower social economic strata, blue has higher subsidy rate than orange

OPTIMAL enrolees had lower odds of developing a fracture 2 years after enrolment into the program (table 4). Patients of older age and of Indian ethnicity were more likely to fracture again at any site. Patients who were older, of male gender, and of Indian ethnicity were more likely to fracture in the hip again after screening. Patients who had spinal fractures might not be accurately represented as the program captured only patients with symptomatic spinal fractures only.

Table 4. Demographics and fracture outcomes when comparing OPTIMAL enrolees with non-enrolees

	any frag_fract	hip_fract	spine_fract	upperlimb_ fract
OPTIMAL y/n	**0.590*** **	**0.529*** **	1.022	**0.430** **
Age	**1.021*** **	**1.029*** **	**1.018*** **	**0.973*** **
Male	0.981	**1.203** **	**0.631*** **	**0.476** **
Tot_CCI_Score	0.995	1.005	0.982	0.965
Diabetes	1.103	1.057	1.170	1.327
Osteoporosis meds before screening	1.100	1.024	1.134	1.554
Osteoporosis meds after screening	1.127	1.170	0.955	1.441
Recent fracture (<12 months)	**0.768*** **	**0.649*** **	1.197	1.053
Old fracture (>=12 months)	**0.894* **	**0.688*** **	**1.579*** **	1.170
HDB 1/2-room/studio	1.096	1.099	0.912	1.428
Race: Chinese as reference	1	1	1	1
Malay	1.026	1.164	0.740	0.928
Indian	**1.255** **	**1.479*** **	**0.663* **	1.032
Others	1.205	1.153	1.298	1.010
Observations	14506	14506	14506	14506

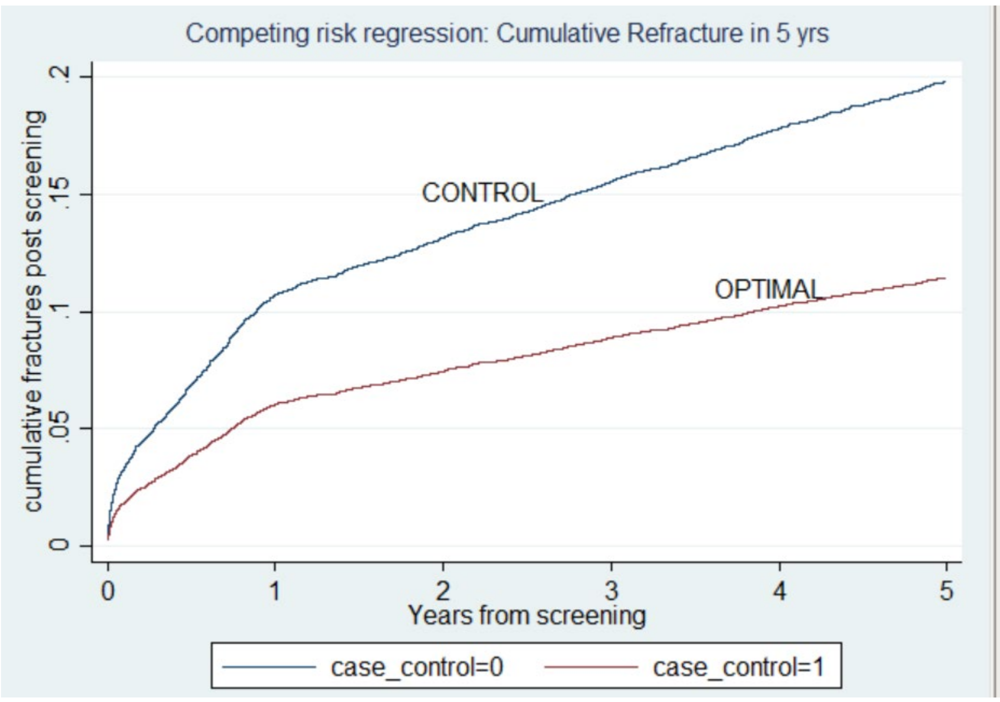
* p<0.05 ** p<0.01 *** p<0.001

Based on the regression modelling, OPTIMAL patients had a hazard ration of 0.550 of fracture when compared with non-enrolees (limited to patients who were screened on or before 31 Dec 2012 and follow up capped at 5 years). Those who were of older age, of male gender, Malay ethnicity and higher Charlson comorbidity index (CCI) had higher odds of fracture after screening (table 5).

Table 5. Hazard ratios of fracture comparing OPTIMAL enrolees versus non-enrolees within 5 years

Re-fracture within 5 years	Hazard Rat
OPTIMAL y/n	0.550***
Age	1.035***
Male	1.155*
CCI	1.041***
Old fracture (>=12 months)	0.843**
Recent fracture (<12 months)	0.700***
HDB 1/2-room/studio	1.124
Race: Chinese as reference	1
Indian	1.105
Malay	1.225*
Others	1.148
Observations	10340

Graph 1. Cumulative refracture rates comparing OPTIMAL enrolees with non-enrolees



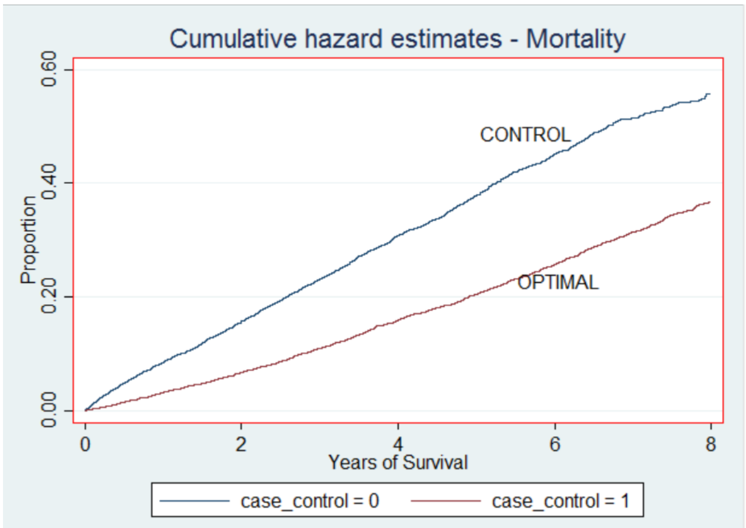
Using Cox proportional hazards regression analysis, patients who were of older age, of male gender, Malay ethnicity and higher Charlson comorbidity index (CCI) had higher hazards of mortality. After adjusting for CCI, Indian ethnicity did not have higher hazards of mortality.

Table 6: Hazard ratios for mortality comparing OPTIMAL enrolees versus non-enrolees within 8 years (stepwise regression modelling)

	(1)	(2)	(3)	(4)	(5)	(6)
OPTIMAL y/n	0.562***	0.639***	0.673***	0.686***	0.763***	0.763***
Age		1.088***	1.090***	1.091***	1.086***	1.086***
Male			2.055***	2.017***	1.851***	1.851***
Race: Chinese as r				1	1	1
Indian				1.212*	1.062	1.062
Malay				1.432***	1.348***	1.348***
Others				1.981***	1.876***	1.876***
CCI					1.179***	1.179***
HDB 1/2-room/stu						0.995
Observations	14659	14604	14604	14604	14604	14604

* p<0.05 ** p<0.01 *** p<0.001

Graph 2: Cumulative hazard estimates of mortality comparing OPTIMAL enrolees with non-enrolees



In patients who developed fractures after screening, OPTIMAL enrolled patients had reduced mortality hazard by 40% (Table 7 and Graph 3). Using stepwise regression, the mortality hazard reduced from 50% for OPTIMAL program as a single variable alone, to 40% for the full model (age, gender, ethnicity and CCI). The housing type of 1 and 2 roomers for patients was not a predictor of mortality, which implied that the socioeconomic status of the patients did not affect the mortality outcomes.

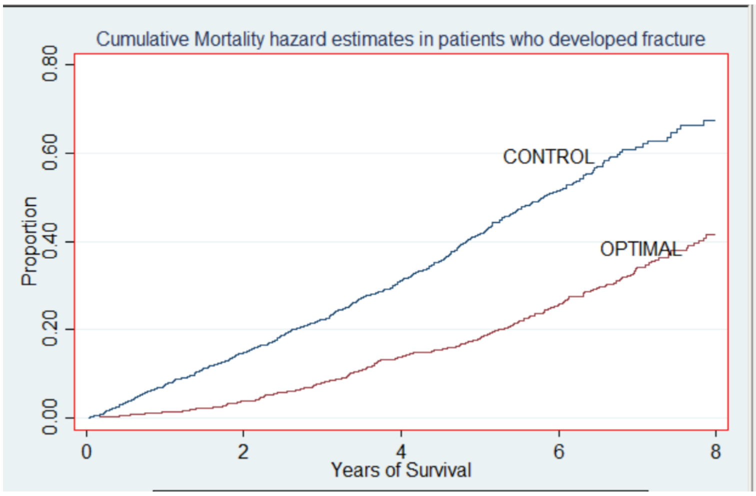
Table 7. Hazard ratios of mortality for OPTIMAL enrolees versus non-enrolees who developed fracture after screening (stepwise regression modelling)

	1	**2**	**3**	**4**	**5**	**6**
OPTIMAL (y/n)	**0.501*** **	**0.508*** **	**0.558*** **	**0.564*** **	**0.605*** **	**0.605*** **
Age		**1.070*** **	**1.076*** **	**1.078*** **	**1.079*** **	**1.079*** **
Male			**2.117*** **	**2.119*** **	**2.012*** **	**2.013*** **
Race: Chinese				**1**	**1**	**1**
Indian				**1.323**	**1.196**	**1.196**
Malay				**1.262**	**1.160**	**1.161**
Others				**2.152*** **	**1.959*** **	**1.959*** **
CCI					**1.166*** **	**1.166*** **
1/2 room flat						**0.989**
Observation	**2587**	**2587**	**2587**	**2587**	**2587**	**2587**

***P<0.001

Number 1 to 6 on first row denotes stepwise regression –the mortality hazard reduced from 50% for OPTIMAL alone to 40% for full model

Graph 3. Cumulative mortality hazard estimates for OPTIMAL enrolees versus non-enrolees who developed fracture after screening



OPTIMAL enrolled patients had lower acute utilisation and healthcare costs at all time points, adjusted for length of follow up during each time period (Table 8). At the 5th year of follow up, OPTIMAL patients utilised $128.83 less per year for Emergency Department (ED) visits, and $3706.78 less per year for inpatient visit.

Table 8. Acute care and healthcare cost utilisation comparing OPTIMAL enrolees with non-enrolees

		CONTROL	OPTIMAL	CONTROL	OPTIMAL
Denominator for		n	n	$	$
	year 1 outcomes	8737	7453		
	year 2	7724	6952		
	year 3	6893	6444		
	5 year follow up	5207	5176		
ED visits	Average				
	1 year before	1.31	1.16	$390.40	$307.98
	year 1	1.19	0.63	$364.54	$169.70
	year 2	0.81	0.63	$257.00	$183.63
	year 3	0.77	0.64	$264.82	$196.15
	Per year over 5 yrs	1.15	0.78	$353.44	$224.61
Inpatient admissions					
	1 year before	1.01	0.82	$9,242.45	$6,691.69
	year 1	1.05	0.53	$9,290.39	$3,781.94
	year 2	1.17	0.69	$9,223.18	$4,800.26
	year 3	0.82	0.75	$6,571.86	$5,829.53
	Per year over 5 yrs	1.02	0.65	$8,620.91	$4,914.13

Due to the pre-determined follow up visits at the specialist outpatient clinics (SOC) in the hospitals or the polyclinics, OPTIMAL patients had greater number of visits at both facilities when compared with non-enrolees (Table 9).

Table 9. Polyclinic and specialist outpatient clinic utilisation comparing OPTIMAL enrolees with non-enrolees

		Utilisation		Costs	
		CONTROL	OPTIMAL	CONTROL	OPTIMAL
Polyclinic visits					
	1 year before	1.22	0.97	$161.24	$119.82
	year 1	1.37	1.10	$190.27	$151.27
	year 2	1.65	1.38	$243.48	$201.30
	year 3	1.72	1.82	$250.82	$270.60
	Per year over 5 yrs	1.61	1.60	$231.29	$241.57
CHAS clinic visits					
	1 year before	0.71	0.55	$39.46	$32.10
	year 1	0.62	0.55	$37.37	$30.83
	year 2	0.83	0.76	$48.42	$41.77
	year 3	1.04	0.91	$61.14	$48.69
	Per year over 5 yrs	0.71	0.66	$40.84	$34.66
SOC visits					
	1 year before	4.19	5.54		
	year 1	5.32	5.26		
	year 2	6.07	5.61		
	year 3	3.74	6.13		
	Per year over 5 yrs	4.10	4.49		

5.4 Discussion

Preventing recurrent fractures in high-risk patients (e.g. patients with prior fragility fractures) is an international challenge. It is being increasingly recognized that interventions based on public and health care education alone are insufficient and unlikely to improve osteoporosis management (141, 142). The Fracture Liaison Service approach, which depends on identification of fractures upon office visits, ensure appropriate osteoporosis evaluation and adherence to medications and other healthy lifestyle interventions over time, has been effective in preventing recurrent fractures. In prospective controlled trials and in meta-analyses (40, 143-145), coordinator-based fracture liaison systems have shown success in significantly reducing fracture rates. The crucial role of committed clinician/medical champions, who will lead/ coordinate service development contextualised to local practices, is able to work with senior management and governmental bodies to secure funding and to devote time and effort to maintain the service, is a key success factor (39, 146). The OPTIMAL program is a clinician champion-driven, case coordinator-run secondary prevention program for osteoporotic fractures. The program strives to narrow the prevalent care gap in osteoporosis care through a judicious combination of fracture case finding, appropriate assessment and evaluation, patient education on osteoporosis and risk factor management, education on nutrition, fall prevention and exercises for muscle strengthening, balance and coordination, in addition to the use of effective anti-osteoporosis pharmacological agents.

The most important finding of this study is the reduction in all sites fracture risk by 41.0% and hip fracture risk by 47.1% of patients enrolled into the OPTIMAL program when compared with non-enrolees after two years. The absolute risk reduction in hip fracture rate was 7.67% (15.58% in non-enrolees versus 7.93% in OPTIMAL enrolled patients) at 5 years. The absolute reduction in refracture risk was 9.0% at 5 years. With an enrolment of 5176, this would be equivalent to 448 hip fractures prevented over a 5 year period. These results compared favourably with other observational studies and randomised controlled trials of similar fracture liaison service program (8). The detail Markov Modelling of the OPTIMAL program to address its cost-effectiveness will be discussed in Chapter 7.

In analysing the outcomes of patients enrolled in the program, we also identified some areas for potential improvement. The first is how to improve medication compliance among patients. Even with government subsidies, some patients still find medication cost prohibitively expensive and this may contribute to some patients being noncompliant despite close follow-up. Hence, although we may not be able to resolve the problem of financial burden, there is still a need to implement strategies to monitor and encourage medication compliance among patients in order to reap the full benefits of the program.

Another area for improvement that would also potentially reduce cost to participating patient would be right-siting of patients. Right-siting, i.e., discharging patients to polyclinics and primary care after initial assessment and therapy initiation [49], remains inadequate in our program. Diverting suitable patients to polyclinics and primary care would reduce cost to patients as well as improving convenience in access. Integrating GPs into the program and providing more seamless transition programs may help overcome this problem.

Furthermore, though we did see a trend towards a decreased hip fracture rate in our followed up patients when compared to a historical control group, a limitation of our audit was that there was no parallel control group. Cost effectiveness of the program remains to be proven.

Notwithstanding these limitations, our data and audit provide the first compelling evidence from an Asian country of the potential effectiveness of a secondary fracture prevention program. The lessons learned during the last 5 years would enable us to implement a revised and more effective program in the near future. The onus also rests on us now is to demonstrate the cost effectiveness and integrate OPTIMAL into the standard of care of the hospital so that no fragility fracture patient is missed, and to strive to ensure that in every patient, the first fracture even if it does happen will really be the last.

Chapter 6: The health and economic burden of osteoporosis in Singapore and the potential impact of increasing treatment options

Abstract

Purpose: This study aims to estimate the health and economic burden of osteoporosis in Singapore from 2017 to 2035, and quantify the impact of increasing the treatment rate of osteoporosis.

Methods: Population forecast data of women and men aged 50 and above in Singapore from 2017-2035 was used along with prevalence rates of osteoporosis to project the osteoporosis population over time. The population projections by sex and age group were used along with osteoporotic fracture incidence rates by fracture type (hip, vertebral, other), mortality rates, and average direct and indirect costs per case to forecast the number of fractures, the number of deaths, the total direct healthcare costs, and the total indirect costs due to fractures in Singapore. Data on treatment rates and effects were used to model the health and economic impact of increasing treatment rate of osteoporosis, using different hypothetical levels.

Results: Between 2017 and 2035, the incidence of osteoporotic fractures is projected to increase from 14,772 to 22,654. The total economic burden (including direct costs and indirect costs to society) associated with these fractures is estimated at S$179.0 million in 2017, forecast to grow to S$381.7 million by 2035. However, increasing the treatment rate for osteoporosis could avert up to 28,618 fractures over the forecast period (2017-35), generating cumulative total cost savings of up to S$363.5 million.

Conclusion: Efforts to improve the detection, diagnosis and treatment of osteoporosis is necessary to reduce the growing clinical, economic and societal burden of fractures in Singapore.

Keywords: Osteoporosis, osteoporotic fractures, economic burden, population projection

6.1 Introduction

According to the World Health Organization (WHO), osteoporosis is the most common metabolic bone condition, characterized by reduced bone density and strength, microarchitectural deterioration, and increased risk of fracture. Osteoporosis is estimated to affect more than 75 million people in Europe, Japan and the United States, and the lifetime risk for hip, vertebral and forearm (wrist) fractures is believed to be around 40% (147).

Given the rapidly aging population in Asia, osteoporosis with its associated high morbidity, mortality and costs is becoming a growing public health concern. Since there is limited knowledge of the epidemiology of osteoporosis and fractures (of all types) in Singapore and its associated costs, this current study aimed to estimate the health and economic burden of osteoporosis in Singapore from 2017 to 2035. Previous studies have mostly focused on the burden of hip fractures, and a study by Cheung et al. projected the number of hip fractures in Singapore to be 4,477 in 2018 and 15,806 in 2050, and the direct health care costs at US$31.0 million in 2018 and US$109.3 million in 2050 (148).

In 2009, the International Osteoporosis Foundation (IOF) Asian Audit reported that 55,000 women aged above 50 years of age in Singapore suffer from osteoporosis, and this number is likely to increase significantly with the aging of the population (149). Furthermore, secondary osteoporosis is being increasingly recognized, with prevalence rates approaching 45% in postmenopausal women and 63% in older men with osteoporosis reported in one study (69).

The clinical and public health implications of osteoporosis are largely attributed to the fractures associated with the disease. More than 50% of all osteoporotic hip fractures are projected to occur in Asia by the year 2050 (1, 5). Between the 1960s and 1990s, the incidence rates of hip fractures increased 5-fold in women and have more than doubled in men in Singapore, although rates have been steadily declining over the last two decades in neighbouring countries (54, 150-152). In a Singaporean study performed between 1991-1998, Koh et al. estimated the age-adjusted rate of hip fractures (per 100,000) at 402 for women and 152 for men (150).

Hip fractures are also associated with significant mortality, with the one-year mortality rate estimated by Tay et al. as 14.4% (12% for women and 25% for men) (153). Of the patients who survive, 20% have been reported as needing help with daily activities of living and 39% experiencing reduced mobility issues (130, 154, 155). Osteoporotic hip fractures usually require prolonged hospital stay for surgery and rehabilitation (154), and the 2013 Asia Pacific Regional Audit reported the total cost of managing hip fractures within the first year in Singapore to be US$17 million in 1998, estimated to reach US$145 million by 2050 (149).

From a population health perspective, osteoporosis is often preventable since many of its causes and risk factors can be effectively treated by pharmacological interventions and non-pharmacological modalities. Indeed, several treatment options have been shown to be effective in reducing the risk of fractures in patients with low bone mineral density (T-score ≤ -2.5 standard variation (SD), with bisphosphonates being the most commonly prescribed. Unfortunately, the treatment rate for osteoporosis in Singapore is low. In a study by Kung et al., only 28% of first-time hip fracture patients in Singapore received prescription medications for osteoporosis in the 6 months after discharge (156). A retrospective analysis performed by Gani et al.(157) of admissions for fragility fractures in a regional general hospital setting in Singapore also revealed a significant gap in the diagnosis and treatment of osteoporosis.

Another major challenge is the low rate of long-term adherence to treatment, which can lead to sub-optimal clinical outcomes for osteoporosis patients (158). According to a study conducted by the International Osteoporosis Foundation, up to 60% of patients who take once-weekly bisphosphonate and nearly 80% of those who take once-daily bisphosphonates discontinue treatment within one year (159). The two most commonly cited reasons for treatment discontinuation cited by women were side effects and inconvenience, while many physicians attributed low adherence rates to inadequate knowledge about the disease amongst patients (159).

Denosumab is a treatment option for osteoporosis that holds potential in addressing the historically low adherence rates reported with bisphosphonates (158). Denosumab is a fully human monoclonal antibody that has been found to reduce the relative risk of radiographic vertebral fractures, hip fractures and nonvertebral fractures by 68%, 40%, and 20% respectively (160). Denosumab is administered once every 6 months as a subcutaneous injection and shows good tolerability and better adherence than alendronate (158). As this treatment addresses the low rate of medication adherence experienced with other standard osteoporosis treatments, the second aim of this study is to estimate the health and economic impact of increasing the historically low treatment rate of osteoporosis in Singapore through the use of an agent such as Denosumab.

6.2 Material and Methods

Study Population and General Approach

Population forecast data of women and men aged 50 years and above in Singapore from 2017 to 2035 (161) was used along with prevalence rates of osteoporosis to project the osteoporosis population over time. The population forecast is available in the Technical Appendix. The population projections by sex and age group were used along with osteoporotic fracture incidence rates by fracture type (hip, vertebral, other), mortality rates, and average direct and indirect costs per case to forecast the number of fractures, the number of deaths due to fractures, the total direct health care costs, and the total indirect costs in Singapore. The incremental health and economic impact of two scenarios was then compared: 1) the status-quo scenario, that assumes that the current treatment rate/options remain unchanged over the forecast period; and 2) the treatment scenario, that assumes increased treatment rates for osteoporosis patients through the use of denosumab.

Epidemiology of Osteoporosis and Fractures in Singapore

The WHO-endorsed clinical diagnosis of osteoporosis is based on bone mineral density (BMD) measurements, which is transformed into a T-score reflecting the number of standard deviations (SD) above or below the mean in healthy young adults. A T-score of ≤ -2.5 SD is the accepted threshold for the diagnosis of osteoporosis. Given the lack of availability of local prevalence rate estimates of osteoporosis in Singapore, data from a national population-based study performed by Lee et al. on the Korean population was leveraged because of its large sample size, validated results by other studies, and availability of prevalence breakdown by age group and sex (Table 1).

Table 1. Prevalence of Osteoporosis by Age Group and Sex

Age Group	Male	Female
50-59	4%	15.2%
60-69	7.2%	36.5%
70-79	15.1%	62.7%
80-89	26.7%	85.8%
Overall	7.8%	37%

The incidence rate of hip fractures was obtained from previously published data by Koh et al. (150), and extrapolated to current rates based on publications from the region, yielding 275 hip fractures per 100,000 people for women and 120 hip fractures per 100,000 people for men. Incidence rates for vertebral and other fractures (defined as non-hip, non-vertebral fractures) were estimated using data on the distribution of osteoporotic fractures observed amongst patients admitted to a tertiary hospital (157), as well as from data on fracture type collected as part of an audit of 4,000 patients screened for recruitment into a fracture liaison service at the largest public hospital in Singapore, the operational details of which has been reported by Chandran et al. (79) We estimated the incidence rate of vertebral fractures at 300 per 100,000 for women and 130 per 100,000 for men, and a rate of other fractures of 465 per 100,000 for women and 205 per 100,000 for men.

The 12-month mortality rate of individuals who have sustained a hip fracture was estimated at 12% for women and 25% for men, derived from a local study by Tay et al. (153) Since mortality rates for vertebral and other fractures are not available for Singapore, data from an Australian study published by Bliuc et al. (162) that compares mortality ratios of hip and vertebral/other fractures was utilized. Based on these mortality rates, the 12-month mortality rate of vertebral fractures in Singapore was estimated at 7.2% for women and 18.8% for men; and of other fractures at 5% for women and 15.3% for men. The case-fatality rates, as well as overall mortality, are presented in Table 4.

Direct and Indirect Costs

The average inpatient cost per case of osteoporotic fractures was derived from a study by Tan et al. (163), to which the post-inpatient 3-month average direct cost per case was added (164). The 3-month costs were derived from a study by Ng et al. (164), and included outpatient services related to physician visits, laboratory tests, rehabilitation, medications, and emergencies. The indirect cost per case of hip fractures was derived from the same study (164), and included productivity losses for the patient (e.g., length of stay, early retirement, sickness absences) and for informal caregivers. Due to the lack of local data on the average cost per case of vertebral and other fractures, these costs were derived using Australian data on the cost ratio between hip fractures compared to vertebral and other fractures (defined as non-hip, non-vertebral fractures) (Table 2) (165). Average costs per case were inflated using a forecast of the inflation rate for Singapore from 2017 to 2035. In the model, the total direct and indirect costs by fracture type were calculated by multiplying the average cost per case by the number of fractures in each year of the forecast period.

Table 2. Average Cost per case, by Type of Fracture and Type of Cost ($S)

Type of Fracture	Direct Cost	Indirect cost
Hip	15,275	4,848
Vertebral	4,581	1,454
Other	6,262	1,988

Estimating the Base Risk

The following relative risk (RR) estimates that quantify the risk of fractures for osteoporosis patients were derived from a study by Marshall et al.(166): hip (RR 1.9, 95% confidence interval (CI) 1.6-2.3), vertebral (RR 2.0, 95% CI 1.8-2.2), other (RR 1.5, 95% CI 1.4-1.6). The base risk is defined as the risk of developing a fracture in the absence of any risk factors, such as osteoporosis. In the model, the relative risk of osteoporosis is added to the base risk in order to forecast the incidence rate of fractures from 2017 to 2035. The base risk is not documented in the literature, therefore it was estimated using data on the prevalence of osteoporosis combined with the relative risks from Marshall et al.[3] The base risk estimates for males and females, broken down by age group, for each type of fracture are available in the Technical Appendix.

Treatment Rate and Effect

In Singapore, the treatment rate for osteoporosis patients is estimated at 28% and bisphosphonates account for almost all prescriptions, with alendronate being the most commonly prescribed treatment (156). A Cochrane systematic review of 11 trials representing 12,068 women found that treatment with alendronate reduces the relative risk of hip fractures by 40%, of vertebral fractures by 45% and of other fractures by 16% (167). However, reports of adverse effects of using bisphosphonates, including atypical fracture of the femur, osteonecrosis of the jaw, and esophageal cancer (168-171), have emerged in recent years. A study in the United States found that, after increased usage for more than a decade, oral bisphosphonate use plateaued in 2006 and declined by greater than 50% between 2008 and 2012 (172). This coincided with reports of safety concerns of bisphosphonates (173-175). Following the decline in oral bisphosphonate use, the incidence of subtrochanteric and diaphyseal fractures also declined (172). The FDA subsequently recommended an update of bisphosphonate labeling. Another issue with bisphosphonate treatment is poor adherence rate. A review of studies published in 2009 also showed consistent evidence of poor adherence rates (both compliance and persistence) with oral bisphosphonate treatment, especially among women (176).

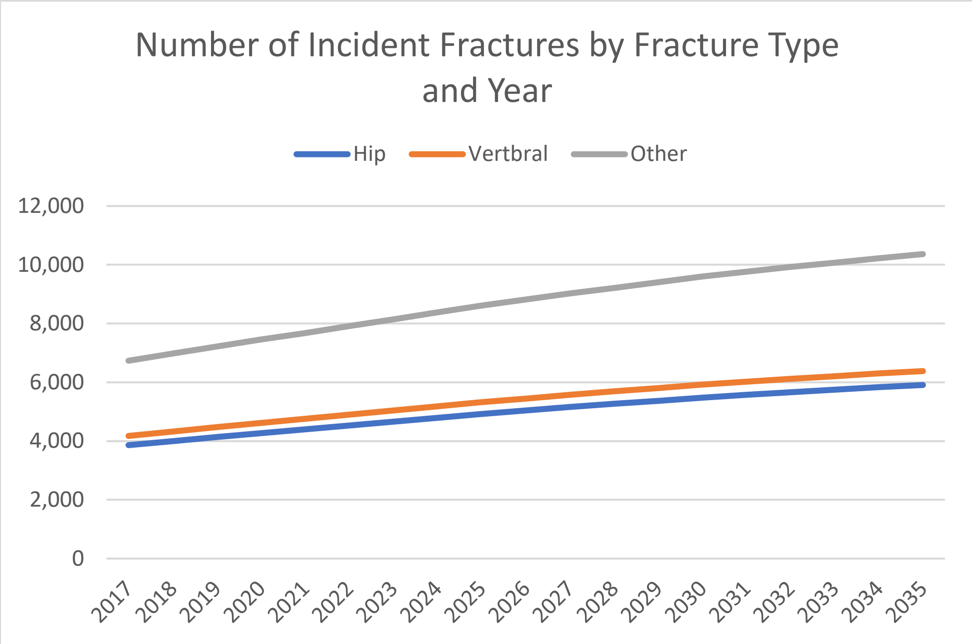
An alternative treatment, denosumab, is an innovative option that has been found to reduce the relative risk of hip fractures by 40%, vertebral fractures by 68% and nonvertebral fractures by 20% (160). Denosumab is administered once every 6 months as a subcutaneous injection and shows good tolerability and better adherence than alendronate (158).

In both the base case and treatment scenarios, 28% of osteoporosis patients are modelled to receive the “status quo” treatment with alendronate. In the treatment scenario, a sensitivity analysis is introduced to model different hypothetical treatment rates for osteoporosis patients: 38%, 48%, 58% and 75%. For all treatment rates, treatment with alendronate remains stable at 28% (this rate is estimated on the basis that treatment rates with alendronate are unlikely to increase in Singapore given the reasons and concerns detailed above), and treatment with denosumab represents the balance of the rate. For example, the 38% treatment rate includes 28% of patients being treated with alendronate and 10% with denosumab, along with their respective efficacy. The difference in fracture morbidity, mortality and costs between the two scenarios represent the incremental impact of enhancing denosumab as a treatment option for osteoporosis patients in Singapore.

6.3 Results

In 2017, the incidence of osteoporotic fractures was estimated at 14,772 cases, distributed between 3,862 hip fractures (women: 2,705; men: 1,157), 4,176 vertebral fractures (women: 2,926; men: 1,250) and 6,735 other fractures (women: 4,738; men: 1,997). In the base case scenario, by the year 2035, the number of incident fractures is projected to increase by 65% to 22,654 cases, distributed between 5,908 hip fractures (women: 4,177; men: 1,732), 6,281 vertebral fractures (women: 4,512; men: 1,869) and 10,364 other fractures (women: 7,365; men: 2,999) (Figure 1). Over the forecast period (2017-2035), this represents a cumulative total of 362,388 incident osteoporotic fractures. The mortality associated with osteoporotic fractures was estimated at 1,602 in 2017, and is projected to increase to 2,438 fractures by 2035, yielding 39,162 cumulative deaths over the forecast period.

Figure 1. Number of Incident Osteoporotic Fractures in Singapore



The overall costs (including both direct and indirect) of incident fractures in Singapore were estimated at S$179.0 million in 2017, forecast to increase by 113.2% (more than doubling) to S$381.7 million by 2035. Hip fractures are responsible for about half of these costs, estimated at S$87.8 million in 2017 and projected to increase to S$186.8 million by 2035 (Figure 2). The cost of other types of fractures follows at S$62.8 million in 2017, set to increase to S$134.4 million by 2035. Vertebral fractures are the least costly yet still significant, costing the Singapore health care system and economy an estimated S$28.5 million in 2017 and S$60.5 million in 2035. For all fractures types, direct costs to the health care system represent the majority of overall costs associated with osteoporotic fractures, while indirect costs to society represent around a fourth of costs.

Figure 2. Cost of Osteoporotic Fractures in Singapore

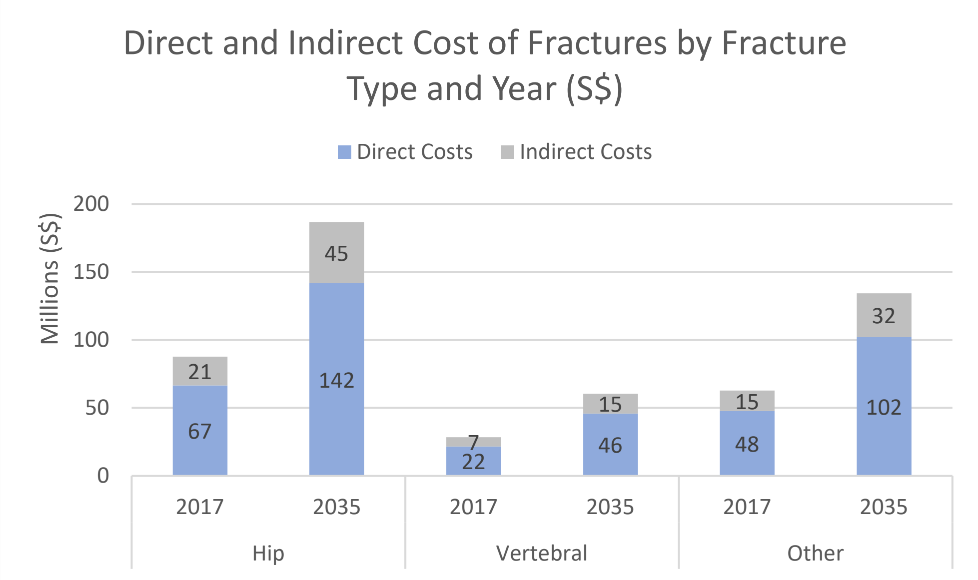


Table 3 presents the potential number of fracture cases averted given different scenarios of treatment rates for osteoporosis patients. Increasing the treatment rate by 10%—from the current 28% to 38%—would lead to 6,089 averted cases of osteoporotic fractures over the forecast period (2017-2035). The majority of averted fractures modelled were vertebral fractures (3,151), followed by hip fractures (1,665) and finally other fractures (1,273). The upper range of the sensitivity analysis models a scenario where 75% of osteoporosis patients would be receiving treatment. Under this scenario, the number of averted fractures is estimated at 28,618 over the forecast period: 14,808 vertebral fractures, 7,825 hip fractures and 5,985 other fractures (Table 3). The number of averted deaths was estimated at between 371 and 2,667 over the forecast period depending on the hypothetical treatment rate.

Table 3. Number of Averted Osteoporotic Fractures by Fracture Type and Treatment Rate with Denosumab

Fracture Type	38%		48%		58%		75%	
	2035	**Cumulative**	**2035**	**Cumulative**	**2035**	**Cumulative**	**2035**	**Cumulative**
Hip	114	1,665	228	3,330	343	4,994	536	7,825
Vertebral	216	3,151	431	6,302	647	9,452	1,014	14,808
Other	88	1,273	176	2,547	264	3,820	415	5,985
Total	**418**	**6,089**	**836**	**12,178**	**1,254**	**18,267**	**1,965**	**28,618**

The cumulative direct and indirect cost savings associated with increased treatment for osteoporosis were estimated at between S$85.7 million and S$363.5 million (S$65.1 million to S$275.9 million indirect health care cost savings and S$20.6 million to S$87.6 million in indirect cost savings), depending on the treatment rate modelled. The greatest cost savings are expected to occur for hip fractures, ranging from S$45.5 million to S$214.0 million over the forecast period, followed by vertebral fractures (S$25.8 million to $121.5 million) and other fractures (S$14.3 million to $28.0 million). Three quarters of savings would be in the form of direct cost savings to the health care system, while the remaining quarter represents indirect cost savings to the Singapore society and economy (Table 4).

Table 4. **Total Cost Savings by Fracture Type and increasing Treatment Rates** (S$, millions)

	38%		**48%**		**58%**		**75%**	
	2035	**Cumulative**	**2035**	**Cumulative**	**2035**	**Cumulative**	**2035**	**Cumulative**
Hip	3.6	45.5	7.2	91.1	10.8	136.6	16.9	214.0
Vertebral	2.0	25.8	4.1	51.7	6.1	77.5	9.6	121.5
Other	1.1	14.3	2.3	28.6	3.4	42.9	3.0	28.0
Total	**6.8**	**85.7**	**13.6**	**171.4**	**20.4**	**257.1**	**29.6**	**363.5**

6.4 Discussion

The current study projected that the total number of osteoporotic fractures in Singapore would increase from 14,772 in 2017 to 22,654 in 2035, assuming the treatment rate is kept constant at 28%. It represents a 65% rise in less than 20 years that can be attributed to aging of the population. This would lead to increased total costs (including direct health care costs and indirect costs to society) which are forecast to grow from S$179.0 million in 2017 to S$381.7 million in 2035. Direct health costs are the greatest contributors to total cost, and are forecast to increase from S$135.9 million in 2017 to S$289.7 million in 2035, while indirect costs are set to increase from S$43.1 in 2017 to S$92.0 in 2035.

Published studies on the burden of osteoporotic fractures in Singapore have focused on hip fractures. Our study estimated the number of hip fractures at 3,862 in 2017, projected to increase to 5,908 by 2035, and the direct health care costs in these two years at S$66.6 million and S$2.0 billion respectively. Using similar methodology, Cheung et al. projected the number of hip fractures in Singapore at 4,477 in 2018 and 15,806 in 2050, and the direct health care costs at US$31.0 million in 2018 and US$109.3 in 2050 (148). These projections assume that there was no substantial change in hip fracture incidence since the original study year (which is 1997-98 for Singapore), although regional trends clearly show decreasing hip fracture rates over the last few decades. Further, the direct medical costs for Singapore included the inpatient hospital stay only, while our study also included 3-month direct costs following discharge.

Though less epidemiological information is available, fractures at other sites also contribute significantly to the burden of osteoporosis, particularly in younger individuals. For example, other fractures accounted for six times the morbidity of that arising from hip fracture for Swedish women between 50 and 54 years old (177). Vertebral fractures, in particular, are associated with increased risk of mortality and are an important risk factor for future vertebral and hip fractures (178, 179). In fact, all major types of osteoporotic fractures are associated with a two- to three-fold increase in mortality for both men and women (180).

Furthermore, osteoporotic fractures often require surgery and rehabilitation, resulting in extended hospital length-of-stays and costly treatments. The indirect cost of fractures, such as those incurred from absenteeism and informal care, are also significant since 20% of patients who have sustained a fracture need help with daily living activities and 39% have reduced mobility (130, 154, 155). Our study is the first to estimate the indirect costs associated with osteoporotic fractures in Singapore, which we estimated at S$43.1 million in 2017, projected to increase to S$92.0 million in 2035.

Although our study highlights the growing burden of osteoporosis in Singapore, fragility fractures are often preventable with adequate pharmacological and other interventions. In the United States, the cost of managing osteoporosis has been estimated at US$17 billion and a very small fraction of this cost is used for the treatment and prevention of osteoporosis (181). Low diagnosis and treatment rates (156, 157), and poor adherence to treatment (158), are also observed in Singapore and contribute to sub-optimal clinical outcomes for osteoporosis patients and significant costs to the health care system and society.

Our study showed that increasing the treatment for osteoporosis has the potential to avert up to 28,618 cases of osteoporotic fractures between 2017-2035, under the scenario where total treatment rate is 75%. This would lead to 2,667 lives saved and S$363.5 million in total cost savings (S$275.9 million in direct health care cost savings and S$87.6 million in indirect cost savings). Even if the treatment rate for osteoporosis increased by 10% use of denosumab (from the current 28% to 38%), the reduced health and economic burden of osteoporosis would be significant.

Study Limitations

This study makes use of the best available information to forecast the health and economic burden of osteoporosis in Singapore. While every effort was made to maximize the accuracy of these forecasts, certain limitations in the data sources and modeling assumptions are worth noting. First, epidemiological estimates leveraged from other countries or from previous years may not be accurate for Singapore or reflect the current disease environment. Also, some of the model inputs (e.g. prevalence rate and average cost per case) for vertebral and other fractures had to be extrapolated using international estimates applied to local hip fracture data. Furthermore, prevalence rates of osteoporosis and incidence rates of fractures were modelled to remain constant over the forecast period, which reflects the anticipated stable nature of the condition and its impact on fractures, yet should be updated as more accurate epidemiological data on fracture rates becomes available. While the sources of the costing data were credible, the cost of pharmaceutical treatment with alendronate or denosumab were not included in the model (182). It has been shown that denosumab is a cost-effective strategy compared to oral bisphosphonates including generic alendronate for the treatment of postmenopausal osteoporotic women (183). Adherence to certain anti-osteoporotic medications could be poor in real -life and may affect clinical and economic outcomes (184). This was not included in our modelling. Also, due to the lack of data for longer term average indirect cost, we have included the 3-month indirect cost and productivity loss per case in the current study. This may underestimate the actual size of the total indirect cost to the society. This study did not include intravenous zoledronic acid, which may also be potentially useful in enhancing the treatment adherence of osteoporotic patients. The reason is that the use of this medication has not been popular in Singapore, due to the following limitations 1) the need for intravenous infusion, 2) it is contraindicated in patients with stage 3 Chronic Kidney Disease, 3) it is in the same class as bisphosphonate and the concern about the risk of atypical fractures with long-term use.

Despite the above limitations, our study still serves to fill an important gap in osteoporosis care in Singapore. By assessing the current and future burden of osteoporosis in Singapore, and quantifying the potential health and economic impact of increased treatment rates, our hope is to shed light on an important public health concern and look at the downstream benefits of tackling the issue of underdiagnoses and undertreatment for these patients. Value Based Healthcare is an important consideration for health systems, and this analysis is meant to complement traditional economic analyses to inform the prioritization of interventions to treat osteoporosis.

6.5 Conclusion

The burden of osteoporosis in Singapore is significant, and is expected to grow over the next 20 years. Fragility fractures are significant events in the lives of osteoporosis patients and their families, and have important economic repercussions on the health care system and society. Efforts to improve the detection, diagnosis and introduction of new efficacious treatment modality of osteoporosis, such as denosumab, is needful to reduce the growing clinical, economic and societal burden of fractures in Singapore.

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Chapter 7: Cost-effectiveness of a fracture liaison service—a real-world evaluation after 5 years of OPTIMAL provision

Abstract

Purpose: The primary objective of this study was to assess the cost- effectiveness of the OPTIMAL program, compared to usual care from the societal perspective of the Ministry of Health, Singapore. The analysis aimed to estimate the incremental costs, quality-adjusted life-years (QALYs), and incremental cost per QALY gained associated with the enrolees to the OPTIMAL program versus non enrolees.

Methods: A Markov model using rates of osteoporosis testing and treatment in the year after fragility fracture from a longitudinal study of the OPTIMAL program, cost of intervention from the program, cost of hip fracture care and QALY estimates from the published literature. The model tracked changes in patients' health states over time as they developed a hip fracture or died. The treatment and interventions reduce the risk of hip fracture and its associated mortality. To capture the long-term effects of avoiding fracture and its associated morbidity, we conducted the analysis with a 10 year horizon.

Results: The OPTIMAL program prevented 77 hip fractures for every 1000 participants and reduce mortality by 40% over five years. This led to significant gains of 228 QALYs per 1000 patients. Patients in the program incurred higher costs due to costs of the intervention, BMD test, and osteoporosis treatment, but preventing subsequent hip fractures also saved costs. Discounting costs and benefits at 5 % per year, the program cost $5,607 more and gained 0.228 QALYs per patient, with an incremental cost-effectiveness ratio (ICER) of $24,636 per QALY gained.

Conclusion: The major finding of our program that is different from the other FLS is that there is a significant 40% reduction in mortality of patients enrolled in our program versus those who are not enrolled, after adjusting for known predictors of mortablity such as age, gender, ethnicity and Charlson comorbidity index (CCI). This has resulted in significant gains in life years of enrolled patients, which is cost effective based on international norms.

Keywords: Osteoporosis, Osteoporotic Fractures, Cost Utility Analysis

7.1 Introduction

In Singapore, as in the rest of Asia, osteoporosis will become an increasingly important public health problem. In the next 50 years, more than half of all hip fractures are projected to occur in Asia(126). Osteoporosis is likely to increase as the population of Singapore is aging rapidly (127). In 2010 only 6% of the population was above the age of 60, but by 2030, this figure is projected to rise to 25% (6). Indeed, osteoporotic fractures at the hip, wrist and spine are increasingly observed clinically. A previous study from Singapore reported a steady increase in age-adjusted hip fracture rates of around 1–1.5% per year in both men and women from 1991 to 1998. Based on these trends, a further 30–50% increase in hip fracture incidence rates over the ensuing 30 years in Singapore has been predicted (7). With an aging population, the prevalence of osteoporosis-related fractures in Singapore will continue to grow in the years to come, generating what is expected to be a heavy burden on health budgets (chapter 6). Better knowledge of the financial consequences of fragility fractures could enable proactive and preventive measures to be undertaken, especially at sites of care with high cost drivers. This would also provide valuable information for health administrators in healthcare resource and budget allocation planning.

Since the late 1990s, different models of care designed to prevent recurrent fractures after a fragility fracture have emerged (38). One such model is a fracture liaison service which includes coordinators to facilitate bone health assessment and evidence-based care (38, 39). Ganda et al. classified fracture liaison services by intensity, ranging from the most intensive model that identifies, assesses, and, as indicated, treats fragility fracture patients for osteoporosis within the fracture liaison service role to a less intensive model that only educates participants (40). In comparison, the more intensive models that included promoting adherence to therapies were cost-effective and those that focussed on educating participants alone had limited impact (40-44). However, there has not been a study on the cost effectiveness of the fracture liaison service in an Asian country, where healthcare financing has a substantial co-payment or out-of-pocket component (45).

In Singapore, the OPTIMAL program (Osteoporosis Patient Targeted and Integrated Management for Active Living) is a clinician champion-driven, case coordinator-run secondary prevention program for osteoporotic fractures. The program strives to narrow the prevalent care gap in osteoporosis care through a judicious combination of fracture case finding, appropriate assessment and evaluation, patient education on osteoporosis and risk factor management, education on nutrition, fall prevention and exercises for muscle strengthening, balance and coordination, in addition to the use of effective anti-osteoporosis pharmacological agents. The OPTIMAL program was moderately effective in increasing treatment rates (79) and reducing recurrent fracture (Chapter 5), but its cost-effectiveness remained unknown. Decision analytic modeling can address this knowledge gap by providing an explicit framework that combines all available evidence to link osteoporosis treatment rates from a single-arm study to comparative cost and effectiveness. The results from the model will help inform clinical decision-making and health policy related to the best strategy in order to improve care for post-fracture patients.

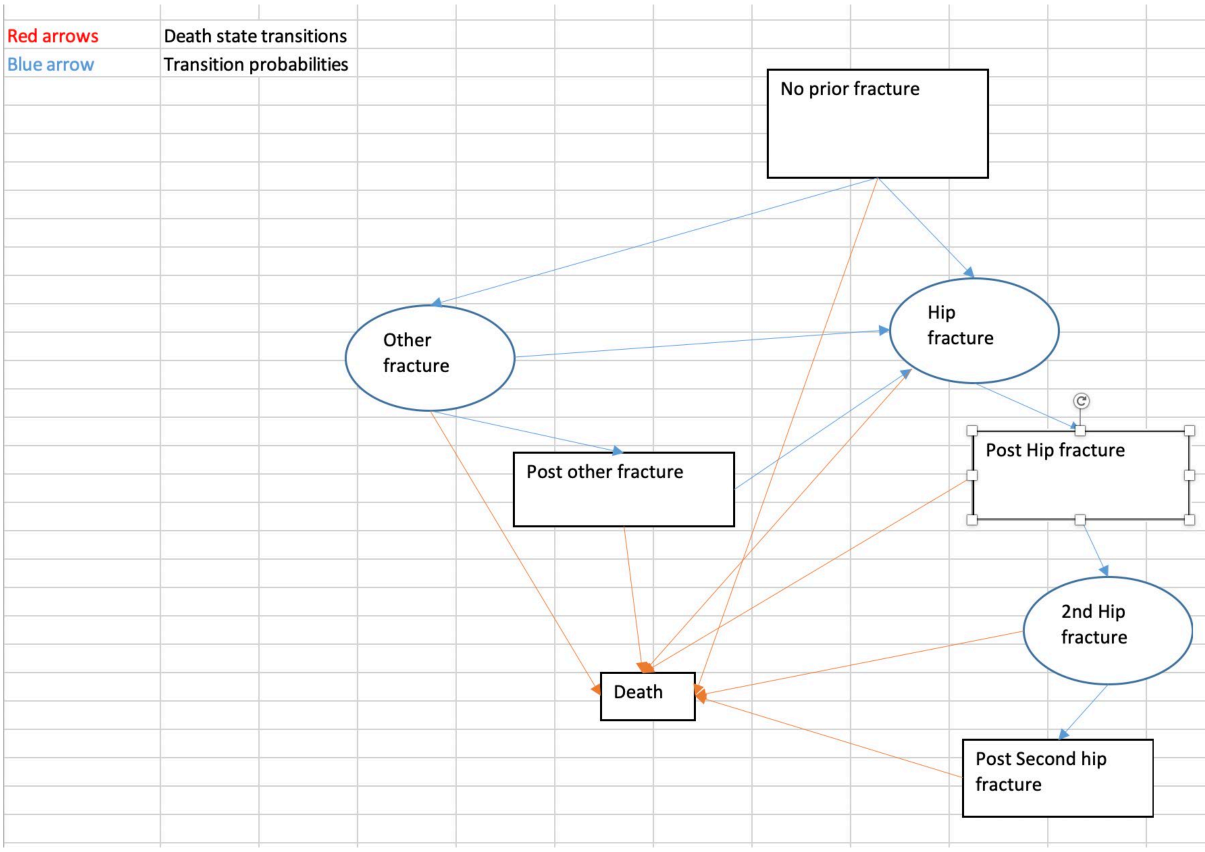
The primary objective of this study was to assess the cost- effectiveness of the OPTIMAL program, compared to usual care from the perspective of the Ministry of Health, Singapore. The analysis aimed to estimate the incremental costs, quality-adjusted life-years (QALYs), and incremental cost per QALY gained associated with the enrolees to the OPTIMAL program versus non enrolees. The target population included those aged 50 years or older who sustained a fragility fracture at the time of screening. The details of the OPTIMAL program can be found in Chapter 5.

7.2 Materials and methods

We developed a Markov model using rates of osteoporosis testing and treatment in the year after fragility fracture from a longitudinal study of the OPTIMAL program, cost of intervention from the program, cost of hip and other fracture care (Chapter 4) and QALY estimates from the published literature. The model tracked changes in patients' health states over time as they developed a hip fracture or other fracture or died. Although we included other osteoporotic fractures in the model, we expected hip fractures to be the most costly and have a substantial impact on health-related quality of life [9, 10]. After an index fracture (hip or other fracture), a proportion of patients received BMD testing and agreed to enrol in the OPTIMAL program and were offered osteoporosis treatment and falls risk reduction interventions as appropriate. The treatment and interventions reduce the risk of fracture and its associated mortality.

The cycle length of the model was 1 year. Every year, patients (enrolee or non-enrolee) with an index fracture could stay in or move to one of the following health states: first year after hip or other fracture, and subsequent years after hip or other fracture or death (from a hip fracture or other causes) (Figure. 1). To capture the long-term effects of avoiding fracture and its associated morbidity, we conducted the analysis with a 10-year horizon. We discounted future costs and quality-adjusted life-years at 5 % per year.

Fig 1: Overview of Markov Model for hip fracture cohort



Model input

Distribution of index fractures, hip fracture risk, testing, and treatment rates

The cohort in the model mirrors the enrolees of the OPTIMAL program, with respect to age, sex, and type of index fractures. For both enrolees and non-enrolees arms of the model, we obtained the fracture distribution, hip fracture rates, testing, and treatment rates from both the OPTIMAL programs and Ministry of Health Singapore administrative database. OPTIMAL patients had a hazard ration of 0.529 of hip fracture when compared with non-enrolees at 5 years (Chapter 5).

Treatment

In the OPTIMAL program, 50% of patients who initiated pharmacotherapy received alendronate, 30% of patients received risedronate, 10% of patients received denosumab, and 10% of patients received strontium ranelate. The OPTIMAL program enrolees have 72.8% persistence with osteoporosis treatment at two years in one of the hospital site (79). We have adjusted the baseline scenario to an adherence rate of 63.41%. Similar to other published cost-effectiveness analyses (185, 186), we assumed that patients who persisted with treatment at 1 year would continue on treatment for the next 5 years. For patients who received treatment for 5 years, we assumed the treatment effect persisted for another 5 years after treatment ended. A study that compared discontinuing treatment at 5 years vs. continuing for 10 years showed that discontinuing treatment for up to 5 years did not significantly increase fracture risk (187). There was no evidence on the effect of treatment after 10 years. To be conservative, we ran the Markov model for a 10 year cycle, as there was no data on fracture efficacy beyond the 10 year period. We have conservatively also assumed that patients who are non-adherent do not enjoy any of the benefits of treatment both in the first 5 years and subsequent 5 years. We have also performed sensitivity analysis varying this adherence from 48% to 79% (table 5).

We did not include the side effects of treatment in the model. Although trials of bisphosphonates suggested a potential increased risk for gastrointestinal side effects, pooled analyses found no significant difference in gastrointestinal side effects for alendronate or risedronate, when compared with placebo (185). The model did not account for long-term side effects such as osteonecrosis of the jaw and atypical sub-trochanteric fractures as these are very rare and therefore unlikely to affect the outcome of the model.

Mortality

In patients who developed fractures after screening, OPTIMAL enrolled patients had reduced mortality hazard by 40% (Chapter 5). Using stepwise regression, the mortality hazard reduced from 50% for OPTIMAL program as a single variable alone, to 40% for the full model (age, gender, ethnicity and CCI). The housing type of 1 and 2 roomers for patients was not a predictor of mortality, which implied that the socioeconomic status of the patients did not affect the outcome of mortality.

Costs of intervention

The cost of the OPTIMAL program included salary, benefits, training cost, and overhead of screening coordinators for their time on the program; salary and benefits were 90% of the cost. We obtained the annual cost of the program from the screening program and divided the cost by the average number of patients screened per year. The program began in six public hospitals and 16 polyclinics in Singapore in 2008. We considered patients as screened only if they completed a partial or complete baseline survey through interaction with a program coordinator. Those patients who were under 50 years of age, who did not describe their fracture as a fragility fracture, and who did not fill out the baseline survey were not considered screened. Based on these criteria, the program, on average, screened 4266 patients and enrolled 1623 patients per year with 8 full-time equivalents of program coordinators, and . The coordinators spent about 55 % of their time on program- related activities. The cost of the program worked out to be $554 per enrolled patient per year.

Costs of bone mineral density testing and osteoporosis treatment

All OPTIMAL patients used dual-energy X-ray absorptiometry (DXA) Bone Mineral Density (BMD) test. Most patients receiving osteoporosis treatment had a DXA test every 2 years and saw their physician two times a year to monitor their treatment (Chapter 5). The cost of BMD and physician consult is $180 per year. The cost of treatment ranged from $240 to $2400 a year, dependent on the choice of pharmacotherapy. The average cost is $590 per patient per year.

Costs of hip fracture

Costs of hip fracture, including inpatient, outpatient, laboratory services, same day surgery, complex continuing care, rehabilitation, long-term care, home care, and prescriptive medications were obtained from unpublished data from Ministry of Health, Singapore. The cost for hip fracture for the first year was $28,421. We assumed that the subsequent year costs were the same as the second-year costs based on the findings from a study that reported 5-year post-fracture costs in Canada (188). Since the hip fracture cohort had a hip fracture before receiving the intervention, we assumed these patients incurred the subsequent year costs as long as they were alive in the model; however, if a patient experienced a subsequent hip fracture, he/she would incur the costs of a first-year hip fracture for that year. All costs were expressed in 2014 Singapore dollars. Costs of hip fracture were inflated by 5% to 2014 dollars.

Health state utilities and quality-adjusted life-years

In the model, we assigned a utility weight to each health state. For each year that a patient spent in a health state, the patient accumulated quality-adjusted life-years (QALYs). For the hip fracture cohort, we assumed patients had a quality of life similar to those who had a hip fracture previously (multiplier, 0.80). For the non-hip fracture cohort, they started the model with the quality of life of the general population, and their quality of life deteriorated when they had a hip fracture. Table 3 summarises the costs, quality adjustments and probabilities of various health outcomes.

Table 1: Parameters showing the base-case values used

Parameter	Base case value	References
Cost ($)		
Hip fracture, first year cost	28,421	MOH[1]
Post-Hip fracture, >1 year after hip fracture	665	MOH[1]
2nd Hip fracture, first year cost	28,421	MOH[1]
Post-2nd Hip fracture, >1 year after 2nd hip fracture	665	MOH[1]
Other fracture, first year cost	4,608	MOH[1]
Post-Other fracture, >1 year after other fracture	570	MOH[1]
Total cost of OPTIMAL intervention	1,144	OPTIMAL[2]
Quality adjustments (Utility)		
Hip fracture, first year utility	0.797	(189)
Post-Hip fracture, >1 year after hip fracture	0.899	(189)
2nd Hip fracture, first year utility	0.797	(189)
Post-2nd Hip fracture, >1 year after 2nd hip fracture	0.899	(189)
Other fracture, first year utility	0.907	(189)[3]
Post-Other fracture, >1 year after other fracture	0.994	(189)[3]
Probabilities from no fracture state (per 100,000 person years)		
Hip fracture, Male/Female	20,000/8,150	OPTIMAL[2]
Other fracture, Male/Female	1,742/1,743	OPTIMAL[2]
OPTIMAL intervention		
Adherence rate	0.63	OPTIMAL[2]
Relative risk of Hip fracture	0.27	OPTIMAL[2]
Relative risk of Other fracture	0.75	OPTIMAL[2]
Relative risk of fractures due to prior Hip fracture		
Hip fracture, Male/Female	0.2/0.41	OPTIMAL[2]
Other fracture, Male/Female	0.37/0.67	OPTIMAL[2]
Relative risk of fractures due to prior Other fractures		
Hip fracture, Male/Female	0.26/0.65	OPTIMAL[2]
Other fracture, Male/Female	1.5/1.45	OPTIMAL[2]

[1] Unpublished data from Singapore Ministry of Health
[2] Data obtained from patients in the OPTIMAL cohort

[3] These utilities also took into account percentages of each type of fracture based on Singapore Ministry of Health Data

7.3 Results

The OPTIMAL program enrolled 8,113 patients between 2008 and 2013. The mean age of enrolees was 74.3 years; most of them were female (86 %) and had recent fracture of less than one year at the time of enrolment (66 %). Among those with follow-up data, 85 % received a bone mineral density test; among those with low bone mass, 77 % received treatment.

Cost-effectiveness of the OPTIMAL program

The OPTIML program prevented 77 hip fractures for every 1000 participants and reduce mortality by 40% over five years. This led to significant gains of 228 QALYs per 1000 patients (Table 4). Patients in the program incurred higher costs due to costs of the intervention, BMD test, and osteoporosis treatment, but preventing subsequent hip fractures also saved costs. Discounting costs and benefits at 5 % per year, the program cost $3,795 more and gained 0.349 QALYs per patient, with an incremental cost-effectiveness ratio (ICER) of $10,864 per QALY gained. One-way sensitivity analysis with the lower and upper range set at 0.75 and 1.25 times the base-case value yields ICER value that is very favourable (table 5). The Tornado diagram for female and male gender sensitivity analysis (figure 2 and 3) indicated the following as important determinants:

1. OPTIMAL adherence rate
2. Cost of OPTIMAL intervention
3. Rate of hip fracture
4. Relative risk of hip fracture after OPTIMAL intervention
5. Cost of other fracture
6. Utility of post-other fracture

Table 2: Costs and health outcomes per patient, base case (all model input were set to mean values)

	OPTMAL enrolees	Non-enrolees	Incremental[b]
Number receive BMD test, per 1000 patients	850	120	730
Number receive treatment, per 1000 patients	770	20	750
Number of hip fracture, per 1000 patients per year	16	31	(15)
QALY (discounted)[a]	7.751	7.402	0.349
Program cost	$1144	$0	$1144
Hip fracture cost	$28,421	$28,421	$0
Total cost (discounted)[a]	$16,060.63	$19855.28	$5,607
ICER (incremental cost per QALY, discounted) [a]			$10,864

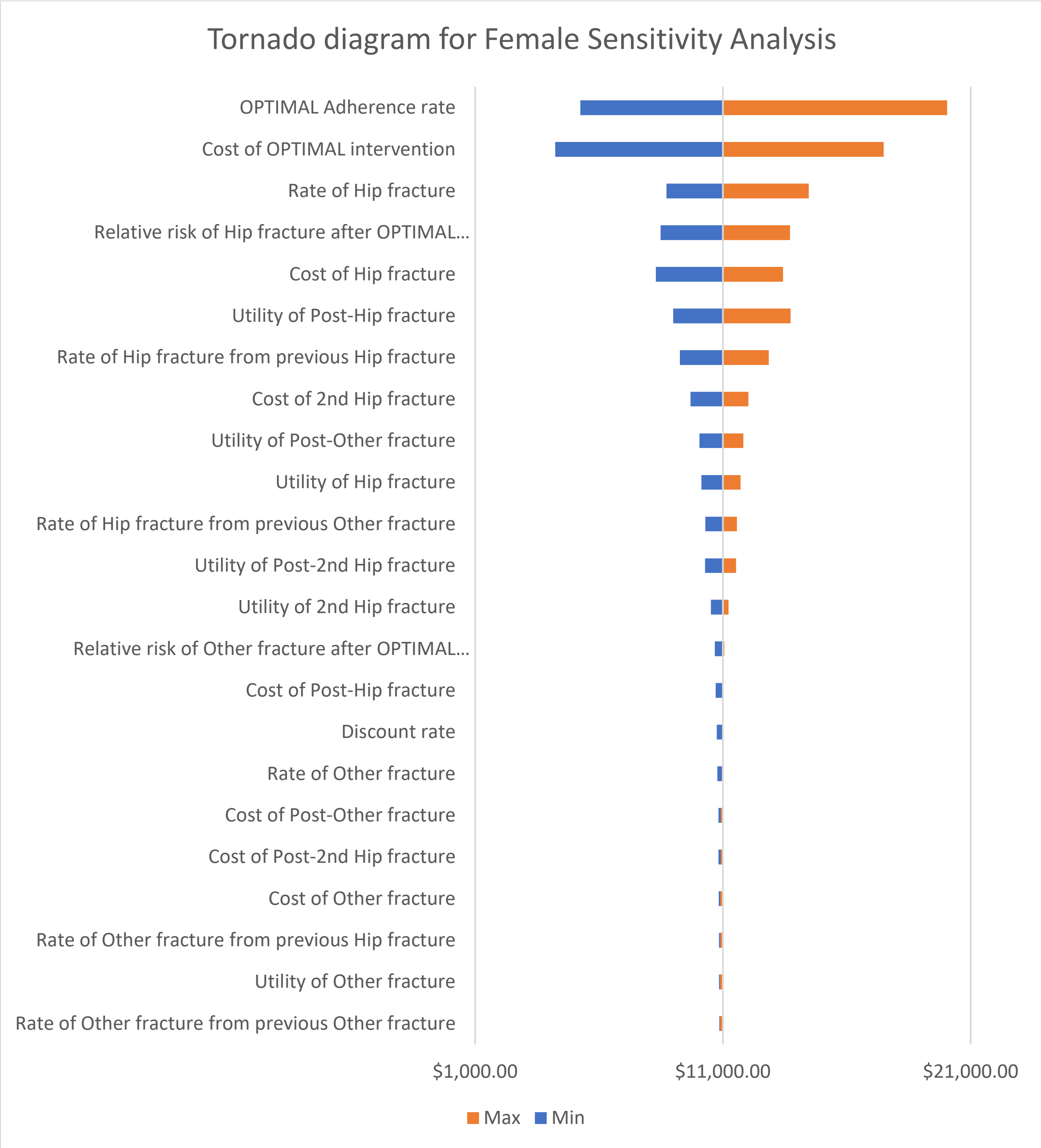
[a] Discounted at 5 % per year

[b] Paracentesis are negative values

Table 3: One-Way Sensitivity Analysis showing the ICER values when the parameters are varied by 25% below and above the base-case value (e.g. 0.75 and 1.25 times of the base-case value)

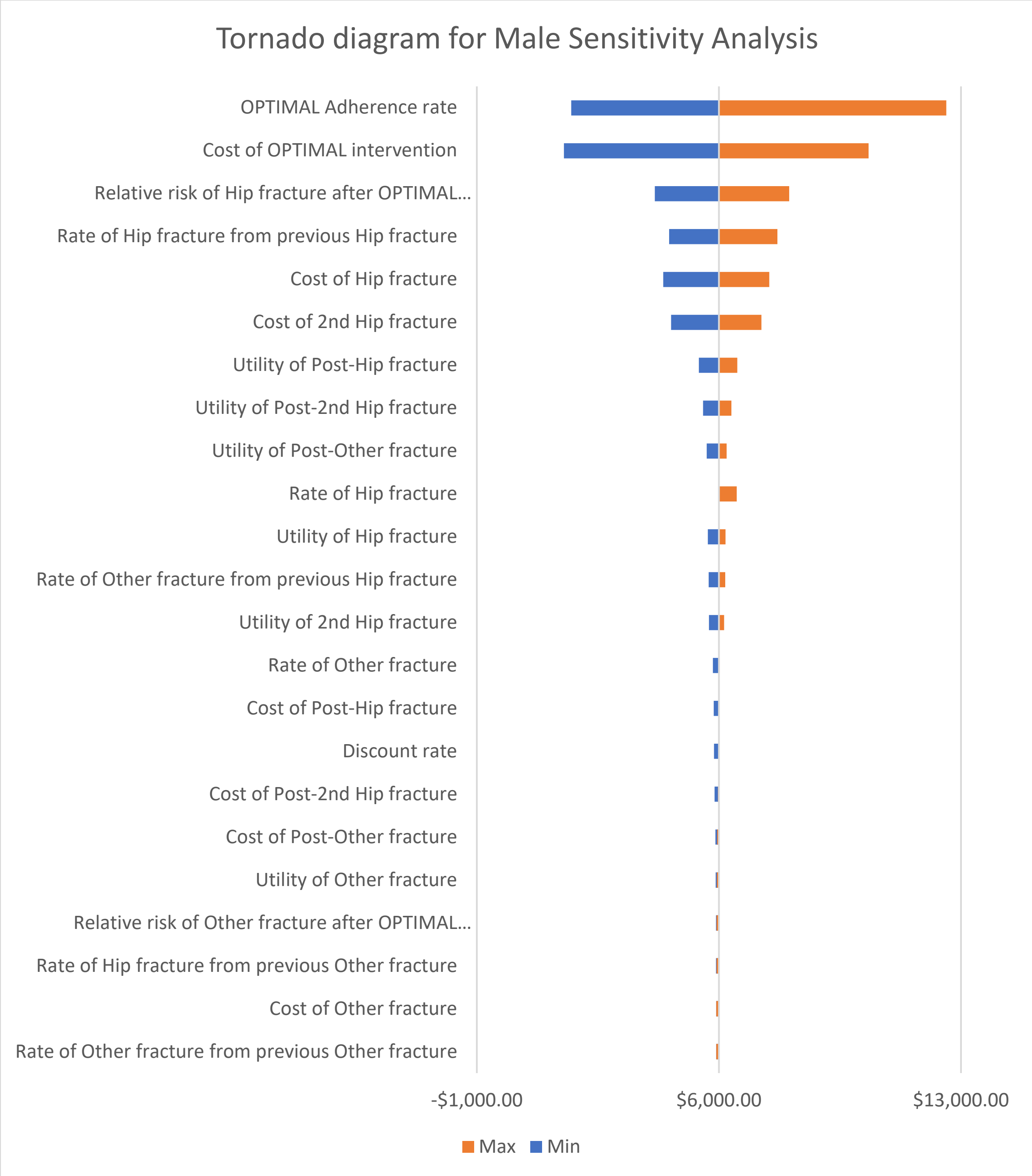
Parameter	Female		Male	
	Low	High	Low	High
Discount rate	$10,749.75	$10,980.95	$5,853.94	$5,989.86
Cost				
Hip fracture	$8,297.59	$13,431.21	$4,392.40	$7,453.70
Post-Hip fracture	$10,709.86	$11,018.94	$5,853.74	$5,992.36
2nd Hip fracture	$9,696.28	$12,032.53	$4,615.88	$7,230.22
Post 2nd Hip-fracture	$10,821.88	$10,906.92	$5,872.46	$5,973.64
Other fracture	$10,835.22	$10,893.58	$5,919.31	$5,926.79
Post-Other fracture	$10,817.96	$10,910.84	$5,895.06	$5,951.04
OPTIMAL intervention	$4,233.57	$17,495.23	$1,516.29	$10,329.80
Utility				
Hip fracture	$10,134.89	$11,707.08	$5,679.28	$6,188.69
Post-Hip fracture	$8,987.84	$13,731.36	$5,415.92	$6,534.96
2nd Hip fracture	$10,519.80	$11,232.34	$5,713.61	$6,148.43
Post 2nd Hip-fracture	$10,274.20	$11,526.55	$5,544.11	$6,357.59
Other fracture	$10,845.63	$10,883.24	$5,909.35	$5,936.81
Post-Other fracture	$10,050.90	$11,821.19	$5,647.60	$6,226.75
Rates				
Hip fracture	$8,720.47	$14,471.15	$5,976.72	$6,513.83
Hip fracture from previous Hip fracture	$9,266.46	$12,849.93	$4,561.37	$7,691.58
Hip fracture from previous Other fracture	$10,291.80	$11,564.55	$5,915.01	$5,931.09
Other fracture	$10,775.76	$10,952.49	$5,822.72	$6,021.59
Other fracture from previous Hip fracture	$10,844.01	$10,884.79	$5,707.70	$6,184.05
Other fracture from previous Other fracture	$10,856.03	$10,872.78	$5,920.64	$5,925.46
OPTIMAL intervention				
Adherence rate	$5,247.71	$20,046.52	$1,731.41	$12,573.87
Relative risk of Hip fracture	$8,487.02	$13,714.78	$4,149.74	$8,028.66
Relative risk of Other fracture	$10,668.95	$11,061.52	$5,915.24	$5,932.52

Figure 2



Tornado diagram for Female Sensitivity Analysis
OPTIMAL Adherence rate
Cost of OPTIMAL intervention
Rate of Hip fracture
Relative risk of Hip fracture after OPTIMAL...
Cost of Hip fracture
Utility of Post-Hip fracture
Rate of Hip fracture from previous Hip fracture
Cost of 2nd Hip fracture
Utility of Post-Other fracture
Utility of Hip fracture
Rate of Hip fracture from previous Other fracture
Utility of Post-2nd Hip fracture
Utility of 2nd Hip fracture
Relative risk of Other fracture after OPTIMAL...
Cost of Post-Hip fracture
Discount rate
Rate of Other fracture
Cost of Post-Other fracture
Cost of Post-2nd Hip fracture
Cost of Other fracture
Rate of Other fracture from previous Hip fracture
Utility of Other fracture
Rate of Other fracture from previous Other fracture
$1,000.00
$11,000.00
$21,000.00
Max
Min

Figure 3:



7.4 Discussion

We evaluated a widely implemented fracture liaison program that identifies, educates, evaluates fracture and falls risk and refers patients for appropriate tests (BMD and other relevant blood tests) and osteoporosis treatment using data collected over 5 years. The major finding of our program that is different from the other FLS is that there is a significant 40% reduction in mortality of patients enrolled in our program versus those who are not enrolled, after adjusting for known predictors of mortality such as age, gender, ethnicity and Charlson comorbidity index (CCI)(Chapter 5). This has resulted in significant gains in life years of enrolled patients, and a ICER of $10,864 per QALY gained, which is cost effective based on international norms. World Health Organisation (WHO) has suggested that healthcare intervention was deemed cost effective if the ICER is between 1 to 3 times of Gross Domestic Product (GDP)/ QALY. The Gross Domestic Product (GDP) per capita of Singapore was $87,108 in 2018, therefore the OPTIMAL program was cost effective.

The results were robust under plausible assumptions and were most sensitive to the baseline risk of the first hip fracture and treatment effectiveness. As such, this would not affect the cost effectiveness of the OPTIMAL program. Therefore, our results are consistent with the published fracture liaison service literature, supporting the observation that more intensive models are more effective in preventing subsequent fracture (40). A fracture liaison service that includes assessment is challenging to implement because it requires medical directive for coordinators to order a BMD test; however, the additional effectiveness and cost- effectiveness could justify the efforts. Besides, our results also provide more information to fill this knowledge gap about cost-effectiveness for implementing such program in an Asian country.

Certainly, our model did have some limitations. Firstly, our model built on other cost-effectiveness analyses of fracture liaison service but a detailed comparison of our results with the other analyses is challenging because the assessed programs are different from our intervention. Furthermore, the other studies made different health economic modelling assumptions and adopted different analytical perspectives (39, 40, 42, 186, 190, 191). Another limitation would be the generalisability of our results to other jurisdictions in Asia due to the difference in organization and financing of the different health care systems, Nevertheless, the overall conclusions from our model and other published models are consistent that more intensive fracture liaison services are cost-effective. This would at least provide some assurance that implementation of a more intensive fracture liaison service should be the preferred option.

Finally, our modelling CEA will provide preliminary evidence confirming the cost-effectiveness of an intensive fracture liaison service in Singapore. Our results also provide the base-line data for future comparison with more complicated model.

Chapter 8. Conclusion

8.1 Major Findings

In this thesis, we first performed a local survey in knowledge, attitude and practice with regard to osteoporosis amongst patients in a polyclinic in Singapore (Chapter 2). The results showed that awareness of osteoporosis, identification of risk factors and knowledge of complications among middle-aged and elderly men and women in Singapore was fair. Among the respondents, older people were less likely to have heard of osteoporosis, especially women older than 65 years. Furthermore, they were the least inclined to exercise. In contrast, most people would go for screening and treatment for osteoporosis. However, even though the oldest people were more at risk for osteoporosis, they were generally the least inclined to take the appropriate health precautions. Our study identified a gap of knowledge and lack of practice of good health habits, especially in the older people, that need to be addressed by public health messages and health professionals in the prevention of osteoporosis.

A previous study from Singapore reported a steady increase in age-adjusted hip fracture rates of around 1–1.5% per year in both men and women from 1991 to 1998. Based on these trends, we predicted a further 30–50% increase in hip fracture incidence rates over the ensuing 30 years in Singapore (7). This will result in a great financial burden to the healthcare system of Singapore (Chapter 6). We therefore conducted a study to have a better understanding of the direct and indirect costs of osteoporotic fractures in Singapore (Chapter 4). The findings were that hospitalization was associated with the highest cost borne by both the hospital and the patients, and informal care dominated indirect costs. With an aging population, the prevalence of osteoporosis-related fractures in Singapore will continue to grow in the years to come, generating what is expected to be a heavy burden on health budgets (chapter 6). Better knowledge of the financial consequences of fragility fractures could enable proactive and preventive measures to be undertaken, especially at sites of care with high cost drivers. This would also provide valuable information for health administrators in healthcare resource and budget allocation planning.

With the available information on patients' knowledge, attitude and practice (chapter 2), as well as the cost burden of fracture management in Singapore (chapter 4 and 6), we therefore undertook a fracture liaison service program (OPTIMAL) to prevent recurrent fractures from 2008 to 2016 (Chapter 5). The OPTIMAL program is a clinician champion-driven, case coordinator-run secondary prevention program for osteoporotic fractures. The program strives to narrow the prevalent care gap in osteoporosis care through a judicious combination of fracture case finding, appropriate assessment and evaluation, patient education on osteoporosis and risk factor management, education on nutrition, fall prevention and exercises for muscle strengthening, balance and coordination, in addition to the use of effective anti-osteoporosis pharmacological agents.

The most important finding of this study was the reduction in all sites fracture risk by 41% and hip fracture risk by 47.1% of patients enrolled into the OPTIMAL program when compared with non-enrolees after two years. The absolute risk reduction in hip fracture rate was 7.67% (15.58% in non-enrolees versus 7.93% in OPTIMAL enrolled patients). The OPTIMAL program prevented 77 hip fractures for every 1000 participants and reduce mortality by 40% over five years. This led to significant gains of 228 QALYs per 1000 patients (Chapter 7). Patients in the program incurred higher costs due to costs of the intervention, BMD test, and osteoporosis treatment, but preventing subsequent hip fractures also saved costs. Discounting costs and benefits at 5 % per year, the program cost $3,795 more and gained 0.349 QALYs per patient, with an incremental cost-effectiveness ratio (ICER) of $10,846 per QALY gained. These results compared favourably with other observational studies and randomised controlled trials of similar fracture liaison service program (8). Taking together with the reduction in fracture, this projected good return of investment would support the cost-effectiveness of implementing such program in Singapore.

In Chapter 3, we undertook a study to examine the incidence of hip fracture In Singapore from 2000 to 2017. We observed several important trends in the occurrence of hip fractures in this study. During the period 2000-2017, absolute numbers of hip fractures continued to increase, with a mean annual increase of 71 fractures per 100,000 and an Average Annual Percentage Change (AAPC) of 3.5% (95% CI: 3.3, 3.8). Nevertheless, the crude fracture rate per 100,000 declined in both men and women, indicating that the increase in absolute number of hip fractures was due to an increase in the numbers of women and men at risk for hip fracture. When crude rates per 100,000 were age-adjusted, fractures trends declined even more steeply, indicating the major contribution of the aging Singapore population to the increase in total number of fractures.

Furthermore, marked ethnic differences were observed, with Chinese women having 1.4- and 1.9-fold higher fracture rates than Malay and Indian women, respectively. However, although having the highest fracture rates, Chinese women were the only ethnic group to show a temporal decline in fracture rate. It is relevant to note that several factors may be associated with this decline. A Singapore study in 2003 revealed that a large fraction (42%) of Chinese women were not aware of the relationship of osteoporosis to fractures (46), whilst a more recent survey done by us in 2009 showed that only 18% of Chinese women were not aware of the relationship (Chapter 2). Between the two-study periods, various initiatives to increase awareness have been implemented in Singapore. For example, the Singapore Health Promotion Board and Osteoporosis Society of Singapore held public forums with extensive press coverage to emphasize the scale of the problem. The OPTIMAL secondary fracture prevention program, which is clinician champion-driven and case manager-run, was established in public hospitals in Singapore in 2008 (Chapter 5). At the same time, anti-osteoporosis drugs such as bisphosphonates are increasingly prescribed and consumed, as costs have fallen with the introduction of generic medications (80). Currently, more than half of Singapore hospitals have implemented fracture liaison services (Chapter 5), resulting in good compliance with osteoporosis medications.

Therefore, the overall results from the studies as presented in the thesis would indicate that with the aging population, there is a likelihood of increased osteoporosis-related fractures. This projected increase is expected to impose heavy financial burden to the health care system in Singapore. However, with a coordinated approach in managing osteoporosis as shown by the OPTIMAL program implemented in Singapore, it may be possible at least to damper the clinical and financial impact of osteoporosis-related fractures. The results from the studies in this thesis would also provide an example of tackling the problem of increased osteoporosis-related fractures faced by other countries.

8.2 Limitations

As with any studies, there are limitations. We are going to have a quick recap of the major limitations in this section.

Firstly, the process of implementing the OPTIMAL program in six public hospitals and 16 polyclinics in Singapore has helped us to identify certain problems and limitations associated with the program and served as valuable learning points for future improvement. These include recognition of the fact that we have been unable to identify all patients with fragility fractures. The problem partly lies in the well-recognized fact that some osteoporotic fractures especially vertebral fractures often go undiagnosed. Another contributing factor to the less than 100% “capture rates” would be the lack of adequate personnel to serve as case managers due to manpower funding issues. Both these problems hopefully will be resolved in the near future after reviewing the cost-benefit of implementing such programs by the government.

One area for improvement in the OPTIMAL program is to improve medication compliance among patients. Even with government subsidies, some patients still find medication cost prohibitively expensive and this may contribute to some patients being noncompliant despite close follow-up. Hence, although we may not be able to resolve the problem of financial burden, there is still a need to implement strategies to monitor and encourage medication compliance among patients in order to reap the full benefits of the program.

Another area for improvement that would also potentially reduce cost to participating patient would be right-siting of patients. Right-siting, i.e., discharging patients to polyclinics and primary care after initial assessment and therapy initiation, remains inadequate in our program. Diverting suitable patients to polyclinics and primary care would reduce cost to patients as well as improving convenience in access. Integrating GPs into the program and providing more seamless transition programs may help overcome this problem. This would be of particular importance to other countries where healthcare resources such as the hospitals are already stressed by the extremely heavy caseloads.

Furthermore, though we did see a trend towards a decreased hip fracture rate in our followed up patients when compared to a control group, a limitation of our study was that there was no randomised control group. Being a pragmatic study, we could not avoid this intrinsic limitation.

Notwithstanding these limitations, our data provide compelling evidence from an Asian country of the potential effectiveness of a secondary fracture prevention program. The lessons learned during the last eight years would enable us to implement a revised and more effective program in the near future. The onus also rests on us now is to demonstrate the cost effectiveness and integrate OPTIMAL into the standard of care of the hospital so that no fragility fracture patient is missed, and to strive to ensure that in every patient, the first fracture even if it does happen will really be the last.

8.3 Recommendations for Future Studies

The data collected from the OPTIMAL program will allow future studies into the evaluation of the cost-effectiveness of the program. In addition, the database will also allow studies into the demographic, social, clinical and therapeutics factors that are predictive of non-adherence, fractures and mortality in our patient population. This will help us design better clinical program to manage osteoporosis and prevent fractures in future.

We are planning for the implementation of the Integrated Mainstreamed OPTIMAL (IM-OPTIMAL) program from 2019 onwards, and it will address many of the challenges faced by OPTIMAL program in terms of engaging primary care doctors (including GPs) for appropriate siting of care, community exercise program for better adherence to exercises. IM-OPTIMAL can be integrated with the hip fracture bundled payment project, and augment it with a secondary prevention of fracture capability and longer term outcome measurements. This will allow better capture of the value of care of fracture prevention and fracture care as an integrated care model.

The IM-OPTIMAL workflow will be similar to the current OPTIMAL program, with one or more fracture liaison coordinators in each participating hospital. The mainstreamed funding will be adequate to employ one or more coordinators per hospital. The role of the coordinator is to ensure that the OPTIMAL workflow is being carried out by various inpatient settings and outpatient clinics via protocol driven care, enabled by electronic medical record (EMR), with augmented intelligence decision aid and predictive analytics for stratified care delivery (e.g. EPIC EMR). There is no need to collect patient data via another patient database system. The automated data collection by the EMR will include the following:

1. Quarterly and yearly fracture incidence in each hospital and nationally

2. Proportion of patients with previous fractures who are on osteoporosis medication (as defined by point 1)

3. Proportion of patients with previous fractures who are still on osteoporosis medication after one and two years and beyond (as defined by point 1)

4. Patient experience of care and health related quality of life measurements such as EQ-5D to enable value driven outcome (192) analytics and cost utility analysis

With the automated data collection and clinical informatics approach, it will be possible to generate dashboard showing the trends of these data, focusing on Value Driven Outcome (192) and Value Based Care (193) that will promote practice change and improve patient outcome at affordable cost. This will be an important step that marks the beginning of a capitation-based funding model, which will pay for quality and value, rather than pay for service. In so doing, the era of moving beyond healthcare to health, beyond quality to value, and beyond hospital to community, will be upon us.

Appendix I Full Publication List

Published Papers

Yong EL, Ganesan G, Kramer MS, Logan S, Lau Tang Ching, Cauley JA, Tan KB. **Hip fractures** in **Singapore**: ethnic differences and temporal trends in the new millennium. Osteoporosis Int. 2019 Apr;30(4):879-886. Epub 2019 Jan 23.

Ng Charmaine Shuyu, Lau Tang Ching, Ko Yu. Cost of Osteoporotic Fractures in Singapore. Value Health Reg Issues. 2017 May;12:27-35. Epub 2017 Apr 26.

Manuscripts Submitted

Tang Ching Lau, Shu-Chuen Li, Lay Hoon Goh
Gaps in knowledge, attitude and practice in the community hinders effective primary prevention of osteoporosis in Singapore

Tang Ching Lau, Ganga G, Kevin Bryan Tan, Manju Chandran, Chionh Siok Bee, Lian Tsui Yee, Rani Ramason, Ang Seng Bin, Lydia Au, Vivien Lim, Gilbert Tan, Keith Tsou, Shu-Chuen Li
The effectiveness of a fracture liaison program in improving outcomes of patients with prior fragility fractures

Manju Chandran, Tang Ching Lau, Isabelle Gagnon-Arpin, Alexandru Dobrescu, Wenshan Li, Man Yee Mallory Leung, Narendra Patil, Zhongyun Zhao
The health and economic burden of osteoporosis in Singapore and the potential impact of increasing treatment options

Tang Ching Lau, Kevin Bryan Tan, Ganga G, Manju Chandran, Chionh Siok Bee, Lian Tsui Yee, Rani Ramason, Ang Seng Bin, Lydia Au, Vivien Lim, Gilbert Tan, Keith Tsou, Shu-Chuen Li
Cost-effectiveness of a fracture liaison service—a real-world evaluation after 5 years of OPTIMAL provision

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