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ORIGINAL ARTICLE

The mortality and direct medical costs of osteoporotic fractures among postmenopausal women in Taiwan

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Abstract
Summary This study estimated the fracture-related mortality and direct medical costs among postmenopausal women in Taiwan by fracture types and age groups by utilizing a nationwide population-based database. Results demonstrated that hip fractures constituted the most severe and expensive complication of osteoporosis across fracture sites.
Introduction The aims of the study were to evaluate the risk of death and direct medical costs associated with osteoporotic fractures by fracture types and age groups among postmenopausal women in Taiwan.
Methods This nationwide, population-based study was based on data from the National Health Insurance Research Database in Taiwan. Female patients aged 50 years and older in the fracture case cohort were matched in 1:1 ratio with randomly selected subjects in the reference control cohort by age, income-related insurance amount, urbanization level, and the Charlson comorbidity index. There were two main outcome measures of the study: age-differentiated mortality and direct medical costs in the first and subsequent years after osteoporotic fracture events among postmenopausal women. The bootstrap method by resampling with replacement was conducted to generate descriptive statistics of mortality and direct medical costs of the case and control cohorts. Student's *t* tests were then performed to compare mortality and costs between the two cohorts.
Results A total of 155,466 postmenopausal women in the database met the inclusion criteria for the fracture case cohort, including 22,791 hip fractures, 72,292 vertebral fractures, 15,621 upper end humerus (closed) fractures, 36,774 wrist fractures, and 7,988 multiple fractures. Analytical results demonstrated that patients experiencing osteoporotic fractures were at considerable excess risk of death and incurred substantially higher treatment costs, notably for hip fractures. Furthermore, results also revealed that the risk of mortality increased with advancing age across the spectrum of fracture sites.
Conclusions The present study confirmed an excess mortality and higher direct medical costs associated with osteoporotic fractures. Moreover, hip fractures constituted the most severe and expensive complication of osteoporosis among fracture types.

Keywords Bootstrap methods · Direct medical costs · Mortality · National health insurance · Osteoporotic fractures · Postmenopausal women

Introduction

Osteoporosis, a common bone disease in which the bones progressively become fragile, leads to nearly 9 million fractures annually worldwide, including hip, forearm, spine, humerus, and other fractures [1]. Approximately 40–50 % of women and 13–22 % of men are at risk of suffering from an osteoporosis-related fracture in their lifespan [2]. Osteoporosis-related fractures can cause severe pain, psychosocial impairment, diminished quality of life, and even decreased life expectancy [3, 4]. The association linking osteoporotic fractures and mortality has been evaluated by several

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groups [5, 6]. There are a number of studies that have shown a higher mortality in patients with hip fractures than the general population [7–10]. After hip fractures, excess mortality is more pronounced in patients with vertebral fractures [5, 11].

In addition, the financial strain of osteoporotic fractures upon patients and the health care system would be substantial [1, 12–14]. On personal level, it was estimated that patients with osteoporotic fractures incurred closely $US10,000 in additional direct health care costs during the 6 months after the fracture, compared to nonfracture patients [15]. As for the economic burden on the health care system, in the USA, direct medical costs of osteoporosis were estimated to be between $13.7 billion and $20.3 billion in 2005, and related expenditures are projected to reach $25.3 billion per year by 2025 [16].

Although the burden of osteoporotic fractures related to health care costs as well as the associated mortality have been evaluated, many previous studies have had limitations that may impact the generalizability of their results, including small sample sizes [5, 17], the assessment of only one site of fracture [8, 17, 18], and the nonrandom selection of subjects [5, 6, 8, 17, 18]. In addition, mortality following osteoporotic fractures is less well appreciated in Asian countries. Previous research had demonstrated that health care costs were highly sensitive to the health care environment, and thus, related analyses generally were country-specific [19]. In Taiwan, according to the Nutrition and Health Survey in Taiwan (NAHSIT 2004–2008), the prevalence of femoral neck osteoporosis in persons aged 50 years or older was 10.7 % for men and 12.1 % for women. The prevalence would increase to 22.6 and 41.2 %, respectively, when osteoporosis was defined as detected in one of the following sites: femoral neck, lumbar spine, and forearm [20]. Stated differently, the prevalence of osteoporotic fractures in Taiwan is similar to that of other developed countries.

Osteoporotic fractures represent a substantial cause of mortality and morbidity particularly for postmenopausal women and the elderly since they may greatly imperil the quality of life and survival of the target population. As Bessette and colleagues [21] argued, comparisons of the burden of osteoporotic fractures among countries with differing health care and administrative structures were fraught with challenge, and thus, the regional medical cost data pertaining to the treatment of osteoporotic fractures were warranted. Furthermore, mortality following osteoporotic fractures is less well appreciated in Asian countries. Therefore, this population-based cohort study set out to estimate the fracture-related mortality and direct medical costs during the first and subsequent years following osteoporotic fractures among postmenopausal women in Taiwan by fracture sites and age groups.

Methods

Data sources

This nationwide retrospective cohort study was based on data from the National Health Insurance Research Database (NHIRD) in Taiwan. Taiwan launched a mandatory-enrollment, single-payer National Health Insurance (NHI) program on March 1, 1995. There are currently more than 25 million enrollees in the program, representing 99 % of the entire population of Taiwan [22]. The NHIRD contains registration files of contracted medical facilities and board-certified physicians, and original claim data for reimbursement for all enrollees, including details of inpatient and ambulatory care orders, dental visits, medical expenditures, prescriptions, laboratory and imaging examinations, and up to five discharge diagnoses or three outpatient visit diagnoses [22]. In the database, the diagnostic codes are in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The NHIRD is perhaps one of the largest and most comprehensive administrative health care databases in the world [23]. The accuracy of diagnosis of major diseases in the NHIRD, such as ischemic stroke, has been validated [23–25].

The privacy and confidentiality of all beneficiaries of NHI are safeguarded by the National Health Research Institute (NHRI) of Taiwan. Data in the NHIRD that could be used to identify patients or care providers, including medical institutions and physicians, are scrambled cryptographically and then released in electronic format to the public annually for research purposes. Since the study utilized de-identified secondary data, it was exempt from full review by the Taipei Medical University Hospital Institutional Review Board.

Study samples

Considering osteoporotic fractures affect mostly postmenopausal women, the study population was thus defined as postmenopausal women in Taiwan. Female patients aged 50 years and older whose medical records within the NHIRD contained the primary or secondary diagnosis of hip fracture (ICD-9-CM codes, 820.0, 820.2, and 820.8), vertebral fracture (805.2, 805.4, 805.6, 805.8, 806.2, and 806.4), upper end humerus (closed) fracture (812.0), wrist fracture (813.4), or multiple fractures in the period from January 1, 2006 to December 31, 2009 were identified as the fracture case cohort. To minimize the likelihood that a normal follow-up physician visit for a previous osteoporotic fracture was selected as a new incident fracture, subjects with any type of fracture history before the index dates were excluded. Figure 1 illustrated the case selection process.

For comparisons of the mortality and direct medical costs of postmenopausal women with osteoporotic fractures and

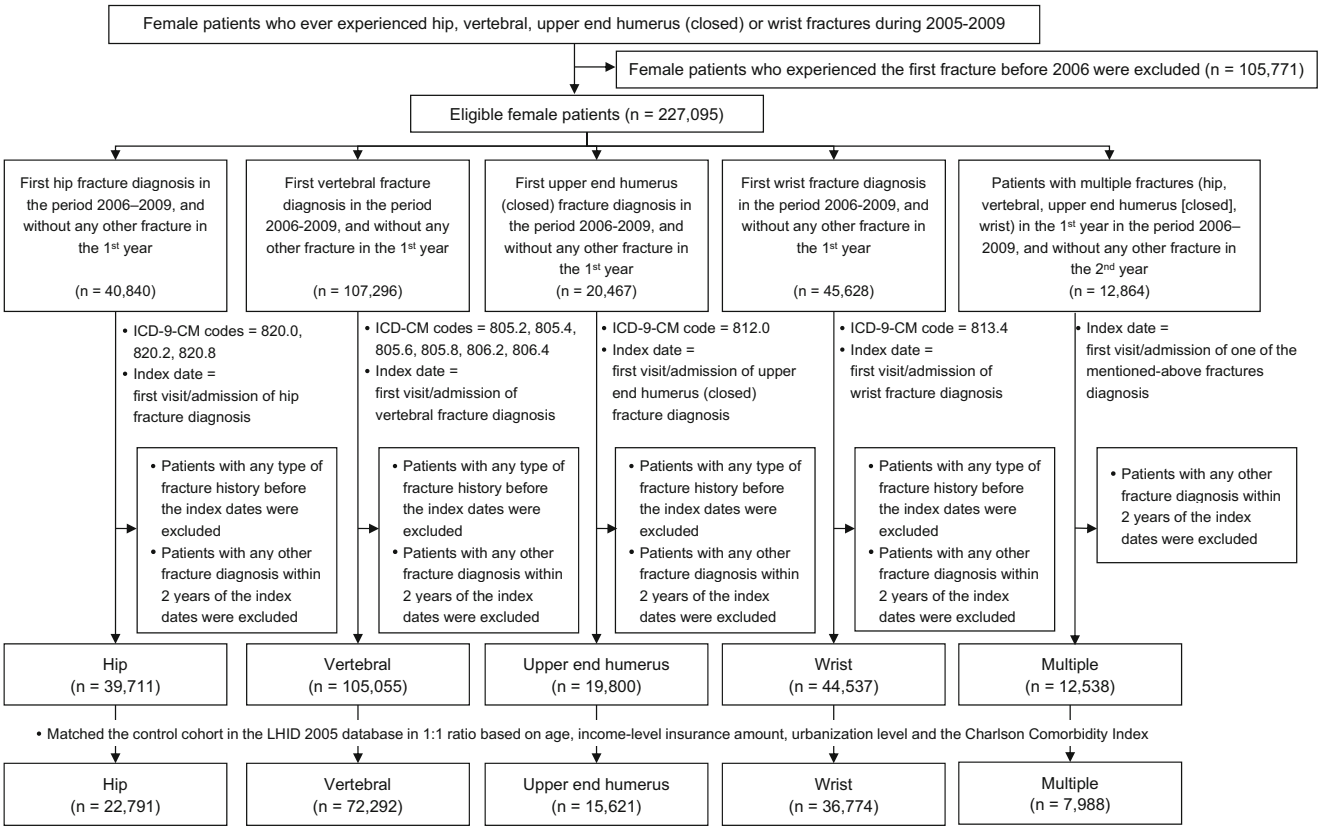

Fig. 1 Flow diagram of patient selection process

those of the general population, a reference control cohort was drawn from a subset of the NHIRD, the Longitudinal Health Insurance Database of 2005 (LHID 2005). The LHID 2005 database contains the entire original claim data of one million beneficiaries (representing about 5 % of the Taiwanese population), randomly sampled from the 2005 Registry for Beneficiaries of the NHIRD. The sampling file was then merged with the insurance claim files that traced back all the reimbursement data files for these matching beneficiaries in each year and followed their medical utilizations in subsequent years. The database contained information about 495,816 men (49.5 %) and 504,184 women (50.4 %). There were no significant differences in the age and gender distributions between patients in the LHID 2005 database and those in the original NHIRD [22].

To maximize the comparability of the case and control cohorts on baseline characteristics, subjects in the reference control cohort were randomly selected and matched in 1:1 ratio with those in the fracture case cohort based on priori matching criteria of age, income-related insurance amount, urbanization level and the Charlson comorbidity index (CCI) [26].

Main outcome measures

There were two main outcome measures of the study: age-differentiated mortality and direct medical costs in the first and following years after osteoporotic fracture events of hip, vertebral, upper end humerus (closed), wrist, and multiple fractures among postmenopausal women in Taiwan. Direct medical costs of fracture treatments were calculated and analyzed from the payer's perspective for osteoporotic fracture cases of the study cohort, and represented the sum of direct medical costs relating to outpatient care, inpatient stays, and emergency department visits of subjects after the index fractures. Differences in direct medical costs between the osteoporotic fracture cases and controls were regarded as attributable to osteoporotic fracture events. Medical cost data were collected and analyzed through the first year as well as the second and following years from the incident fracture date since complications from fractures regularly occur into the second year post-fracture. The estimated annual costs by age groups were inflation-normalized to 2009 New Taiwan dollar (NT$) as to represent the annual direct medical costs associated with these fractures, in comparison of the annual costs of the reference control cohort (the average exchange rate in 2009 was US$1.00=NT$32.23).

Statistical analyses

For the descriptive results of baseline characteristics of the case and control cohorts, categorical variables were expressed using frequencies and percentages, whereas continuous

variables were reported using means and standard deviations. Furthermore, considering the distributions of medical cost data tend to be truncated and highly skewed to the right with large coefficients of variation, the non-parametric bootstrapping method by resampling with replacement was performed to generate more accurate arithmetic mean costs and other descriptive statistics for both case and control cohorts [27, 28]. The bootstrapping procedure produced 1,000 bootstrap samples with replacement of subjects within each stratum. Finally, Student's *t* tests were conducted to assess the differences of mortality and direct medical costs between case and control cohorts.

Statistical significance was set at $p<0.05$ (two-tailed). All analyses were performed using the SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the case and control cohorts

A total of 155,466 postmenopausal women in the database met the inclusion criteria for the osteoporotic fracture case cohort, including 22,791 hip fractures, 72,292 vertebral fractures, 15,621 upper end humerus (closed) fractures, 36,774 wrist fractures, and 7,988 multiple fractures. In other words, vertebral fractures were more prevalent than other fracture types in the case cohort. Table 1 lists baseline characteristics of the case and control cohorts under study. Age seemed to be associated with the likelihood of having osteoporotic fractures. Older women were more likely to have hip fractures except the very old (aged 90 years and older). The tendency is mostly the same as that of vertebral fracture except two age groups (80–89, 90, and older). On the contrary, age was negatively associated with the likelihood of having upper end humerus (closed) or wrist fractures. With respect to comorbid conditions of the population under study, most patients had a CCI score of 0.

Mortality

Table 2 shows the results of age-group specific mortality of the first and subsequent years after osteoporotic fractures. Generally speaking, female patients experiencing osteoporotic fractures were at considerable excess risk of death, compared with the non-fracture control cohort for all age groups, except wrist fractures (all p values <0.001). Overall, the highest relative risk of death was associated with hip fractures. Furthermore, results also demonstrated that the risk of mortality increased with advancing age across the spectrum of fracture sites.

Figure 2 depicted mortality of the first and subsequent years after fracture events across fracture sites. Correspondingly to the results of Table 2, compared with the matched non-fracture control cohort, higher mortality rates were observed in the case cohort for all fracture types, except wrist fractures. Furthermore, among all fracture types, excess mortality was more pronounced in patients with hip fracture in both the first and subsequent years for the most part. In the first year, after hip fractures, upper end humerus (closed) fractures produced the second-leading mortality rates. Nonetheless, comparative results of mortalities among fracture types were not so discernible in subsequent years.

Direct medical costs

Direct medical costs by cohorts and fracture sites are illustrated in Table 3. As expected, patients with osteoporotic fractures incurred comparatively larger direct medical costs in both the first and subsequent years than their counterparts for all fracture sites (all p values <0.001). Take hip fractures. Direct medical costs during the first year following hip fractures were more than two times higher for cases than their matched controls in all age groups. In addition, direct medical costs of the first years were larger than those of subsequent years for all fracture types. Lastly, hip fractures were associated with substantially higher direct medical costs and incremental costs than other types of fractures for all age groups in the first year and subsequent years for the most part, followed by multiple fractures.

Figure 3 illustrated direct medical costs of the first and subsequent years after fracture events among fracture types. Similar to the results of Table 3, Fig. 3 decisively demonstrated that patients with osteoporotic fractures incurred substantial higher direct medical costs than their counterparts across all fracture sites in both the first and subsequent years, except the very old group (≥90) of wrist fractures in subsequent years. Moreover, among all fracture types, hip fractures constituted the most expensive complication of osteoporosis for all age groups, followed by multiple fractures. The comparative results were especially noticeable in the first year.

Discussion

Osteoporotic fractures have garnered substantial attention from researchers of relevant fields as they are known to generate a profound burden of morbidity and medical costs. With the aging of the population in Taiwan and other developed countries, the mortality and medical costs of osteoporotic fractures are increasingly significant public health concerns and require further elucidation. The relevance of this study's finding can be appreciated within such a context. Even though there are numerous studies conducted to evaluate the mortality and economic burden of osteoporotic fractures, the majority of them focus on hip and vertebral fractures, while existed data

Table 1 Baseline characteristics of the study and comparison cohorts

	Hip fracture					Vertebral fracture					Upper end humerus (closed)					Wrist fracture					Multiple fractures				
	Case cohort		Control cohort		*p*	Case cohort		Control cohort		*p*	Case cohort		Control cohort		*p*	Case cohort		Control cohort		*p*	Case cohort		Control cohort		*p*
	(*n*=22,791)		(*n*=22,791)			(*n*=72,292)		(*n*=72,292)			(*n*=15,621)		(*n*=15,621)			(*n*=36,774)		(*n*=36,774)			(*n*=7,988)		(*n*=7,988)		
	n	%	*n*	%		*n*	%	*n*	%		*n*	%	*N*	%		*n*	%	*n*	%		*n*	%	*n*	%	
Age					0.999					0.518					0.981					0.963					0.986
50–59	2,829	12.41	2,825	12.40		17,055	23.59	17,045	23.58		6,066	38.83	6,081	38.93		15,455	42.03	15,455	42.03		1,586	19.85	1,597	19.99	
60–69	4,484	19.67	4,506	19.77		22,521	31.15	22,782	31.51		5,058	32.38	5,077	32.5		13,119	35.67	13,189	35.87		2,000	25.04	2,020	25.29	
70–79	7,651	33.57	7,657	33.60		22,386	30.97	22,120	30.60		3,231	20.68	3,187	20.4		6,304	17.14	6,232	16.95		2,600	32.55	2,589	32.41	
80–89	6,552	28.75	6,526	28.63		9,383	12.98	9,412	13.02		1,131	7.24	1,142	7.31		1,731	4.71	1,734	4.72		1,567	19.62	1,544	19.33	
≥90	1,275	5.59	1,277	5.60		947	1.31	933	1.29		135	0.86	134	0.86		165	0.45	164	0.45		235	2.94	238	2.98	
Income-related insurance amount[a]					1.000					1.000					1.000					1.000					1.000
Fixed	18,466	81.02	18,466	81.02		46,568	64.42	46,568	64.42		9,269	59.34	9,269	59.34		20,047	54.51	20,047	54.51		5,717	71.57	5,717	71.57	
≤22,800	305	1.34	305	1.34		1,590	2.20	1,590	2.20		546	350	546	350		1,290	3.51	1,290	3.51		167	2.09	167	2.09	
22,801–36,300	142	0.62	142	0.62		1,004	1.39	1,004	1.39		345	2.21	345	2.21		898	2.44	898	2.44		87	1.09	87	1.09	
36,301–57,800	61	0.27	61	0.27		383	0.53	383	0.53		142	0.91	142	0.91		359	0.98	359	0.98		32	0.40	32	0.40	
≥57,801	3,817	16.75	3,817	16.75		22,747	31.47	22,747	31.47		5,319	34.05	5,319	34.05		14,180	38.56	14,180	38.56		1,985	24.85	1,985	24.85	
Urbanization level					1.000					1.000					1.000					1.000					1.000
1 (high)	9,082	39.85	9,082	39.85		26,025	36.00	26,025	36.00		5,923	37.92	5,923	37.92		13,023	35.41	13,023	35.41		2,922	36.58	2,922	36.58	
2	7,120	31.24	7,120	31.24		22,970	31.77	22,970	31.77		5,058	32.38	5,058	32.38		11,885	32.32	11,885	32.32		2,566	32.12	2,566	32.12	
3	2,822	12.38	2,822	12.38		9,092	12.58	9,092	12.58		1,982	12.69	1,982	12.69		4,578	12.45	4,578	12.45		1,076	13.47	1,076	13.47	
4 (low)	3,767	16.58	3,767	16.58		14,205	19.65	14,205	19.65		2,658	17.02	2,658	17.02		7,288	19.82	7,288	19.82		1,424	17.83	1,424	17.83	
Charlson comorbidity index					1.000					1.000					1.000					1.000					1.000
0	14,623	64.16	14,623	64.16		64,362	89.03	64,362	89.03		13,601	87.07	13,601	87.07		33,810	91.94	33,810	91.94		6,389	79.98	6,389	79.98	
1–2	6,652	29.19	6,652	29.19		6,367	8.81	6,367	8.81		1,685	10.79	1,685	10.79		2,658	7.23	2,658	7.23		1,333	16.69	1,333	16.69	
3–5	1,218	5.34	1,218	5.34		1,193	1.65	1,193	1.65		255	1.63	255	1.63		236	0.64	236	0.64		231	2.89	231	2.89	
≧ 6	298	1.31	298	1.31		370	0.51	370	0.51		80	0.51	80	0.51		70	0.19	70	0.19		35	0.44	35	0.44	
Hospitalization					<0.001					<0.001					<0.001					<0.001					<0.001
	20,164	88.47	7,497	32.89		31,331	43.34	15,854	21.93		8,157	52.22	3,029	19.39		21,801	59.28	6,297	17.12		6,418	80.35	2,208	27.64	

[a] The data are in New Taiwan Dollar (NT$). The average exchange rate in 2009 was US$1.00=NT$32.23

[b] Chi-square tests were used to examine the differences between case and control cohorts

Table 2 Age-group specific mortality of the first and subsequent years after fractures

	Hip fracture				Vertebral fracture				Upper end humerus (closed)			
	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*
1st Year												
Age												
50–59	0.041 [0.0042]	0.010 [0.0020]	0.031 0.0045]	***	0.012 [0.0009]	0.005 [0.0006]	0.007 [0.0010]	***	0.008 [0.0013]	0.006 [0.0011]	0.002 [0.0016]	
60–69	0.062 [0.0040]	0.025 [0.0026]	0.037 [0.0047]	***	0.020 [0.0010]	0.009 [0.0007]	0.011 [0.0012]	***	0.022 [0.0022]	0.015 [0.0019]	0.007 [0.0028]	
70–79	0.108 [0.0041]	0.069 [0.0032]	0.039 [0.0051]	***	0.044 [0.0015]	0.035 [0.0014]	0.009 [0.0019]	***	0.056 [0.0046]	0.034 [0.0035]	0.022 [0.0057]	
80–89	0.167 [0.0056]	0.114 [0.0045]	0.053 [0.0074]	***	0.086 [0.0033]	0.073 [0.0030]	0.013 [0.0043]	***	0.116 [0.0111]	0.090 [0.0102]	0.026 [0.0147]	
≧90	0.279 [0.0170]	0.186 [0.0130]	0.093 [0.0209]	***	0.185 [0.0152]	0.161 [0.0141]	0.024 [0.0207]	***	0.242 [0.0525]	0.151 [0.0372]	0.091 [0.0651]	
Subsequent Years												
Age												
50–59	0.022 [0.0026]	0.007 [0.0014]	0.015 [0.0029]	***	0.009 [0.0007]	0.005 [0.0005]	0.004 [0.0009]	***	0.008 [0.0011]	0.005 [0.0009]	0.003 [0.0015]	
60–69	0.040 [0.0028]	0.025 [0.0022]	0.015 [0.0035]	***	0.019 [0.0009]	0.010 [0.0006]	0.009 [0.0011]	***	0.015 [0.0017]	0.010 [0.0014]	0.005 [0.0023]	
70–79	0.081 [0.0035]	0.048 [0.0026]	0.033 [0.0043]	***	0.042 [0.0013]	0.033 [0.0012]	0.009 [0.0018]	***	0.052 [0.0041]	0.038 [0.0035]	0.014 [0.0053]	
80–89	0.136 [0.0050]	0.099 [0.0040]	0.037 [0.0065]	***	0.086 [0.0032]	0.086 [0.0031]	0.0001 [0.0046]	***	0.105 [0.0103]	0.077 [0.0082]	0.028 [0.0137]	
≧90	0.235 [0.0160]	0.210 [0.0145]	0.025 [0.0220]	***	0.178 [0.0156]	0.155 [0.0135]	0.023 [0.0204]	***	0.259 [0.0567]	0.125 [0.0360]	0.134 [0.0652]	

	Wrist fracture				Multiple fractures			
	p	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*
1st Year									
Age									
50–59	***	0.004 [0.0006]	0.004 [0.0005]	0.0001 [0.0007]	***	0.008 [0.0024]	0.006 [0.0020]	0.002 [0.0032]	***
60–69	***	0.006 [0.0007]	0.008 [0.0009]	−0.002 [0.0012]	***	0.021 [0.0034]	0.011 [0.0023]	0.010 [0.0042]	***
70–79	***	0.020 [0.0019]	0.033 [0.0025]	−0.013 [0.0031]	***	0.049 [0.0044]	0.040 [0.0041]	0.009 [0.0059]	***
80–89	***	0.060 [0.0064]	0.076 [0.0073]	−0.016 [0.0094]	***	0.089 [0.0081]	0.090 [0.0084]	−0.001 [0.0116]	***
≧90	***	0.215 [0.0427]	0.117 [0.0311]	0.098 [0.0509]	***	0.173 [0.0278]	0.146 [0.0269]	0.027 [0.0380]	***
Subsequent Years									
Age									
50–59	***	0.004 [0.0005]	0.003 [0.0005]	0.001 [0.0007]	***	0.015 [0.0029]	0.006 [0.0018]	0.009 [0.0034]	***
60–69	***	0.010 [0.0008]	0.007 [0.0007]	0.003 [0.0011]	***	0.025 [0.0033]	0.012 [0.0022]	0.013 [0.0039]	***
70–79	***	0.027 [0.0020]	0.035 [0.0024]	−0.008 [0.0032]	***	0.068 [0.0048]	0.043 [0.0039]	0.025 [0.0062]	***
80–89	***	0.076 [0.0071]	0.081 [0.0072]	−0.005 [0.0102]	***	0.121 [0.0085]	0.085 [0.0072]	0.036 [0.0109]	***
≧90	***	0.172 [0.0409]	0.164 [0.0399]	0.008 [0.0584]	***	0.348 [0.0411]	0.149 [0.0291]	0.169 [0.0504]	***

[a] *t* tests were used to examine the differences between case and control cohorts

***$p<0.001$

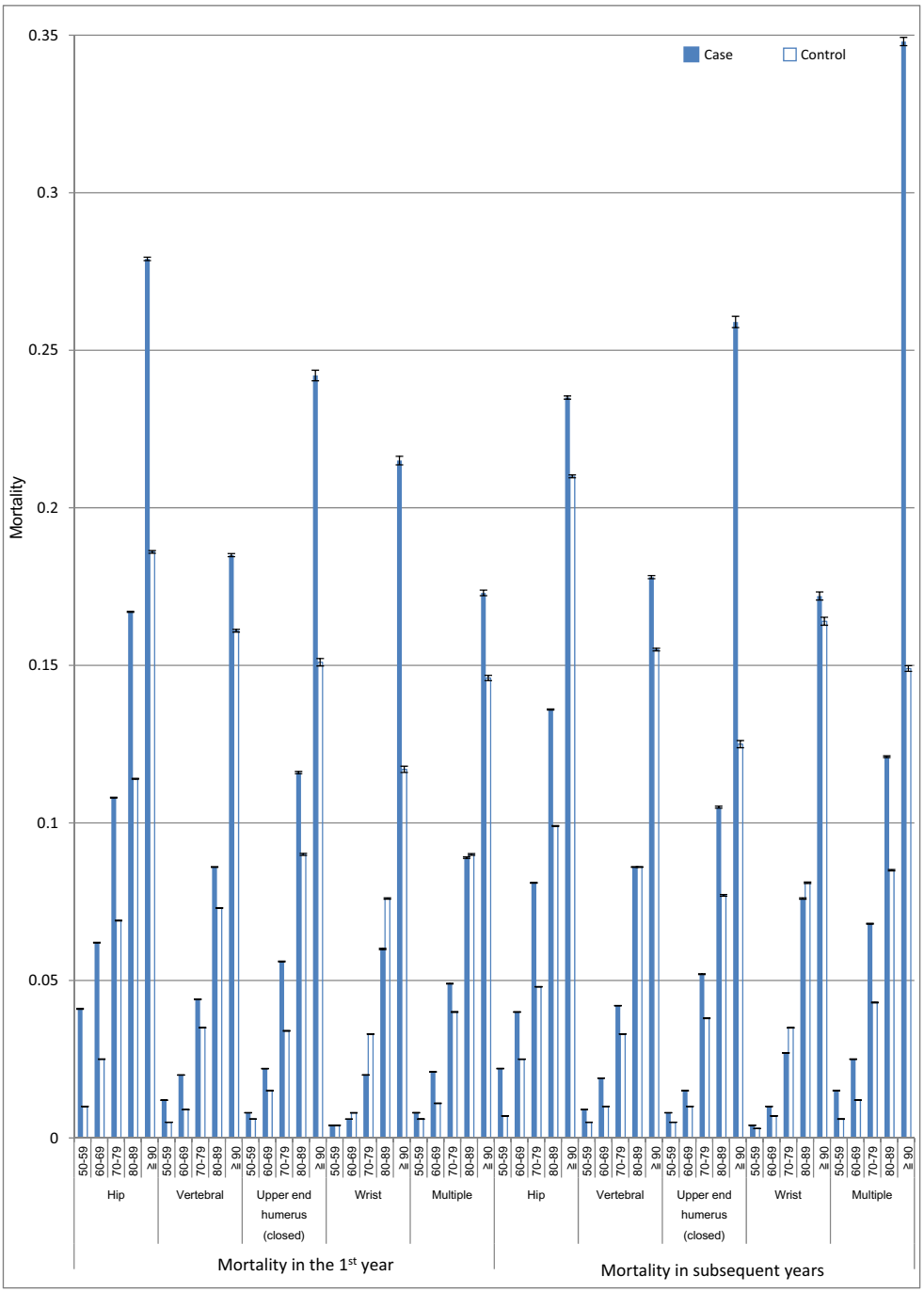

Fig. 2 Age-group specific mortality of the first and subsequent years

regarding non-hip and non-vertebral fractures are still limited [5, 6, 12, 14]. In addition, many previous studies have had limitations that may impact the generalizability of their results, such as using regional samples. Moreover, fracture-related mortality and medical costs remain under-recognized in many countries. Hence, this nationwide, population-based study contributes to better elucidating fracture-related mortality and direct medical costs among postmenopausal women .

Overall, this study provides evidence that the impacts of osteoporotic fractures on treatment costs and survival vary with the sites of fractures. The literature suggests that across different sites of osteoporotic fractures, hip fractures are associated with excess mortality and the greatest healthcare costs [3–5, 7, 9–14]. For example, Grønskag et al. [29] reported that elderly women who experienced hip fracture had higher mortality than the general population. The study has validated an excess mortality associated with osteoporotic fractures, compared with the matched non-fracture control cohort. Specifically, analytical results of the study demonstrated that hip fractures constituted the most severe and expensive

Table 3 Direct medical costs of the first and subsequent years after fractures in different age groups

	Hip fracture				Vertebral fracture				Upper end humerus (closed)			
	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	*p*	Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	
1st Year												
Age												
50–59	4,450 [124.67]	1,454 [89.69]	2,996 [144.60]	***	2,032 [33.61]	844 [20.67]	1,188 [37.68]	***	2,086 [39.27]	893 [38.39]	1,193 [52.38]	
60–69	5,833 [117.97]	2,256 [76.90]	3,577 [131.24]	***	2,682 [31.50]	1,299 [22.38]	1,383 [36.67]	***	2,945 [70.59]	1,451 [54.78]	1,494 [83.18]	
70–79	6,621 [98.58]	2,981 [76.31]	3,640 [116.30]	***	3,327 [37.75]	1,974 [30.68]	1,353 [46.28]	***	3,642 [108.72]	2,116 [90.96]	1,526 [135.93]	
80–89	6,303 [106.50]	2,596 [65.10]	3,707 [122.61]	***	3,621 [64.34]	2,066 [48.94]	1,555 [80.14]	***	4,235 [237.91]	2,240 [125.59]	1,995 [263.98]	
≧90	5,673 [232.70]	2,358 [171.65]	3,315 [286.18]	***	3,307 [192.98]	2,165 [162.26]	1,142 [258.94]	***	3,636 [662.05]	2,024 [296.43]	1,612 [714.11]	
Subsequent Years												
Age												
50–59	2,209 [115.35]	1,066 [68.07]	1,143 [131.84]	***	1,376 [31.55]	849 [23.20]	527 [38.40]	***	1,232 [45.43]	860 [40.14]	372 [59.91]	
60–69	2,975 [105.97]	2,071 [86.21]	904 [134.36]	***	1,992 [30.03]	1,313 [25.68]	679 [39.25]	***	2,016 [79.53]	1,450 [63.66]	566 [100.01]	
70–79	3,529 [94.47]	2,684 [76.11]	845 [122.23]	***	2,510 [36.95]	1,983 [33.55]	527 [47.91]	***	2,721 [130.45]	2,266 [109.65]	455 [165.89]	
80–89	3,624 [115.61]	2,376 [70.50]	1,248 [133.89]	***	2,988 [79.11]	2,091 [53.08]	897 [96.94]	***	3,127 [273.47]	2,065 [141.99]	1,062 [309.79]	
≧90	3,112 [241.35]	2,773 [211.30]	339 [326.22]	***	2,912 [257.34]	2,659 [233.70]	253 [351.37]	***	4,595 [1,251.89]	2,608 [653.86]	1,987 [1,055.74]	

	p	Wrist fracture			*p*	Multiple fractures			*p*
		Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]		Case cohort Mean [SD]	Control cohort Mean [SD]	Incremental Mean [SD]	
1st Year									
Age									
50–59	***	1,748 [21.93]	810 [21.41]	938 [29.40]	***	3,209 [118.65]	823 [62.61]	2,386 [124.07]	***
60–69	***	2,053 [28.43]	1,186 [26.67]	867 [37.27]	***	4,210 [124.37]	1,457 [82.25]	2,753 [138.61]	***
70–79	***	2,529 [47.18]	1,886 [55.73]	643 [66.80]	***	5,693 [125.30]	2,323 [107.01]	3,370 [153.66]	***
80–89	***	2,886 [118.52]	1,999 [109.90]	887 [150.73]	***	5,454 [176.29]	2,087 [120.25]	3,367 [205.60]	***
≧90	***	2,397 [289.10]	1,751 [310.10]	646 [356.85]	***	5,108 [450.20]	1,687 [270.56]	3,421 [505.20]	***
Subsequent Years									
Age									
50–59	***	902 [23.29]	806 [23.57]	96 [33.24]	***	1,504 [116.15]	761 [55.92]	743 [131.00]	***
60–69	***	1,318 [31.48]	1,217 [29.75]	101 [42.96]	***	2,336 [123.70]	1,463 [100.72]	873 [160.51]	***
70–79	***	1,886 [59.32]	1,868 [63.54]	18 [88.48]	***	3,518 [150.08]	2,195 [108.67]	1,323 [183.68]	***
80–89	***	2,242 [146.50]	1,849 [105.82]	393 [179.91]	***	3,804 [207.26]	2,128 [131.27]	1,676 [241.02]	***
≧90	***	1,872 [386.51]	2,604 [620.09]	−732 [751.89]	***	3,380 [470.65]	2,962 [519.91]	418 [698.47]	***

[a] The data are in New Taiwan Dollar (NT$). The average exchange rate in 2009 was US$1.00=NT$32.23

[b] *t* tests were used to examine the differences between case and control cohorts

***$p<0.001$

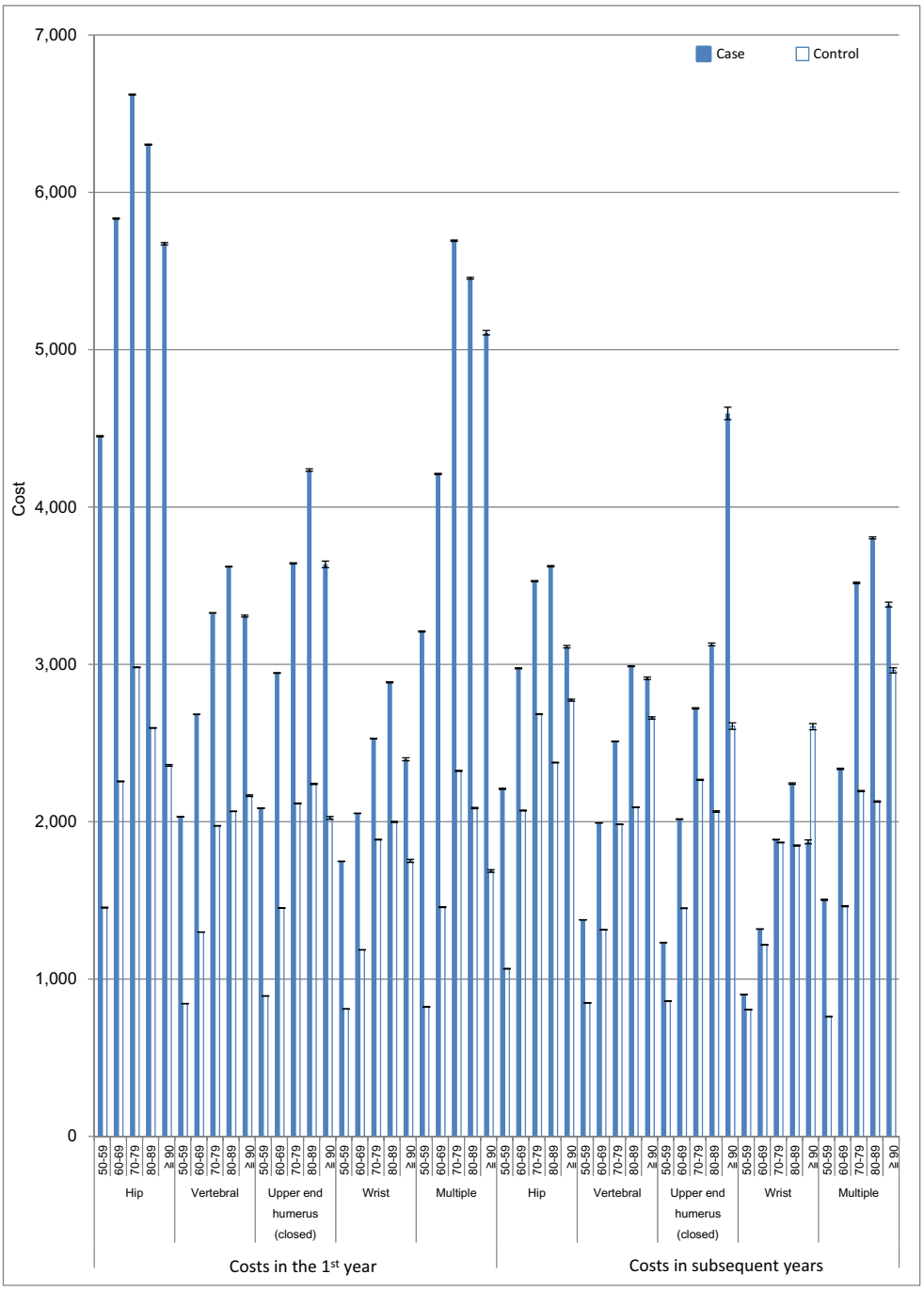

Fig. 3 Age-group specific direct medical costs of the first and subsequent years. Costs data are in New Taiwan Dollar (NT$). The average exchange rate in 2009 was US$1.00=NT$32.23

complication of osteoporosis across fracture sites. These findings corroborate those from previous research [6, 10, 18, 30, 31].

Furthermore, excess mortality associated with osteoporotic fractures could be attributed to advanced age, the acute effects of the injury, comorbidities, postoperative complications, a prior fracture history, poor pre-fracture functional status, and a solitary life [32, 33]. For instance, Maggi and colleagues [34] evaluated the predictors of mortality for hip fracture patients. They demonstrated that six-month mortality was positively associated with increasing age for hip fracture. This study also provided evidence that the risk of mortality increased with advancing age across the spectrum of fracture sites.

However, it should be noted that analytical results of the study indicated that the differences in mortality between the case and control cohorts with respect to wrist fractures were not really large, especially in subsequent years, although they were statistically significant (Table 2). Conventional wisdom holds that in an "over-powered" study (such as the present

study where a large national database was used), group differences which are found to be statistically significant may not translate into clinically meaningful or policy-relevant. In the light, interpretations of analytical results of the study should be taken with caution.

With regard to direct medical costs of osteoporotic fractures, research findings of the present study are largely in line with the literature regarding the economic burden of osteoporotic fractures [12–14, 35]. Overall, there are considerable discussions that osteoporotic fractures impose a substantial financial burden on personal resources and health care system. Previous studies indicated that the economic burden of hip fractures was typically the heaviest across different types of osteoporotic fractures. With a similar study population as in the present study (postmenopausal women aged 50 years and older), Bessette and colleagues [21] reported that direct medical costs of treating hip fractures were the highest ($46,664 Canadian dollar [CAD] per fracture), while treating other fractures also accounted for substantial economic burden ($5,253 to $10,410 CAD per fracture). Moreover, total attributable treatment costs of hip fractures could be conservatively estimated to be $1.65 billion annually. Even for the less expensive patients who had wrist fractures, the aggregate annual healthcare costs were about $85 million.

Along the same lines, Burge et al. [16] assessed the treatment costs of fractures in the USA and concluded that while the incidence of hip fractures was ranked the third (14 %, after vertebrae fractures of 27 % and wrist fractures of 19 %), the treatment costs of hip fractures were highest, accounting for 72 % of the total economic burden. The results are roughly comparable to the present study's findings.

The present study provides a contemporary look at the fracture-related mortality and direct medical costs among postmenopausal women across age-groups. The strengths of the research are numerous. The main strength of the study, while the majority of previous studies assessing the relationships between osteoporotic fractures and mortality as well as healthcare costs have lacked of, is that we used a nationwide, population-based database. In addition, we matched osteoporotic fracture cases with appropriate controls by age, income-related insurance amount, urbanization level and the CCI. Accordingly, the study has the capabilities to reduce confounding errors and thus lead to robust estimates of fracture-related mortality and direct medical costs.

Furthermore, we employed the bootstrapping with replacement subsampling method to generate more accurate arithmetic mean costs and mortality for both case and control cohorts. Using the bootstrapping method has the advantage of generating normally distributed data. Consequently, we could perform a more efficient and powerful Student's *t* test for comparing means in lieu of the Wilcoxon rank-sum test which is often used when data are skewed.

Moreover, thanks to the large sample size in the study, statistical analyses could be performed with more valid results, and it is vital as age is a risk modifier. In addition, the effect of age was taken into account by using age-matched control groups within each of the sub-groups.

Finally, another asset of the study is the relatively homogeneous study population covered by a universal healthcare system. More than 98 % of the population of Taiwan is of Han Chinese ethnicity, thereby minimizing the biases which occur due to the heterogeneity of population subgroups and variations of healthcare access in previous studies conducted in western countries.

While the study benefits from taking advantage of a highly representative dataset, those caveats and limitations inherent in using a national registry database still apply. First of all, diagnosis of a fracture event in the study relies solely on the ICD-9-CM codes, not being further validated using medical chart review, and it may have affected diagnostic accuracy. Relying on relevant diagnosis codes only may give rise to ascertainment bias [15]. Nonetheless, by using computerized Medicare files in regard to diagnoses of fractures, Ray and colleagues [36] yielded a positive predictive value (PPV) of 94 % for all fractures. As for individual fracture sites, PPVs were ranged from 79 % (tibia/fibula) to 98 % (hip). Consequently, they postulated that computerized Medicare claim data could be used for fracture ascertainment. Other researchers have also suggested that the magnitude of under- or over-ascertainment of fracture events by using administrative datasets would be modest [37]. With respect to the validity of data extracted from the NHIRD in the present study, the accuracy of diagnosis of major diseases in the NHIRD has been validated [23–25]. Hence, even though some patients may be misclassified into the fracture or control cohorts, the principal conclusions of the study should still hold.

Yet cautions need to be exercised with respect to vertebral fractures. A critical review of the literature suggests that it is notoriously difficult to reliably identify vertebral fractures, compared to hip fractures, by using administrative claims data [21, 37–39]. It is because vertebral fractures are commonly asymptomatic and do not come to medical attention at the time of their occurrence [37]. Consequently, current diagnostic algorithms for vertebral fractures in administrative data are suboptimal, with limited sensitivity and low PPVs [38, 39].

Secondly, data on anthropometric variables (such as bone mineral density), heavy alcohol use, smoking status, nutritional practices, sedentary lifestyle, family history of hip fracture, and other possible predictors of fracture risk were not available in the NHIRD dataset [40]. Accordingly, this study could only capture clinically diagnosed osteoporotic fractures and might inadvertently exclude patients with sub-clinical fractures that did not reach medical attention. As a result, research findings of the study may have been biased downwards.

Hence, we propose that in the future researchers would recruit subjects with risk factors for fractures but without confirmed osteoporosis so that they could more fully capture the mortality and healthcare costs of osteoporotic fractures by disentangling confounding factors.

Thirdly, study samples of this study were patients who had ambulatory visits to physicians or were admitted to acute hospital wards, not including residents in long-term care institutions. As residents in those facilities are probably frailer, the relationship between fracture sites and patient outcomes should be more notable among them.

Fourthly, the scope of our cost estimate is limited in that we did not estimate indirect costs to patients and society. Further work that evaluates the impacts of osteoporotic fractures on productivity loss and the financial strain on society is also warranted.

Finally, we could not rule out the possibility that results of the study were influenced by surveillance bias, whereby patients with fractures were subjected to increased clinical surveillance, thereby increasing their utilization of health care services in comparison to that for the general population. However, we cannot validate this speculation because of a lack of information in the database.

Despite these limitations, this study contributes to better elucidating fracture-related mortality and direct medical costs among postmenopausal women. In this study we evaluate a large cohort of a younger population of women (≥50 years) with different fracture sites and compared them with a parallel cohort of patients. Our results reveal strong associations between hip and vertebral fractures and patient outcomes in terms of mortality and healthcare costs. Hence, hip and vertebral fractures remain important targets for improved prevention and treatment. These research findings signify potential benefits from interventions aimed at curbing looming osteoporosis-related costs and reducing the likelihood of mortality after fractures.

Lastly, it should be emphasized that among the most important policy concerns relevant to health care is to allocate limited financial, institutional and technical resources across a number of diseases in geriatric populations. Accordingly, characterizing the burden of an illness pertaining to health care resources utilization plays a vital role in optimal management of constrained resources [41]. Moreover, it has been proposed that optimal osteoporosis management may affect the risk of death [42]. Hence, it is imperative to optimize health status preoperatively and prevent postoperative complications in the elderly in the hope of reducing the mortality and costs of osteoporosis-related fractures. Possible management strategies include the use of hip protectors, nutritional supplementation and dietetic assessment, osteoporosis medications, optimal treatment of all major comorbidities, specialist medical assessment, and management of older persons with fractures before and after surgery [32, 43].

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Conflicts of interest None.

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