

Anti-osteoporosis drugs reduce mortality in cancer patients: A national cohort study of elderly with vertebral fractures

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ABSTRACT

Introduction: The most prevalent type of fragility fractures is osteoporotic vertebral fractures (OVFs). However, only a few studies have examined the relationship between anti-osteoporosis treatments and malignancy-related mortality following an OVF. The goal of this study is to determine the effect of anti-osteoporosis therapy on mortality in OVF patients with and without cancer.

Method: Data from older people over the age of 65 who were hospitalised for OVFs between 1 January 2003 and 31 December 2018 were analysed retrospectively. A total of 6139 persons getting osteoporosis treatment and 28,950 who did not receive treatment were analysed, together with 2 sets of patients, comprising cancer patients (794) and cancer-free patients (5342), using anti-osteoporosis medication or not, in 1:1 propensity score-matched analyses. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated.

Results: In all, 35,089 patients with OVFs were included in the population; 29,931 people (85.3%) were women, and the mean (standard deviation) age was 78.13 (9.27) years. Overall survival was considerably higher in those undergoing osteoporosis therapy. This was true both for those without cancer (adjusted HR 0.55; 95% CI 0.51–0.59; $P < .0001$) as well as those with cancer (adjusted HR 0.72; 95% CI 0.62–0.84; $P < .0001$). Even among cancer patients, those who received anti-osteoporotic drugs had a lower mortality rate than those who did not.

Conclusion: Our findings suggest that anti-osteoporosis therapy should be initiated regardless of the presence of cancer in the elderly, as it increases survival following OVFs.

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Keywords: cancer, elderly, mortality, osteoporosis, osteoporotic vertebral fracture

CLINICAL IMPACT

What is New

- Administering anti-osteoporosis drugs following osteoporotic vertebral fractures are associated with a significant reduction in overall mortality rate among cancer patients.

Clinical Implications

- Anti-osteoporosis therapy should be considered for the initiation of treatment in elderly cancer patients with osteoporotic fractures, as our study indicates that such treatment can effectively reduce overall mortality in this population when tolerated.

INTRODUCTION

Osteoporotic vertebral fractures (OVFs) are the most prevalent type of fragility fractures, affecting 25% of adults in their early 70s and 43% of those over the age of 80.^{1,2} Following an OVF, persistence of the vertebral deformity may lead to spinal kyphosis, which is associated with chronic lower back discomfort, neuropathy of the lower extremities, and diminished respiratory and digestive function.³⁻⁵ Previous research identified a correlation between treatment outcomes following OVF and older age, male sex, mobility and other health issues.^{6,7} Women who have experienced a severe vertebral fracture are 4 times more likely than those who have not to suffer another vertebral fracture.⁸ Furthermore, in the first year following an OVF, the risk of death ranges from 6.7% to 28%, which is comparable to the risk of death

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following a hip fracture.^{9–11} However, relatively few studies have investigated the relationship between treatment-related variables and malignancy-related mortality following an OVF. The purpose of this study is to examine the influence of anti-osteoporosis therapy on mortality in OVF patients with and without cancer.

METHOD

Data sources

We conducted a nationwide retrospective cohort study using de-identified secondary data from the National Health Insurance Research Database (NHIRD). To protect privacy and simplify follow-up, this step replaced individual identification numbers with unique numbers. The NHIRD contains information from a national, mandatory-enrolment, single-payer healthcare system established in 1995. The system covers around 99% of Taiwan's population and maintains all electronic insurance claims records for 97% of the country's hospitals and clinics. The system is also linked to Taiwan's Death Registration Database and the Registry for Catastrophic Illness Patients Database.¹² The NHIRD allows the release of database information for research purposes. Access to the NHIRD does not require patient consent. The Taipei Medical University Joint-Institutional Review Board approved this study (No. N202302026). Informed consent was waived due to the retrospective nature of this study. For cohort studies, we followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

Cohort selection

We identified patients with various disorders using the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and the International Classification of Diseases, Tenth Edition, Clinical Modification (ICD-10-CM). We identified 49,548 potentially eligible individuals that experienced spinal fractures (ICD-9-CM: 806.x, ICD-10-CM: S12.x, S22.0x, S32.x) between 2003 and 2018 and were over the age of 65 from the NHIRD. Cases of unknown sex, unknown age, unknown date of death, previous treatment for osteoporosis, or death within 2 years of the first fracture were excluded. Of these, 20,598 received osteoporosis treatment and 28,950 did not. Patients with osteoporosis who had not received osteoporosis treatment within 1 year of their fracture or who had received treatment for less than 2 years were excluded, leaving 6139 people.

We further separated the above cases into 2 groups: (1) patients who received subsequent osteoporosis treatment (osteoporosis treatment

group) and (2) patients who did not receive osteoporosis treatment (no osteoporosis treatment group). Bisphosphonates (ATC codes: M05BA04, M05BA07, M05BA06, M05BA08), monoclonal antibodies (ATC code: M05BX04), oestrogen receptor modulators (ATC codes: G03XC01, G03XC02) and anabolic agents (ATC code: H05AA02) are examples of the therapeutic agents that the osteoporosis treatment group received. Cases in the osteoporosis treatment group were excluded if treatment was not commenced within 1 year following the fracture. Each case was tracked until the case died or the study period ended (31 December 2018). To prevent confounding effects from baseline characteristics, we performed a 1:1 propensity score-matched analysis of 794 cancer patients and 5342 non-cancer patients with or without antiosteoporosis medication for OVFs based on age, sex and index year (Table 1). Race and ethnicity data were not collected. Fig. 1 depicts a full study flow diagram.

Measurements

The endpoints in this study are all-cause mortality and a variety of comorbidities that were employed as adjustment factors. The comorbidities include hyperuricaemia (ICD-9: 401–405; ICD-10: I10–I13 and I15), hyperlipidaemia (ICD-9: 272; ICD-10: E78), type 2 diabetes (ICD-9: 250; ICD-10: E10–E14), hyperuricaemia (ICD-9: 790.6; ICD-10: E79.0), stroke (ICD-9: 430–434; ICD-10: I60–I63, I65, I66), chronic kidney disease (ICD-9: 585; ICD-10: N18), heart disease (ICD-9: 410–414, 420–429, ICD-10: I20–I25, I30–I50), liver disease (ICD-9: 571.0–571.3, 571.8, 07041, 07044, 07051, 07054, V0262, 0702, 0703, V0261; ICD-10: B16, B17.0, B18.0, B18.1, B19.1, B17.1, B18.2, B19.2, K74.4, K75.81, K76.0, K76.89, R16.2 and K70), depression (ICD-9: 296.2–296.3, 300.4, 311; ICD-10: F32–F33.31), dementia (ICD-9: 290.0–290.4, 294.1, 331.0 and 331.1–331.2; ICD-10: F00, F01, F02, F03, G30, F051, G311) and anaemia (ICD-9: 280–285; ICD-10: D50–D64).

Statistical analysis

Multiple logistic regression analyses were performed to estimate propensity scores for maximum likelihood estimations with anti-osteoporosis treatment based on baseline covariates. With a calliper width of 0.2, 1-to-1 greedy matching was implemented. The balance of variables between 2 groups in the overall population and the propensity score-matched population was then assessed using standardised mean differences with a cutoff value of 0.10. The Kaplan–Meier method was used to plot survival curves of participants receiving or not receiving anti-osteoporosis treatment in the general study population and the

Fig. 1. Flow chart of the eligible study population.

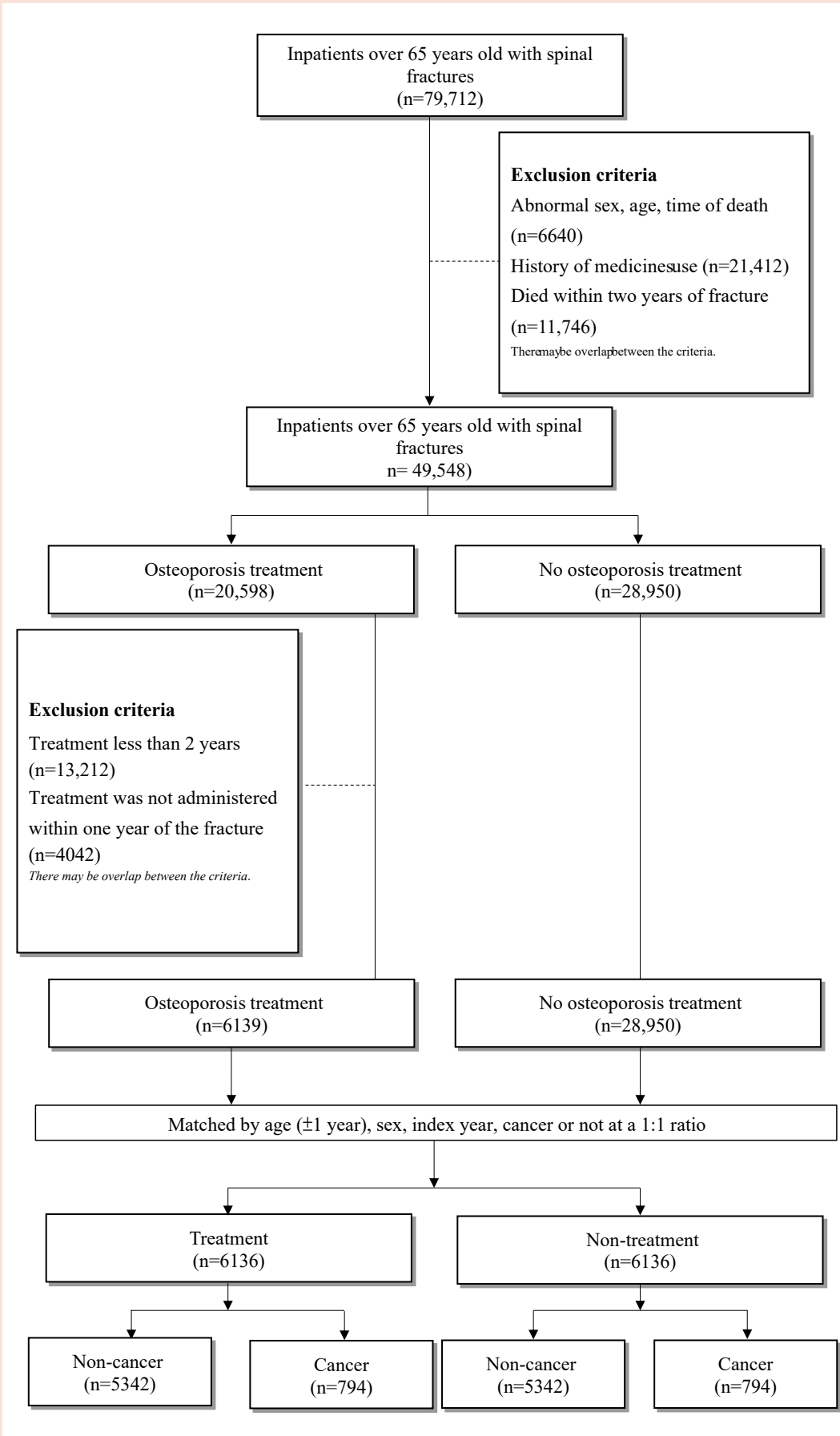


Table 1. Demographic characteristics of the study population after matching.

	Non-cancer					Cancer				
	No osteoporosis treatment n=5342		Osteoporosis treatment n=5342			No osteoporosis treatment n=794		Osteoporosis treatment n=794		
	no.	%	no.	%	<i>P</i> value	no.	%	no.	%	<i>P</i> value
Sex					1					1
Male	733	13.72	733	13.72		175	22.04	175	22.04	
Female	4609	86.28	4609	86.28		619	77.96	619	77.96	
Age, years					.961					.960
65–69	895	16.75	881	16.49		128	16.12	133	16.75	
70–79	2691	50.37	2713	50.79		417	52.52	408	51.39	
80–89	1617	30.27	1614	30.21		229	28.84	231	29.09	
≥90	139	2.60	134	2.51		20	2.52	22	2.77	
Initial treatment										
Bisphosphonates			2924	54.74				458	57.68	
Denosumab			760	14.23				100	12.59	
Selective oestrogen receptor modulators			1400	26.21				206	25.94	
Anabolic agents			258	4.83				30	3.78	
Comorbidity										
Stroke	245	4.59	617	11.55	<.001	29	3.65	80	10.08	<.0001
Chronic kidney disease	133	2.49	169	3.16	.036	25	3.15	35	4.41	.188
Heart disease	609	11.4	1632	30.55	<.001	78	9.82	239	30.1	<.001
Liver disease	42	0.79	176	3.29	<.001	25	3.15	61	7.68	<.001
Depression	139	2.60	384	7.19	<.001	21	2.64	70	8.82	<.001
Dementia	183	3.43	407	7.62	<.001	21	2.64	49	6.17	<.001
Anaemia	78	1.46	200	3.74	<.001	19	2.39	37	4.66	.014

propensity score-matched group. The log-rank test was also used to compare the differences between the curves. Using univariate and multiple Cox proportional hazards regression models, the crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for survival were calculated. Multiple regression models were used to account for variables such as age, sex, hypertension, hyperlipidaemia, hyperuricaemia, type 2 diabetes, chronic kidney disease, dementia, depression, stroke, liver disease, heart disease and anaemia. Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc) was used for all statistical studies. Two-sided $P < 0.05$ was established as the statistical threshold for significance.

RESULTS

Basic characteristics of the study subjects

In total, 35,089 OVF patients were included in the population; 29,931 (85.3%) were women, and the mean (standard deviation) age was 78.13 (9.27). Among those without cancer, males were also less frequent than females (13.72% versus [vs] 86.28%), and more than half were between the ages of 70 and 79. Bisphosphonates were used by 54.74% of osteoporosis patients without cancer, followed by selective oestrogen receptor modulators (SERMs) (26.21%), denosumab (14.08%) and anabolic agents (4.83%). Patients receiving anti-osteoporosis treatment had greater incidences of stroke, chronic kidney disease heart disease, liver disease,

depression, dementia and anaemia among those who did not have cancer. Severe comorbidities were more prevalent in non-cancer individuals who received osteoporotic medications than in those who did not get osteoporotic drugs.

Males were less common than females among those diagnosed with cancer (22.04% vs 77.96%), and more than half were between the ages of 70 and 79. Bisphosphonates were used by 57.68% of osteoporosis patients with cancer, followed by SERMs (25.94%), denosumab (12.59%) and anabolic agents (3.78%). Patients with cancer who received anti-osteoporosis treatment had significantly greater incidences of stroke, heart disease, liver disease, depression, dementia and anaemia than those who did not. Similarly, severe comorbidities were more common in cancer patients who received osteoporotic treatments than in those who did not.

Analysis of overall survival with and without osteoporosis treatment

Fig. 2 depicts the overall survival analysis for the non-cancer and cancer populations with and

without osteoporosis treatment. Overall survival was significantly higher in the osteoporosis treatment groups compared to the no osteoporosis treatment groups in both the non-cancer (adjusted HR 0.55; 95% CI 0.51–0.59; $P<.0001$) and cancer (adjusted HR 0.72; 95% CI 0.62–0.84; $P<.0001$) populations (Table 2).

A multivariable stratified analysis of the risk of death in cancer and non-cancer patients

Fig. 3 shows the relative risk of death in the non-cancer population based on numerous variables. Patients over the age of 70 as well as those with type 2 diabetes (adjusted HR 1.52; 95% CI 1.40–1.65), chronic kidney disease (adjusted HR 1.88; 95% CI 1.66–2.13), dementia (adjusted HR 1.55; 95% CI 1.41–1.71), stroke (adjusted HR 1.31; 95% CI 1.19–1.44), heart disease (adjusted HR 1.34; 95% CI 1.25–1.45) and anaemia (adjusted HR 1.49; 95% CI 1.28–1.72) had significantly higher mortality rates. Female patients (adjusted HR 0.71; 95% CI 0.65–0.78) and those with hyperlipidaemia (adjusted HR 0.69; 95% CI 0.62–0.76), on the other hand, had a significantly lower risk of death.

Fig. 2. Survival curves for anti-osteoporosis treatment in cancer and non-cancer patients.

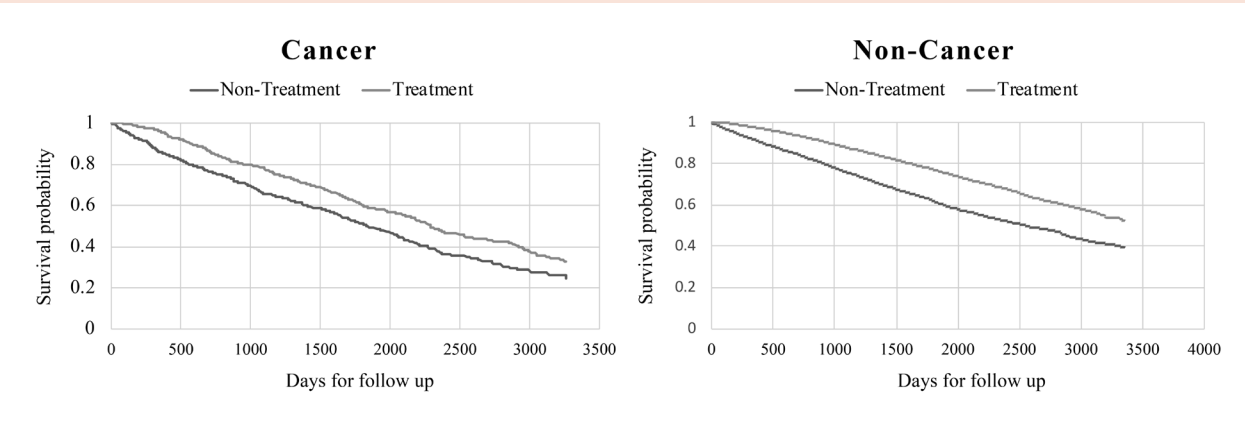


Table 2. Comparison of mortality rates in cancer and non-cancer groups who received or did not receive osteoporosis treatments following osteoporotic vertebral fractures.

	Osteoporosis treatment			No osteoporosis treatment			Crude HR	Adjusted HR ^a
	Event (no.)	Person-year	Mortality rate ^a	Event (no.)	Person-year	Mortality rate ^a		
Non-cancer	1310	12,406,210	1.06	1831	10,803,104	1.69	0.57 ^b (0.53–0.61)	0.55 ^b (0.51–0.59)
Cancer	339	1,772,600	1.91	383	1,555,798	2.46	0.70 ^b (0.61–0.82)	0.72 ^b (0.62–0.84)

HR: hazard ratio
^a Adjusted for age, sex, hypertension, hyperlipidaemia, hyperuricaemia, type 2 diabetes, chronic kidney disease, dementia, depression, stroke, liver disease, heart disease and anaemia.
^b $P<.0001$

Fig. 4 illustrates the relative risk of death among those with cancer based on numerous variables. Patients over the age of 70, those with type 2 diabetes (adjusted HR 1.32; 95% CI 1.11–1.57) and those with chronic kidney disease (adjusted HR 1.88; 95% CI 1.44–2.45) had a considerably higher risk of death. Conversely, female patients had a significantly higher survival rate (adjusted HR 0.76; 95% CI 0.64–0.90).

DISCUSSION

This real-world data study examines the impact of anti-osteoporotic drug therapy on mortality in cancer patients and non-cancer patients who experienced vertebral fractures using a large national database. The results show that individuals with OVFs, whether they had cancer or not, had lower all-cause mortality when they received osteoporosis drugs. Although the retrospective nature of this study precludes the establishment of a cause–effect relationship between anti-osteoporotic

medications and mortality, the data indicate that anti-osteoporotic treatments are independently associated with reduced mortality after adjusting for multiple confounders (age, sex, stroke, chronic kidney disease, heart disease, liver disease, depression, dementia and anaemia). Furthermore, whether the patients had cancer or not, the group receiving osteoporosis drug treatment had a higher proportion of severe comorbidities than the group not receiving anti-osteoporotic treatment, but its mortality rate was lower, whether adjusted or not.

Prior research has suggested that treating osteoporosis after a fracture may reduce mortality.^{13–15} Furthermore, patients undergoing bisphosphonate treatment have been reported to experience benefits in ways other than solely fracture prevention.¹⁶ For example, in individuals who have suffered recent hip fractures, zoledronic acid treatment is associated with a considerably reduced risk of new fractures and a lower mortality rate.¹⁷ Zoledronic acid mitigates accumulated DNA

Fig. 3. Crude and adjusted hazard ratios for non-cancer patients receiving anti-osteoporosis therapy.

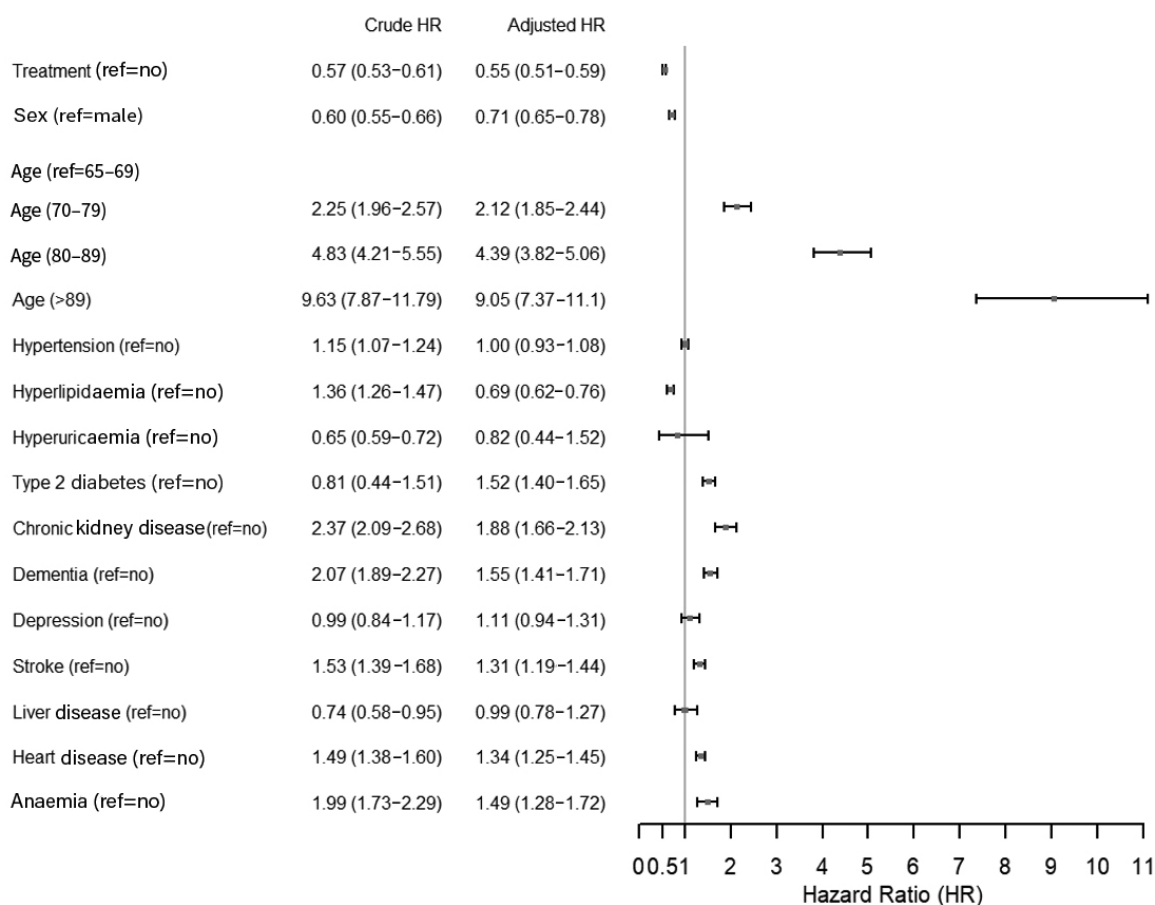
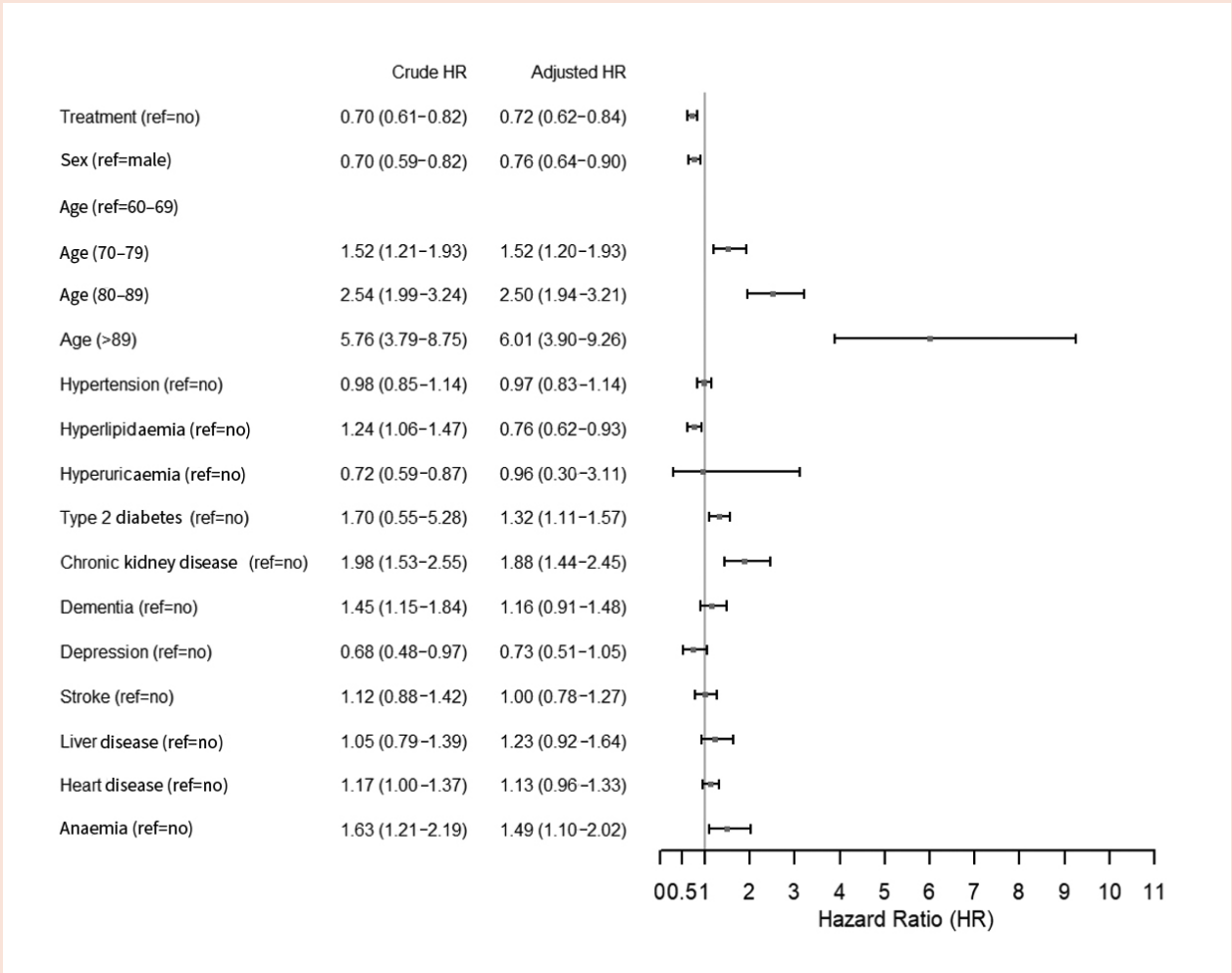


Fig. 4. Crude and adjusted hazard ratios for cancer patients receiving anti-osteoporosis therapy.



damage in mesenchymal stem cells.¹⁸ Additionally, bisphosphonates bind to calcium deposits in the walls of large arteries, thereby reducing the negative sequelae of atherosclerosis.¹⁹ Furthermore, nitrogen-containing bisphosphonates have pharmacological effects similar to statins in that they raise serum high-density lipoprotein cholesterol levels, lower low-density lipoprotein cholesterol levels, and block inflammatory cytokine secretion by inhibiting the enzyme farnesyl pyrophosphate synthase in the mevalonate pathway.²⁰ A comprehensive review of the vascular effects of bisphosphonates suggested that they can ultimately reduce the formation of atherosclerotic plaque.²¹

Bisphosphonates also have anti-cancer properties. They deplete cells of the isoprenoid lipids farnesyl diphosphate and geranylgeranyl diphosphate, which are necessary for the post-translational prenylation of members of the small G-protein superfamily, including small GTPases Ras,

Rac and Rho.^{22–24} Isoprenylated proteins are crucial signalling proteins that regulate a range of cellular processes required for normal cell activity and survival, and they have also been linked to various malignancies.²² Numerous cancer cell functions, such as proliferation, invasion, adhesion and migration, are all inhibited by bisphosphonates.²⁴ As a result, it is possible that they play a role in preventing tumour recurrence and bone metastasis. This may help explain why cancer patients who use anti-osteoporosis drugs have a higher survival rate than those who do not. Patients who use bisphosphonates after menopause have a lower incidence of breast and colorectal cancers.^{25,26} It has also been demonstrated that zoledronic acid improves bone-metastasis-free survival in patients with various advanced solid malignancies.²⁷

SERMs, such as raloxifene, were also included in this trial as an osteoporosis treatment. Unlike oestrogens, which are uniform agonists at oestrogen receptors, and anti-oestrogens, which

are uniform antagonists at oestrogen receptors, SERMs have an unusual tissue-selective pharmacology. They are oestrogen agonists in certain tissues (bone, liver and the cardiovascular system), antagonists in others (brain and breast) and mixed agonists/antagonists in the uterus.²⁸ SERMs therefore can provide the benefits of oestrogen activity on the bones and heart, but by acting as oestrogen antagonists in the breast and uterus, SERMs can avoid the detrimental effects of oestrogen on these tissues.²⁹ Such an activity may allow SERMs to contribute to the reduction in overall mortality among women with OVs that was observed in this study.

Despite the fact that denosumab's mechanism of action differs from those of bisphosphonates and SERMs, current hypotheses suggest that the drug's induction of receptor activator of nuclear factor nuclear factor- κ B (RANK) receptor activation by the ligand (RANKL) may improve survival. RANK activity affects the immune and vascular systems through the inhibition of pro- and anti-inflammatory cytokine production as well as changes in the molecular expression of proteins involved in immune processes and anti-inflammatory responses.³⁰ Previous research revealed that the intrinsic expression and activity of RANK and RANKL inside mammary tissue control mouse mammary gland development during pregnancy, demonstrating a key role for the RANKL pathway in epithelial biology.^{31–33} These data support the idea that RANKL, in addition to supporting osteoclastogenesis, may directly influence carcinogenesis and metastatic progression. High levels of RANKL or RANK mRNA expression were associated with considerably lower disease-free survival and bone metastasis free survival.³⁴ Denosumab suppresses RANKL, thereby decreasing osteoclast-mediated bone deterioration, and is useful in the treatment of bone metastases.³⁵ Furthermore, denosumab has been shown to be superior to the previous standard of therapy, zoledronic acid, in avoiding or delaying skeletal consequences in patients with advanced cancer and bone metastases.³⁶ Denosumab extends lifespans without bone metastases and delays the time to develop bone metastases in men with non-metastatic castration-resistant prostate cancer compared to placebo.³⁷ Finally, denosumab has the potential to improve survival in cancer patients with OVs.

Regarding anabolic drugs (e.g. teriparatide), an alleged increase in the risk of osteosarcoma is the most concerning adverse effect. However, the incidence of osteosarcoma in patients using teriparatide around the world is low, and it does not exceed the incidence of osteosarcoma in the

general population.³⁸ Because the proportion of patients who received anabolic drugs in this study was low, analysis of the effects of these drugs on survival was limited.

Limitations and strengths

The lack of baseline data regarding factors affecting the prescription of certain treatments is a significant limitation of this study. Variables such as bone mineral density, comorbidities, socioeconomic status and lifestyle factors may influence the likelihood of death and OV as well as the likelihood of prescribing and complying with anti-osteoporosis medications. However, because all subjects had a minimum T-score ≤ -2.5 , the effects of the lack of BMD data were minimised. Additionally, because the study grouped all types of osteoporosis treatments together, the effects of individual drugs were unable to be determined separately. However, the finding in support of the efficacy of osteoporosis treatments in general should increase clinicians' confidence to switch between various treatment regimens when necessary. Finally, because there was no accurate data on drug discontinuation, the lower risk of death found in the osteoporosis treatment groups cannot be definitively linked to the drugs themselves. Data regarding treatment durability and adherence would be useful to better clarify the utility of the drugs.

Real-world studies examining the effects of certain treatments using large databases offer results that directly reflect the general population and utilise real complete mortality data. Randomised clinical trials do not offer the same level of external validity that is offered by this study, which can only come from the use of such a large data source.

CONCLUSION

According to this national database population research, the prescription of anti-osteoporosis drugs following OVs is associated with a significant reduction in cancer patients' all-cause mortality. Anti-osteoporosis therapy should be initiated in the elderly with cancer who have osteoporotic fractures.

Data availability statement

Data about this study are included in the manuscript and supplementary information. All datasets are freely available upon request to the corresponding authors.

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