Cohort Study

Incidence and Mortality of Vertebral Compression Fracture Among All Age Groups: A Nationwide, Population-based Study in the Republic of Korea

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Background: Although several studies have examined the epidemiological features of vertebral compression fractures (VCF) among elderly patients, few studies have reported the epidemiology of VCF among younger individuals.

Objective: To examine trends in the incidence and mortality of VCF in both the old (≥ 65 years) and young (< 65 years) age groups. This study aimed to investigate the incidence and mortality of VCF among all age groups in Korea.

Study Design: Population-based cohort study.

Setting: A nationwide, population-based setting.

Methods: Using the Korean National Health Insurance database, which has complete population coverage, we identified patients diagnosed with VCF between 2005 to 2018. Differences in incidence, survival and mortality were compared across groups using Kaplan-Meier analysis and Cox regression for all age groups and both genders.

Results: We identified a total of 742,993 VCF patients and the annual incidence was 140.09/100,000 individuals. Although the incidence of VCF was significantly higher in the older age compared to younger age group (556.38/100,000 vs. 44.09/100,000 individuals), the mortality rate ratio for VCF patients was higher among younger compared to older individuals (old: 1.59 vs. young: 2.87). In our multivariable-adjusted analysis, the hazard ratio for multiple fractures, traumatic injury and osteoporosis were higher in patients aged < 65 years compared to patients aged ≥ 65 years, suggesting that the impact of these clinical variables on mortality is more significant in the younger age group.

Limitation: A limitation of this study was its lack of information on clinical features, such as disease severity and laboratory data. The precise cause of death of VCF patients could not be confirmed from the study database.

Conclusions: The mortality rate ratio and hazard ratio were significantly higher among younger patients with VCF, indicating the need for further research on VCF in younger age groups.

Key words: Cohort study; hazard ratio; incidence; mortality; mortality rate; mortality rate ratio; population-based cohort study; vertebral compression fracture

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A vertebral compression fracture (VCF) is characterized by the collapse of the vertebral body, leading to deformity and loss of vertebral body height (1). VCFs can significantly affect a patient's quality of life and life expectancy (2,3), as they experience severe pain and disability.

VCFs are directly correlated with increasing age; there are studies suggesting that VCFs are associated with an increased mortality risk in elderly patients (4). In Europe and the United States, the estimated incidence of VCF is about 0.7–1.5 million fractures per year (5,6). Studies have reported that VCF incidence and prevalence increases from 0.9% and 5%-10%, respectively to 1.7% and 30% respectively among middle-aged individuals and those older than 80 years (7,8). Although the incidence and prevalence of VCF tend to vary between age groups, most previous studies have examined VCF only among elderly patients.

Additionally, studies have investigated mortality in VCF only among elderly patients; data for young adults are lacking. According to research on the US Medicare population, the overall 3-year survival rate was only 53.9% among patients aged 65 years and over with a VCF (9); moreover, this rate dropped to 42.3% in patients who did not undergo surgery (10). Therefore, population-based studies are needed to examine the incidence and mortality trends of VCF in both older and younger age groups.

The Korean National Health Insurance (NHI) database includes the entire Republic of Korea (South Korea) population (50 million residents). We used this database to conduct a large-scale, population-based cohort study to assess the incidence and mortality of VCF and to analyze VCF according to age and gender.

Methods

Data Source

This study used data from patients with a VCF from the South Korean NHI database, which contains health claim information from all medical facilities in South Korea. This database includes the following data for each patient: demographics, medical visits, hospitalizations, procedures, and comorbidities based on the Korean Classification of Disease (KCD; modified version of the International Classification of Disease, 10th edition [ICD-10]).

For the analysis of VCF mortality, data were acquired from the Statistics Korea database, as verified by physicians at the time of death. Data were collected for all patients who died, and the number of person-years was calculated for each patient from the start of the study to their time of death.

Study Population (Patient Selection and Comparison Cohort)

Of the 50 million individuals in the South Korean NHI database, we identified 742,993 patients diagnosed with a VCF (VCF group) from inpatient and outpatient claims from January 1, 2005, through December 31, 2018. Patients with a VCF were defined as individuals who had physician visits or hospitalization with a principal diagnosis of KCD-7 code M48.4 (fatigue or stress fracture of the vertebra); M48.5 (collapse of vertebra not elsewhere classified); or S22.0, S22.1, S32.0, or S32.1 (fracture of cervical, thoracic, lumbar, or sacrum/coccyx vertebra, respectively). Patients were excluded if they were diagnosed with a malignant neoplasm, defined by the KCD-7 code M49.5 (metastatic fracture of the vertebra).

A comparison cohort (control group) was selected to evaluate the survival of patients following a VCF with a ratio of 5:1. A total of 3,714,965 controls were selected for the 742,993 patients with a VCF. These frequency-matched case-control groups formed the basis of the survival comparison.

Verification of Diagnoses

To verify the accuracy of the diagnosis, a case definition of VCF was developed using several algorithms based on the number of physician visits with the VCF KCD-7 code (M48.4, M48.5, S22.0, S22.1, S32.0, S32.1). We examined the medical records of all patients with a VCF in the NHI database at a single hospital (according to the previously defined KCD-7 codes). The gold standard for VCF diagnosis was defined as decreased vertebral body height on x-ray images or changes in magnetic resonance imaging signals. Records of suspected non-VCF cases, such as spinal stenosis (KCD-7, M48.0), were reviewed to identify misclassification.

Two experienced, independent physicians examined the medical records of the VCF group to confirm the diagnoses. We also calculated the specificity, sensitivity, and positive and negative predictive values of each algorithm. The case algorithm selected for this study (sensitivity, 95.6%; specificity, 98.8%) had VCF as the principal diagnosis.

Statistical Analysis

The incidence of VCF in South Korea was analyzed from 2005 through 2018. A 3-year washout period (2002–2004) was used to prevent prevalent cases from interfering with the data. An incident case referred to a patient newly diagnosed with a VCF in a given year. Incidence was defined as the number of incident cases in a given year per 100,000 persons, using the resident registration population as of July 1 of that year (https://jumin.mois.go.kr/). We calculated the age- or gender-

specific incidence by dividing the number of cases in a specific age or gender group by the corresponding population of the group.

We analyzed osteoporosis, multiple fracture, and traumatic injury with VCF and stratified 742,993 patients with a VCF according to age. From NHI data, we defined osteoporosis as KCD-7 code M80, M81, multiple fractures as VCF with other fracture (KCF code S00-S99, T02), and traumatic injury as VCF with open wounds, crushes, amputations, and other abrasions (KCD-7 code T00, T01, T03, T04, T05, T06, T07).

The mortality of patients with a VCF and controls was summarized by calculating the total person-years of follow-up, number of deaths, the mortality rate, and the mortality rate ratio, which is defined as the ratio of the mortality rates. We performed a Cox regression analysis to evaluate the effect of osteoporosis, multiple fractures, and traumatic injury on VCF mortality. We also performed a Cox regression analysis to evaluate mortality due to pneumonia, acute myocardial infarction, ischemic stroke, and hemorrhagic stroke among patients with a VCF.

The survival of patients with a VCF was calculated using the Kaplan-Meier method and was compared with the survival of corresponding age- and gender-matched population groups. The Kaplan-Meier survival curves provided a graphical view of the different mortality between patients with a VCF and controls.

To account for the health status of each patient in this comparison, we performed the Charlson Comorbidity Index (CCI) and adjusted confounding factors. The CCI defines 17 comorbidities on the basis of the clinical diagnoses and procedures recorded for each patient, then summarized into an overall index. Rather than adjusting for each individual confounding factor, we adjusted for comorbidities using CCI, which is an aggregate summary of comorbidities. The CCI scores were then categorized as 0,1,2, or ≥ 3.

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Results

Incidence of VCF

A total of 742,993 VCF cases were identified from 2005 through 2018, of which 202,412 were men and 540,581 women (ratio, 1:2.67). The annual VCF incidence was 140.09/100,000 individuals. The incidence of VCF in different age groups and both genders is shown in Table 1.

Overall, VCF incidence increased as age increased. The incidence was significantly higher in patients more than 65 years old compared to those younger than 65 years (556.38/100,000 vs 44.09/100,000 individuals). There was a sharp rise in incidence after the age of 60 years, being 355.27/100,000 in the 60-69 age group increasing to 883.55/100,000 in the 70-79 age group.

The distribution of incidence based on age group showed that although VCF incidence was similar for both genders in those younger than 50 years (men: 24.08/100,000, women: 26.16/100,000 individuals), the VCF incidence in women was higher than that of men in the age group 50 to 65 (men: 77.86/100,000, women: 138.14/100,000 individuals), and it was significantly higher in women older than 65 years (men: 272.18/100,000, women: 792.7/100,000, individuals).

Survival and Mortality

Table 2 outlines the general characteristics of patients with a VCF and their matched controls. Although differ-

Table 1. *Age specific annual incidence of vertebral compression fracture in the Republic of Korea, 2005–2018.*

Age Group (y)	Age-specific Population			Number of Incident Cases			Incidence per 100,000/year		
	Total	Men	Women	Total	Men	Women	Total	Men	Women
20-29	6,088,900	3,167,936	2,920,964	14,868	6,881	7,987	15.26	13.58	17.09
30-39	7,110,588	3,625,526	3,485,032	24,429	12,095	12,334	21.47	20.85	22.12
40-49	7,555,131	3,841,663	3,713,468	44,026	21,992	22,034	36.42	35.78.	37.08
50-59	6,180,623	3,101,462	3,079,162	106,697	38,638	68,059	88.27	62.86	114.55
60-69	3,847,023	1,840,367	2,006,656	218,680	54,367	164,313	355.27	184.63	511.78
70-79	2,364,700	979,640	1,385,060	334,293	68,439	265,854	883.55	436.63	1199.65
Total	33,146,965	16,556,594	16,590,342	742,993	202,412	540,581	140.09	76.41	203.65

Table 2. *Demographic characteristics and Charlson Comorbidity Index of patients with a vertebral compression fracture and controls.*

	Patients with a Vertebral Compression Fracture (n = 742,993)		Controls (n = 3,714,965)		
	No.	%	No.	%	Standard Difference
Overall	742,993	100.00	3,714,965	100.00	
Gender					0.00
Men	202,412	27.24	1,012,060	27.24	
Women	540,581	72.76	2,702,905	72.76	
Age(y)					0.00
20-29	14,868	2.00	74,340	2.00	
30-39	24,429	3.29	122,145	3.29	
40-49	44,026	5.93	220,130	5.93	
50-59	106,697	14.36	533,485	14.36	
60-69	218,680	29.43	1,093,400	29.43	
70-79	334,293	44.99	1,671,465	44.99	
Charlson Comorbidity Index					
0	6,889,989	92.9	3,574,972	96.2	0.15
1	19,281	2.6	40,210	1.1	
2	24,907	3.4	72,986	2.0	
≥ 3	8,816	1.2	24,797	0.7	
Cerebrovascular disease	15,966	2.15	52,071	1.40	0.06
Malignancy	15,157	2.04	48,130	1.30	0.06
Diabetes without chronic complication	15,315	2.06	34,629	0.93	0.09
Chronic pulmonary disease	14,419	1.94	27,360	0.74	0.10
Liver disease	7,711	1.04	11,320	0.30	0.09
Peptic ulcer disease	7,515	1.01	14,578	0.39	0.07
Rheumatic disease	2,275	0.31	2,327	0.06	0.06
Congestive heart failure	4,027	0.54	10,960	0.30	0.04
Gastrointestinal disease	1,172	0.16	1,399	0.04	0.04
Diabetes with chronic complication	5,798	0.78	16,627	0.45	0.04
Congestive heart failure	4,027	0.54	10,960	0.30	0.04
Peripheral vascular disease	1,754	0.24	4,571	0.12	0.03
Renal disease	2,499	0.34	8,947	0.24	0.02
Myocardial infarction	1,583	0.21	5,862	0.16	0.01
Hemiplegia or paraplegia	3,340	0.45	13,955	0.38	0.01
AIDS/HIV	31	0.00	37	0.00	0.01
Dementia	4,036	0.54	19,534	0.53	0.00

ences in comorbidities exist between patients with a VCF and controls, we adjusted for these differences using the CCI. During the study period, 742,993 patients with a VCF accumulated 4,766,719 person-years of follow-up and 3,714,965 controls accumulated a total of 24,649,338 person-years of follow-up. By December 31st, 2018, 123,472 deaths of patients with a VCF were identified, with a death rate of 25.90 deaths/1,000 person-years, while in the control group, there were 435,752 deaths with a death rate of 17.68 deaths/1,000 person-years.

Figure 1 shows the comparison of survival between patients with a VCF and their controls in both genders. Survival was worse for patients with a VCF compared to controls. With respect to age, the survival was higher in patients aged ≥ 65 than those aged < 65 years. With respect to gender, women had higher survival rates than men.

The person-years, the number of deaths, the mortality rate, and the mortality rate ratio are described in detail in Table 3. The mortality rate ratio, defined as the ratio of the mortality rates of patients with a VCF and their matched controls, was 1.46 (95% CI, 1.45 – 1.47). The mortality rate increased with age at the time of fracture, both for patients with a VCF and controls. However, the mortality rate ratio increased when the age at the time of fracture was younger. The mortality rate of patients < 65 years old was 2.87 times that of age-matched controls, while the mortality rate of patients ≥ 65 years old was 1.59 times that of age-matched controls. According to gender, the mortality rate ratio was 1.74 and 1.35 in men and women patients, respectively.

Although persons aged ≥ 65 years had higher mortality rates than those aged < 65 years, the mortality rate ratio of patients compared to controls was higher when patients were younger at the time of the fracture. In addition, pneumonia and

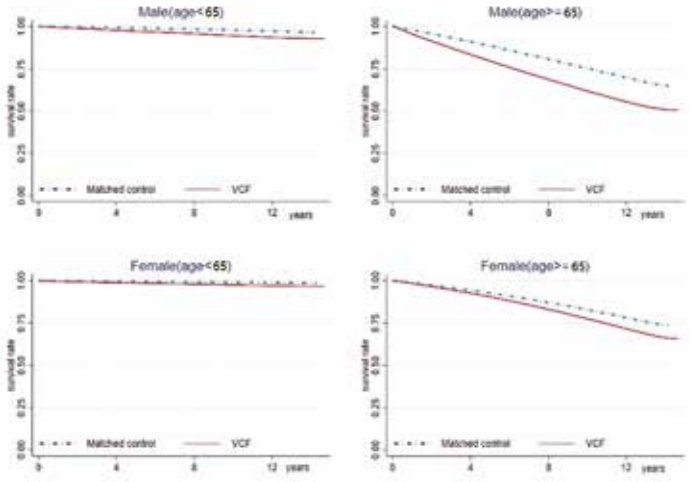

Fig. 1. *Survival curves for different age and gender groups.*
Survival declined as age increased. The survival rate was higher in the age group under 65 than in the age group over 65. Although the survival rate was higher in the age group under 65 than in the age group over 65, the mortality rate ratio was higher in individuals aged less than 65 years compared to those older than 65. The difference in mortality between patients with a vertebral compression fracture and controls was greater in men than women.

Table 3. *Mortality in vertebral compression fracture*

	Patients with vertebral compression fracture				Control				Comparison	
	Person-years	No. of deaths	Mortality Rate	95% CI	Person-years	No. of deaths	Mortality Rate	95% CI	Mortality Rate Ratio	95% CI
Overall	4,766,719.10	123,472	25.90	25.76-26.05	24,649,338.00	435,752	17.68	17.63-17.73	1.46	1.45-1.47
Gender										
Men	1,187,971.50	43,659	36.75	36.41-37.10	6,375,099.10	134,300	21.07	20.96-21.18	1.74	1.72-1.76
Women	3,578,747.60	79,813	22.30	22.15-22.46	18,274,239.00	301,452	16.50	16.44-16.56	1.35	1.34-1.36
Age (y)										
20-29	58,531.89	81	1.38	1.11-1.72	292,656.53	117	0.40	0.33-0.48	3.46	2.57-4.63
30-39	148,609.13	325	2.19	1.96-2.44	747,425.83	497	0.66	0.61-0.73	3.29	2.85-3.79
40-49	251,783.41	1,196	4.75	4.49-5.03	1,275,761.10	2,035	1.60	1.53-1.67	2.98	2.77-3.20
50-59	548,982.32	4,459	8.12	7.89-8.36	2,797,439.20	8,970	3.21	3.14-3.27	2.53	2.44-2.63
60-69	1,111,696.00	14,947	13.46	13.23-13.66	5,699,811.30	38,171	6.70	6.63-6.76	2.01	1.97-2.05
70-79	1,994,600.90	60,617	30.39	30.15-30.63	10,353,257.00	212,871	20.56	20.47-20.65	1.48	1.46-1.49
80-89	652,515.46	41,847	64.13	63.52-64.75	3,482,987.00	173,091	49.70	49.46-49.93	1.29	1.28-1.30

cardiovascular events showed a higher incidence and mortality in patients with a VCF compared to the controls. The mortality hazard ratio (HR) for pneumonia and cardiovascular events—acute myocardial infarction, ischemic stroke, hemorrhagic stroke—following a VCF were higher in patients with a VCF aged < 65 years compared to patients aged ≥ 65 years (Table 4).

Mortality Comparison with Cox Regression Analysis

In our multivariable-adjusted analysis, multiple fractures or traumatic injury had an effect on mortality (HR 1.42, 95% CI, 1.40 - 1.43; 1.45, 95% CI, 1.08 - 1.96, respectively), while osteoporosis did not (HR 0.95, 95% CI, 0.94 - 0.95) (Table 5). According to age, the HRs for multiple fractures, traumatic injury, and osteoporosis were higher in patients aged < 65 years compared to patients aged ≥ 65 years, suggesting that the effect of these clinical variables on mortality was more significant in the younger age group. According to gender, HRs were higher in men compared to women.

Table 4. *Hazard ratio of mortality of pneumonia and cardiovascular event following vertebral compression fracture.*

	Total		Men		Women	
	Hazard Ratio	**95% CI**	**Hazard Ratio**	**95% CI**	**Hazard Ratio**	**95% CI**
Total						
Pneumonia	2.23	2.18-2.28	2.30	2.25-2.37	1.98	1.95-2.05
Acute myocardial infarction	1.61	1.57-1.66	1.77	1.71-1.82	1.29	1.22-1.36
Ischemic stroke	1.43	1.41-1.46	1.52	1.49-1.55	1.22	1.19-1.26
Hemorrhagic stroke	1.66	1.62-1.71	1.79	1.74-1.86	1.43	1.36-1.51
Aged Under 65						
Pneumonia	2.52	2.48-2.56	2.80	2.74-2.85	2.20	2.15-2.28
Acute myocardial infarction	2.18	1.88-2.53	4.54	3.58-5.75	1.64	1.35-1.98
Ischemic stroke	2.01	1.82-2.23	2.82	2.37-3.34	1.74	1.53-1.97
Hemorrhagic stroke	2.90	2.61-3.22	3.98	3.32-4.78	2.59	2.29-2.94
Aged Over 65						
Pneumonia	1.94	1.89-1.98	2.10	2.05-2.18	1.78	1.72-1.82
Acute myocardial infarction	1.60	1.55-1.64	1.26	1.20-1.34	1.75	1.69-1.80
Ischemic stroke	1.42	1.40-1.44	1.20	1.16-1.24	1.51	1.48-1.54
Hemorrhagic stroke	1.61	1.56-1.65	1.31	1.24-1.38	1.76	1.70-1.82

Table 5. *Cox regression analysis of mortality in vertebral compression fracture.*

	Total		Male		Female		Age < 65		Age ≥ 65	
	Hazard ratio	**95% CI**	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**	**Hazard ratio**	**95% CI**
VCF	1.38	1.37-1.39	1.60	1.58-1.63	1.27	1.26-1.28	1.88	1.76-2.00	1.37	1.36-1.38
Osteoporosis	0.95	0.94-0.95	1.06	1.04-1.09	0.94	0.93-0.95	1.32	1.14-1.54	0.95	0.94-0.96
Multiple fractures	1.42	1.40-1.43	1.60	1.57-1.62	1.31	1.29-1.33	1.70	0.55-5.29	1.40	1.39-1.42
Traumatic injury	1.45	1.08-1.96	1.51	0.94-2.20	1.37	0.90-2.08	2.06	1.93-2.21	1.42	1.04-1.94

Discussion

Most previous studies have focused primarily on osteoporotic VCF among patients aged 65 years and older (11-14), whereas, this nationwide, population-based study identified 742,993 VCF cases among the entire South Korean population from 2005 through 2018. In this study, the annual incidence of VCF was 140.09/100,000 individuals, and it was 556.38/100,000 individuals in those aged 65 and over. The incidence of VCF among persons older than 65 years was similar to those reported in other countries. These previous studies have found VCF incidences of 306/100,000 persons in Japan (15), 445/100,000 persons in Hong Kong (11), 611/100,000 persons in Sweden (12), and 1,030/100,000 persons in the Netherlands (13).

We found that the incidence of VCF was 44.09/100,000 in patients aged < 65 years. Although this age group had a lower VCF incidence than patients aged ≥ 65, this value still indicates that the incidence of VCF is significant among younger individuals. When we collected clinical information on osteoporosis, multiple fractures, and traumatic injury in patients with a VCF and analyzed according to age, we found that the effect of these clinical variables was more significant among patients aged < 65 years compared to the older age group. In particular, the effect of traumatic injury was more pronounced among the younger age group. In Table 5, the HR for traumatic injury was significantly higher in patients aged < 65 years (HR 2.06, 95% CI, 1.93 - 2.21) compared to patients aged ≥ 65 years (HR 1.42, 95% CI, 1.04 - 1.94). This is supported by previous studies that have associated VCF occurrence in young adults with trauma. Cooper et al (16) showed that 74.47% of patients with a VCF aged 64 years and younger followed a severe traumatic injury, including traffic accidents and falls from above the patients' height, while Kanis et al (17) attributed higher hospital

admissions among people younger than 50 years to a high incidence of traumatic VCFs in young and middle-aged patients.

According to gender, the incidence of VCF was overwhelmingly higher in women over 65 years of age, which was 2.91 times that in men of the same age. This phenomenon was due to menopause. There have been reports suggesting an exponential increase in VCF rates in women around the average age of menopause (18-19). Additionally, it has been suggested that menopause around the age of 51 years contributes to postmenopausal osteoporosis (20-21). Studies have shown that bone mineral density is reduced on average by 10% during perimenopause, and older women lose one-half of the bone density of the vertebral column in their 80s (22-25).

We observed 123,472 deaths in patients with a VCF among 742,993 incident cases. Mortality rates in patients with a VCF were significantly higher than those in the age- and gender-matched control group. Many studies have reported that VCF increases mortality risk (14,26-29). For example, Edidin et al (30) observed a 4-year survival rate of 50.0% (30), and Chen et al (10) identified a 3-year survival rate of only 42.3% in patients with a VCF (10).

In our study, the overall VCF mortality rate was 25.90 and patients with a VCF had a 1.46-fold higher mortality compared to controls. The mortality rate ratio of patients with a VCF aged < 65 years and ≥ 65 years was 2.87 and 1.59, respectively. The mortality rate ratio was higher in patients who were younger at the time of fracture, indicating that the difference in mortality between patients with a VCF and controls was greater when the patients were younger. We suggest that this is because VCF in younger patients is often due to trauma, whereas VCF in older patients is due to osteoporosis. In a study by Leucht et al (31), traumatic VCF had a significantly higher incidence in patients younger than 60 years and occurred approximately 3.18 times more often in those aged 11-60 years than in those over 60 years of age. The study reported that most patients sustained spinal injuries between 20 and 50 years of age, and the mean age of those who experienced traumatic VCF was 43.8 years (range, 6–100 years).

In this study, although VCF was more prevalent in women, the mortality rate and mortality rate ratio were higher in men than in women, which is consistent with other studies. Center et al (32) found that men had a higher mortality risk than women. Additionally, Lee et al (33) observed a higher mortality risk for men than for women, a result maintained after adjusting for the general population by the standardized mortality ratio.

We propose that the higher VCF-related mortality observed among men compared to women in our study may be due to the higher incidence of traumatic injury among male patients with VCF. A previous study that assessed functional outcome after trauma at the Maryland Institute of Emergency Medicare demonstrated that 78% of the patients aged 16-45 were male (26), and it has been reported that high hospital admission rates in men reflect a high incidence of traumatic VCF in young and middle-aged patients (34). A study found that traumatic VCF occurred approximately 1.60 times more often in men than in women (31). This hypothesis is indirectly supported by studies on VCF or other fractures, which have shown higher mortality rates for men than for women (35-39).

Limitation

A limitation of this study was its lack of information on clinical features, such as disease severity and laboratory data, because the NHI database does not include detailed clinical information. Another limitation is that the precise cause of death could not be ascertained from the study database. However, we used the CCI to validate and correct the underlying pathology that may affect VCF mortality. We also performed a Cox regression analysis to evaluate mortality due to pneumonia and cardiovascular events among patients with a VCF. This study had several strengths. First, we tracked the largest number of patients to date to examine the trends in incidence and mortality for VCF in all age groups, while most previous studies were conducted only among elderly patients (40,41). Second, a major strength of our study is that we evaluated a large number of patients with a VCF based on nationwide population-based data with a 16-year period of data collection.

Conclusion

In conclusion, our population-based cohort study demonstrated a higher mortality rate ratio and hazard ratio among younger patients with a VCF, indicating the need for further studies on VCF among younger age groups.

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