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Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Vertebral Fracture: A Nationwide Population-based Cohort Study

Running title: Vertebral Fracture and Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome Risks

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Abstract

Objective: Studies on the association between vertebral column fractures (VCFs) and the subsequent risk of cardiopulmonary diseases, including aortic dissection (AD), congestive heart failure (CHF), pneumonia, and acute respiratory distress syndrome (ARDS), are scarce. Therefore, we used the National Health Insurance Research Database to investigate whether patients with VCF have a heightened risk of subsequent AD, CHF, pneumonia and ARDS.

Design: The National Health Insurance Research Database was used to investigate whether patients with VCFs have an increased risk of subsequent AD, CHF, pneumonia, and ARDS.

Participants: This cohort study comprised patients aged ≥ 18 years with a diagnosis of VCF and were hospitalized at any point during 2000–2010 (n = 111,532). Each VCF patient was frequency-matched to four non-VCF hospitalized patients based on age, sex, index year and comorbidities (n = 446,029). The Cox proportional hazard regressions model was used to estimate the adjusted effect of VCF on AD, CHF, pneumonia, and ARDS risk.

Results: The overall incidence of AD, CHF, pneumonia, and ARDS was higher in the VCF group than in the non-VCF group (5.11 versus 4.24, 124.5 versus 93.5, 297.4 versus 193.9, and 9.98 versus 5.13/10,000 person-years, respectively). After

adjustment for age, sex, and comorbidities, patients with VCF had a 1.26-fold higher risk of AD, 1.39-fold higher risk of CHF, 1.63-fold higher risk of pneumonia, and 2.02-fold higher risk of ARDS than did those without VCF. Patients with cervical VCF and SCI were more likely to develop pneumonia and ARDS.

Conclusions: Our study demonstrates that VCFs are associated with an increased risk of subsequent cardiopulmonary diseases. Future investigations are encouraged to delineate the mechanisms underlying this association.

Strengths and limitations of this study:

1. This is the first population-based, longitudinal cohort study to focus on the correlation between VCF and the subsequent risks of specific cardiopulmonary diseases.

2. By sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, stable outcomes could be achieved with such adequate, representative samples.

3. All disease definitions and sample selection in our study were based on the ICD-9-CM coding. Therefore, miscoding or misclassification might exist, although it is considered rare.

4. Because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Keywords: Vertebral column fracture, aortic dissection, congestive heart failure, pneumonia, acute respiratory distress syndrome, National Health Insurance Research Database.

Key messages:

• VCF is significantly associated with an increased risk of specific cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS.

• Patients with cervical VCF and SCI were more likely to develop pneumonia and ARDS.

• Patients with VCF should be targeted for further screening and preventive interventions for cardiopulmonary diseases.

Introduction

Vertebral column fractures (VCFs) constitute a major healthcare burden worldwide because of its high incidence and strong influence on individuals' quality of life, medical resource consumption, and direct or potential unfavorable impacts on socioeconomic development[1-3]. Approximately 1.4 million new cases of VCF are diagnosed globally every year[4], and among these, osteoporosis, trauma, and malignancy are the major etiologies[5-9]. Acute aortic dissection (AD) remains the major life-threatening vascular emergency, with a steadily increasing incidence because of population aging and the explosive growth of radiologic technology[10]. Without early recognition and timely treatment, the prognosis of AD would be extremely poor, and half the patients would die within 48 h[10]. Congestive heart failure (CHF) is the major cause of hospitalization in old age, with more than 650,000 new cases confirmed annually in the United States, and more than 1 million people were hospitalized for decompensated CHF, resulting in costs exceeding 39 billion[11-13]. Pneumonia is one of the most common infectious diseases in elderly adults and is also the leading cause of death in Americans older than 65 years[14 15]. Acute respiratory distress syndrome (ARDS) is a complex syndrome characterized by diffuse hydrostatic pulmonary edema, alveoli damage, and persistent hypoxemia, which are mainly triggered by infection, inflammation, trauma, or other etiologies. The

in-hospital mortality rate for this condition could reach 40% even when managed with the standardized lung protective ventilator strategy[16 17].

Studies have demonstrated that elderly patients with a history of osteoporotic VCF have an increased risk of cardiovascular events, including stroke (ischemic or hemorrhagic) and coronary heart disease[18-21]. In addition, chronic, worsened and longstanding backache accompanied with VCF might result in a long-term increase of sympathetic tone, fatigue, stress reaction, low physical activity, depressive tendency, diminished pulmonary function, and, consequently a poor quality of life, which might be correlated with cardiopulmonary disease risk[3 5 7 8 22]. Therefore, we hypothesized that an association exists between VCF and the risk of cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS. Accordingly, we conducted a nationwide, population-based data analysis to verify this hypothesis and tried to provide essential evidence-based information for clinical practice.

Methods

Data Source

This retrospective cohort study used datasets from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National Health Insurance (NHI) program in March 1995, and 99% of the 23.74 million residents were enrolled[23]. The details of the NHIRD and NHI program are well

presented in previous studies[24] [25]. The NHIRD records diseases according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. This study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115).

Sampled Participants

Patients aged ≥18 years with newly diagnosed VCF (ICD-9-CM codes, 805 and 806) from January 1, 2000, to December 31, 2010, were identified as the VCF cohort. The location of VCF was defined in two ways as follows: (1) cervical spine (ICD-9-CM codes, 805.0-805.18 and 806.0-806.19), thoracic spine (ICD-9-CM codes, 805.2, 805.3, and 806.2-806.39), lumbar spine (ICD-9-CM codes, 805.4, 805.5, 806.4, and 806.5), and sacrum plus coccyx (ICD-9-CM codes, 805.6, 805.7, and 806.6-806.79) and (2) without spinal cord injury (SCI) (ICD-9-CM codes, 805-805.9), and with SCI (ICD-9-CM codes, 806-806.9). The date of first-time VCF diagnosis at admission was defined as the index date. For each VCF patient, four non-VCF participants were frequency-matched by the index year of VCF diagnosis, age (every 5-year span), sex, and comorbidities of diabetes (ICD-9-CM code, 250), hypertension (ICD-9-CM codes, 401-405), hyperlipidemia (ICD-9-CM code, 272), atrial fibrillation (ICD-9-CM code, 427.31), chronic kidney disease (CKD; ICD-9-CM codes, 580-589), and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes, 491, 492, and 496). We constructed a 1:4 matched cohort study to increase the statistical efficiency

and power, and to control possible confounding. We excluded participants with prior AD (ICD-9-CM codes, 441.0, 441.00, 441.01, 441.02, and 441.03), CHF (ICD-9-CM code, 428), pneumonia (ICD-9-CM codes, 480-488), and ARDS (ICD-9-CM codes, 518.82 and 518.5) at baseline in both the VCF and non-VCF cohorts.

Outcome

The main outcome was hospitalization with a new diagnosis of AD, CHF, pneumonia, or ARDS during the follow-up period. Both the VCF and non-VCF cohorts were followed up until the diseases appeared or they were censored because of loss to follow-up, death, or the end of December 31, 2011, whichever occurred first.

Statistical analysis

A chi-square test and Student's *t*-test were used to evaluate the differences in the distribution of categorical and continuous variables, respectively, between the VCF and non-VCF cohorts. The overall, sex-, age-, and comorbidity-specific incidence densities of AD, CHF, pneumonia, and ARDS were estimated for each cohort. The relative risks of AD, CHF, pneumonia, and ARDS in the VCF cohort compared with the non-VCF cohort were analyzed using univariable and multivariable Cox proportional hazard regression models and presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable models were simultaneously adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, atrial

fibrillation, CKD, and COPD. Further analysis was performed to assess whether the association of VCF with AD, CHF, pneumonia, and ARDS varied according to the levels of VCF. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA), and we set the significance level at less than 0.05 for two-sided testing of P-values.

Results

In this study, 111,532 VCF patients and 446,029 matched non-VCF participants with similar distributions of age, sex, and comorbidities were assessed (Table 1). In the VCF cohort, ≥44.7% of patients were aged ≥65 years, and 55.0% of the patients were women (Table 1). The mean age of the patients was 59.0 ± 18.9 years in the VCF cohort and 58.5 ± 18.9 years in the non-VCF cohort. Both cohorts had a medical history of hypertension (26.1%), diabetes (15.3%), COPD (5.50%), hyperlipidemia (5.22%), atrial fibrillation (1.30%), and CKD (3.63%).

Table 1. Comparison of demographics and comorbidity between vertebral column fracture patients and controls

	Vertebral column fracture		
	Yes (N=111532) n(%)	No (N=446029) n(%)	*p*-value
Age, years			0.99
≤49	36946(33.1)	147763(33.1)	

50-64	24715(22.2)	98848(22.2)	
≥65	49871(44.7)	199418(44.7)	
Mean (SD) †	59.0(18.9)	58.5(18.9)	0.001
Gender			0.99
Female	61352(55.0)	245347(55.0)	
Male	50180(45.0)	200682(45.0)	
Comorbidity			
Hypertension	29143(26.1)	116526(26.1)	0.98
Diabetes	17016(15.3)	68023(15.3)	0.96
Hyperlipidemia	5833(5.23)	23269(5.22)	0.86
Atrial fibrillation	1461(1.31)	5779(1.30)	0.71
CKD	4061(3.64)	16209(3.63)	0.91
COPD	6151(5.52)	24530(5.50)	0.84

Chi-square test examined categorical data; †T-test examined continuous ;

Overall, the incidence of AD was 1.20-fold higher in the VCF cohort than in the non-VCF cohort (5.11 vs. 4.24 per 10,000 person-years), with an adjusted HR (aHR) of 1.26 (95% CI = 1.11-1.43) (Table 2). The aHR of AD among women was significantly higher in the VCF cohort than in the non-VCF cohort (aHR = 1.39, 95% CI = 1.16-1.66). The age-specific relative risk of AD in the VCF cohort was higher than that in the non-VCF cohort for all age groups. The relative risk of AD was higher in the VCF cohort than in the non-VCF cohort for patients without comorbidities (aHR = 1.44, 95% CI = 1.18–1.76). In all stratifications, the risk of CHF, pneumonia, and ARDS remained higher in the VCF cohort than in the non-VCF cohort.

Table 2. Incidence and adjusted hazard ratio of outcome by sex, age and comorbidity for vertebral column fracture patients compared to controls

Variables	Vertebral column fracture						Compared to Control	
	Yes			No				
	Events n	PY	Rate#	Events n	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
Aortic dissection								
All	310	606079	5.11	1083	2552211	4.24	1.20(1.06, 1.37)**	1.26(1.11, 1.43)***
Gender								
Female	158	330690	4.78	480	1379047	3.48	1.37(1.15, 1.65)***	1.39(1.16, 1.66)***
Male	152	275389	5.52	603	1173164	5.14	1.07(0.90, 1.28)	1.15(0.96, 1.37)
Age, years								
≤49	21	238047	0.88	50	958814	0.52	1.69(1.01, 2.81)*	1.71(1.03, 2.85)*
50-64	43	142801	3.01	127	593672	2.14	1.41(1.00, 2.00)*	1.43(1.01, 2.02)*
≥65	246	225231	10.9	906	999724	9.06	1.21(1.05, 1.39)**	1.23(1.07, 1.42)**
Comorbidity§								
No	126	423394	2.98	388	1759071	2.21	1.35(1.10, 1.65)**	1.44(1.18, 1.76)***
Yes	184	182684	10.1	695	793140	8.76	1.15(0.98, 1.35)	1.16(0.99, 1.37)
Congestive heart failure								
All	7362	591293	124.5	23434	2506566	93.5	1.33(1.30, 1.37)***	1.39(1.36, 1.43)***
Gender								
Female	5027	320276	157.0	15806	1347497	117.3	1.34(1.30, 1.38)***	1.37(1.32, 1.41)***
Male	2335	271018	86.2	7628	1159069	65.8	1.31(1.25, 1.37)***	1.44(1.37, 1.51)***
Age, years								
≤49	253	237424	10.7	631	957288	6.59	1.61(1.39, 1.87)***	1.66(1.44, 1.92)***
50-64	778	140974	55.2	2476	587448	42.2	1.31(1.21, 1.42)***	1.33(1.23, 1.44)***
≥65	6331	212896	297.4	20327	961830	211.3	1.41(1.38, 1.46)***	1.42(1.38, 1.46)***
Comorbidity§								
No	2293	418658	54.8	6585	1746146	37.7	1.45(1.39, 1.53)***	1.56(1.49, 1.63)***
Yes	5069	172636	293.6	16849	760420	221.6	1.33(1.29, 1.37)***	1.33(1.29, 1.37)***
Pneumonia								
All	17088	574670	297.4	47887	2469960	193.9	1.53(1.51, 1.56)***	1.63(1.60, 1.66)***
Gender								
Female	9332	313517	297.7	26911	1332159	202.0	1.48(1.44, 1.51)***	1.51(1.47, 1.55)***
Male	7756	261153	297.0	20976	1137801	184.4	1.61(1.57, 1.65)***	1.78(1.74, 1.83)***
Age, years								
≤49	1604	232911	68.9	2566	951743	27.0	2.55(2.40, 2.72)***	2.60(2.44, 2.76)***
50-64	2168	137755	157.4	5561	581203	95.7	1.65(1.57, 1.73)***	1.68(1.59, 1.76)***

≥65	13316	204004	652.7	39760	937013	424.3	1.55(1.52, 1.58)***	1.57(1.54, 1.61)***
Comorbidity§								
No	6914	409031	169.0	15760	1729775	91.1	1.86(1.81,1 .91)***	2.00(1.94, 2.05)***
Yes	10174	165639	614.2	32127	740185	434.0	1.42(1.39, 1.45)***	1.44(1.41, 1.47)***
Acute respiratory distress syndrome								
All	605	6906281	9.98	1311	2553547	5.13	1.94(1.76, 2.14)***	2.02(1.84, 2.23)***
Gender								
Female	281	330769	8.50	655	1379507	4.75	1.79(1.56, 2.06)***	1.81(1.57, 2.08)***
Male	324	275511	11.8	656	1174039	5.59	2.10(1.84, 2.40)***	2.25(1.97, 2.57)***
Age, years								
≤49	85	237971	3.57	79	958844	0.82	4.33(3.19, 5.88)***	4.41(3.24, 5.99)***
50-64	73	142861	5.11	168	593844	2.83	1.81(1.37, 2.38)***	1.82(1.39, 2.40)***
≥65	447	225448	19.8	1064	1000858	10.6	1.87(1.67, 2.09)***	1.90(1.70, 2.12)***
Comorbidity§								
No	255	423421	6.02	444	1759620	2.52	2.39(2.05, 2.79)***	2.52(2.16, 2.94)***
Yes	350	182859	19.1	867	793926	10.9	1.75(1.55, 1.98)***	1.77(1.56, 2.01)***

PY, person-years; Rate#, incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio;
Adjusted HR†: adjusted hazard ratio controlling for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD;
Comorbidity§: Patients with any one of the comorbidities hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD were classified as the comorbidity group
*p<0.05, **p<0.01, ***p<0.001

Compared with patients without VCF, the risk of AD was 1.38-fold (95% CI = 1.20-1.59) higher in VCF-lumbar patients and was 1.27-fold (95% CI = 1.12-1.45) higher in VCF patients without SCI (Table 3). The risk of CHF and pneumonia remained higher in patients with various levels of VCF than in patients without VCF. Table 3 also shows that patients with various levels of VCF, except for those with sacrum or coccyx fractures, had a significantly higher risk of ARDS than did patients without VCF.

Table 3. Comparisons of Incidence, and Hazard Ratios of outcome by subtypes of vertebral column fracture

Variables	N	Event	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
Aortic dissection					
Non-Vertebral column fracture	446029	1083	4.24	1(Reference)	1(Reference)
Cervical spine	10594	14	2.43	0.57(0.34, 0.97)*	0.97(0.57, 1.65)
Thoracic	32895	100	5.87	1.38(1.13, 1.70)**	1.20(0.98, 1.47)
Lumbar	72135	241	6.15	1.45(1.26, 1.67)***	1.38(1.20, 1.59)***
Sacrum and coccyx	7594	6	1.24	0.29(0.13, 0.65)**	1.00(0.45, 2.23)
Without SCI	101171	286	5.26	1.24(1.09, 1.41)**	1.27(1.12, 1.45)***
With SCI	13705	34	4.10	0.97(0.69, 1.36)	1.19(0.84, 1.67)
Congestive heart failure					
Non-Vertebral column fracture	446029	23434	93.5	1(Reference)	1(Reference)
Cervical spine	10594	296	52.0	0.56(0.50, 0.62)***	1.40(1.25, 1.57)***
Thoracic	32895	2862	174.0	1.86(1.79, 1.94)***	1.47(1.41, 1.53)***
Lumbar	72135	5355	140.6	1.50(1.46, 1.55)***	1.43(1.38, 1.47)***
Sacrum and coccyx	7594	156	32.6	0.35(0.30, 0.41)***	1.35(1.15, 1.58)***
Without SCI	101171	6735	126.9	1.36(1.32, 1.39)***	1.38(1.35, 1.42)***
With SCI	13705	910	112.5	1.20(1.12, 1.28)***	1.59(1.49, 1.70)***
Pneumonia					
Non-Vertebral column fracture	446029	47887	193.9	1(Reference)	1(Reference)
Cervical spine	10594	1256	230.7	1.19(1.12, 1.26)***	2.44(2.30, 2.58)***
Thoracic	32895	6001	375.3	1.94(1.89, 1.99)***	1.62(1.58, 1.67)***
Lumbar	72135	11891	321.0	1.65(1.62, 1.69)***	1.60(1.57, 1.64)***
Sacrum and coccyx	7594	466	99.3	0.51(0.47, 0.56)***	1.79(1.63, 1.96)***
Without SCI	101171	15388	298.0	1.54(1.51, 1.56)***	1.60(1.57, 1.63)***
With SCI	13705	2437	315.1	1.62(1.56, 1.69)***	2.10(2.01, 2.18)***
Acute respiratory distress syndrome					
Non-Vertebral column fracture	446029	1311	5.13	1(Reference)	1(Reference)
Cervical spine	10594	63	10.9	2.13(1.66, 2.75)***	3.71(2.87, 4.79)***

Thoracic	32895	214	12.6	2.45(2.12, 2.83)***	2.10(1.82, 2.43)***
Lumbar	72135	404	10.3	2.01(1.80, 2.24)***	1.92(1.72, 2.15)***
Sacrum and coccyx	7594	11	2.28	0.44(0.25, 0.80)**	1.40(0.77, 2.55)
Without SCI	101171	532	9.78	1.90(1.72, 2.10)***	1.95(1.76, 2.16)***
With SCI	13705	103	12.4	2.41(1.97, 2.95)***	2.94(2.40, 3.59)***

Rate[#], incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio; Adjusted HR[†]: adjusted hazard ratio controlling for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD; ICD-9-CM: Cervical spine: 805.0-805.18, 806.0-806.19; Thoracic: 805.2, 805.3, 806.2-806.39; Lumbar: 805.4, 805.5, 806.4, 806.5; Sacrum and coccyx: 805.6, 805.7, 806.6-806.79; SCI involved or Not: Without SCI: 805-805.9 & With SCI: 806-806.9
*p<0.05, **p<0.01, ***p<0.001

Figures 1A–1D show that the VCF cohort had a significantly higher cumulative proportion of AD (P = 0.001; Figure 1A), CHF (P < 0.001; Figure 1B), pneumonia (P < 0.001; Figure 1C), and ARDS (P < 0.001; Figure 1D) than did the non-VCF cohort.

Discussion

To the best of our knowledge, this is the first population-based, longitudinal cohort study to focus on the correlation between VCF and the subsequent risks of specific cardiopulmonary diseases. The main results demonstrated that VCF is significantly associated with an increased risk of several specific cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS. In our study, patients older than 65 years and females accounted for the majority of participants. The incidence and prevalence of vulnerable fractures, accompanied with population aging and

subsequent frequently occurring home accidents, are steadily rising[26]. In addition, VCF in women is constantly a consequence of postmenopausal bone loss[5 7 8]. According to recent studies, the prevalence of women older than 50 years who experienced at least one VCF event was 23% - 26%, which was higher than that of men (21.5%)[27-29].

AD represents a complicated, life-threatening emergency and is associated with high morbidity and mortality[30 31]. In our analysis, with or without VCF, the incidence of AD was higher in men, elderly patients older than 65 years, and those with coexisting comorbidities; this finding is in line with previous epidemiological investigations[30-32]. Notably, most studies examining the incidence of AD have been confined to specific geographic regions or focused on inpatients; thus, the true incidence is hard to be reflected[30]. Moreover, compared with non-VCF patients, VCF patients, especially female patients and those without comorbidities, bore a higher risk of subsequent AD development. Studies that have focused on this correlation are scarce, and the current literature describes only a few cases of aortic injury following thoracolumbar spine fractures in polytrauma victims[33-37]. We suppose that the intractable pain induced by fractures, accompanied with increments in sympathetic tone, stress, hypertension, and the impact on the vascular wall, as well as an unfavorable sedentary life style all might contribute to the formation of AD.

In this study, VCF was associated with an increased risk of CHF, and the results remained statistically significant across various age and sex strata, as well as with or without comorbidities. In a cross-sectional analysis, Lyons et al.[38] demonstrated that more than one-tenth of heart failure patients had radiologic recognizable VCF, and among those, multiple VCF accounted for one half, indicating the close correlation between these two diseases. Moreover, the most common etiology of VCF, osteoporosis, together with CHF, are conventionally deemed to be independent diseases. However, recent investigations have indicated that the two diseases share common risk factors, including advantaged age, female sex, hypovitaminosis D, renal insufficiency, diabetes, and a smoking habit, as well as the same etiologic mechanisms, including activation of the renin-angiotensin-aldosterone system, hypersecretion of parathyroid hormones, and oxidative / nitrosative stress[21 38-42]. Furthermore, unfavorable outcomes following fracture, including a loss of functional and social activities, dependency with poor quality of life, higher serum cortisol levels accompanied with depressive disorder, higher inflammatory markers, lower drug and diet compliance, a sedentary life style, and arrhythmia or cardiac ischemic events caused by high sympathetic activity, might all contribute to the deterioration of heart function[40 43].

Our study results reveal that patients with VCF bore a significantly heightened

risk of subsequent pneumonia and ARDS across all strata of age and sex and irrespective of the presence of comorbidities. Further analyses demonstrated the strongest correlation between cervical VCF combined with SCI and risks of pneumonia and ARDS. In a 2-year retrospective multicenter trauma registry analysis, Fletcher et al.[44] noted that 16% of elderly patients older than 65 years with cervical spine trauma ultimately developed pneumonia. Other studies have revealed the incidence of pulmonary complications following cervical spine trauma to be 35% - 95%[45 46], and among these complications, the most common type was pneumonia and atelectasis, although ARDS was the most severe type and represented the predominant contributor to morbidity and mortality[47-49]. There are several possible explanations. First, deformity of the vertebral body or even kyphosis might decrease the lung capacity and therefore impair the pulmonary function. Prior studies have indicated that a single VCF would decrease the predicted forced vital capacity by 9%, increase the risk of restrictive lung disease, and lead to a 3-fold risk of mortality[1 2 50]. Second, cervical VCF combined with SCI might cause paralysis of the diaphragm and hypoactivity of the respiratory accessory muscles, which results in hypoventilation. In addition, the imbalance of sympathetic-parasympathetic interactions would result in an elevated airway tone, bronchorrhea, and poor clearance, which are all associated with the development of various pulmonary complications[51 52]. Third, Chen et al.[51]

proposed that in upper cervical spine trauma and SCI patients, hypoalbuminemia would not only indicate nutrition status but would also impair the function of respiratory muscles, leading to respiratory complications. However, additional investigations are necessary for verification before definite conclusions are established. Fourth, patients with SCI are prone to develop aspiration and subsequent pulmonary infection due to impaired neuromuscular transmission.

The major strength of our study is sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, and stable outcomes could be achieved with such adequate, representative samples. However, the inevitable limitations should be discussed. First, all disease definitions and sample selection in our study were based on the ICD-9-CM coding, which has been rigorously scrutinized and peer-reviewed by clinical physicians, the declaration unit of medical institutions and finally the NHI administration. However, miscoding or misclassification might still exist, although it is considered rare. Second, retrospective dataset analysis results cannot be used to determine causal relationships. Third, several crucial variables could not be obtained from our dataset, including family history, education and socioeconomic status, information of life style and physical activity, body weight, smoking habits, disease severity, laboratory results, radiologic reports, and estimated pain scores, which are potential confounders that might have affected the results.

Fourth, a considerable portion of VCF patients with slight or no symptoms might not have been diagnosed or might have even been overlooked in clinical settings; thus, the incidence of VCF could be underestimated. Fifth, patients with VCF might have one or more overlapping etiologies include osteoporosis, trauma and malignancies, etc. Therefore, it was technically infeasible to simply divide the VCF patients into several subgroups for sub-analysis based on the coding of etiologies. Finally, because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Conclusion

In conclusion, our study results support the hypothesis that VCF is associated with subsequent risks of AD, CHF, pneumonia, and ARDS. Future studies are warranted to delineate the actual pathophysiologic mechanisms underlying this correlation and to develop optimal strategies for reducing the heath care burden of VCF and its complications. Based on our results, we suggest that patients with VCF should be targeted for further screening and preventive interventions for cardiopulmonary diseases.

Abbreviations:

VCFs: vertebral column fractures; AD: aortic dissection; CHF: congestive heart failure; ARDS: acute respiratory distress syndrome; NHIRD: National Health Insurance Research Database; NHI: National Health Insurance; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; SCI: spinal cord injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; aHRs: adjusted hazard ratios; CI: confidence interval; SD: standard deviation.

Declarations:

Acknowledgements

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Ethics approval and consent to participate

This study was approved by the Ethics Review Board of China Medical University and Hospital, Taiwan (CMUH-104-REC2-115). The IRB waived the consent

requirement.

Availability of data and materials

Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Owing to the Personal Information Protection Act, these cannot be made publicly available (http://nhird .nhri.org.tw).

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

The authors' individual contributions are outlined as follows. Conception and design: F-Y.L. and T.-Y.Y. Administrative support: T.-Y.Y. Data collection and organization: All authors. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval of the manuscript: All authors.

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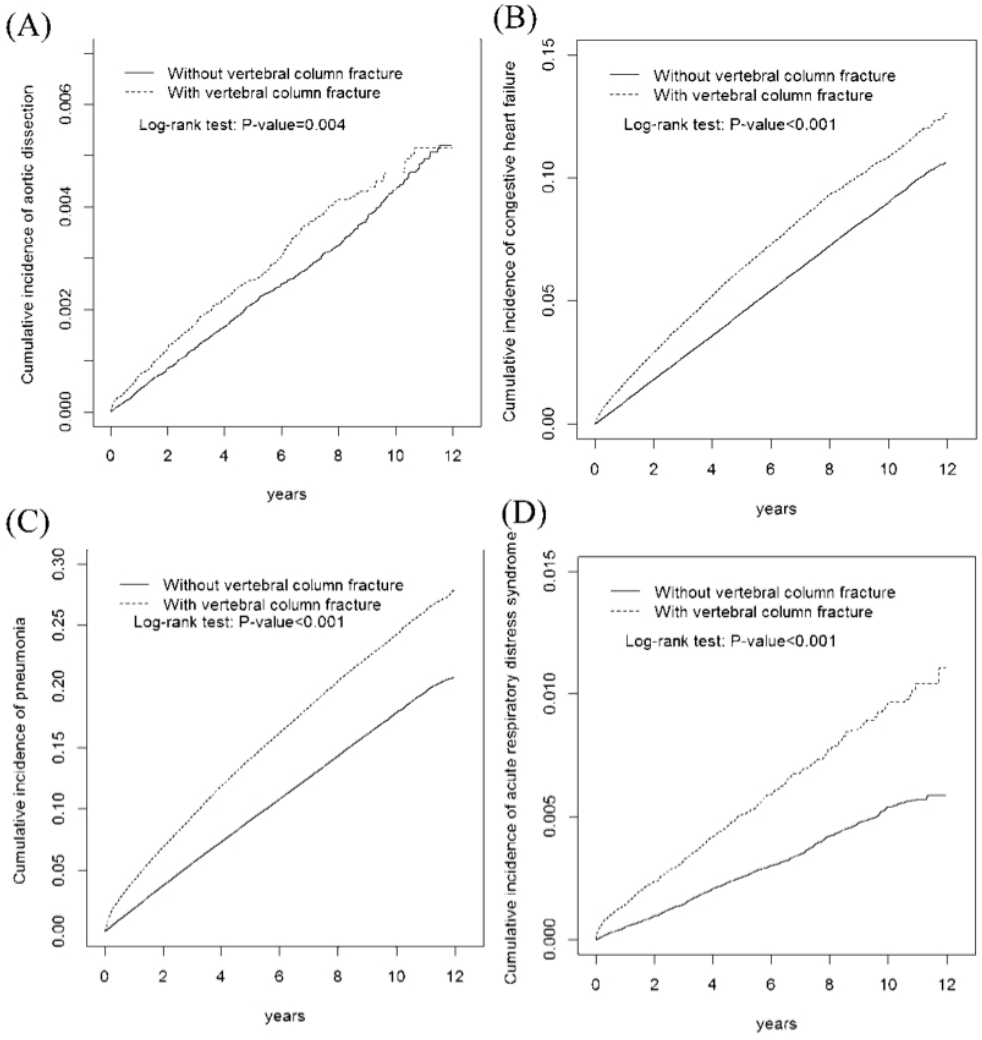

Figure1

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1&3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	8-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	10-11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	12-15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-15
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-15
Discussion			
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Clinical Vertebral Fracture: A Nationwide Population-based Cohort Study in Taiwan

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Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Public health, Respiratory medicine
Keywords:	aortic dissection, congestive heart failure, pneumonia, acute respiratory distress syndrome, National Health Insurance Research Database, Clinical Vertebral fracture

Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Clinical Vertebral Fracture: A Nationwide Population-based Cohort Study in Taiwan

Running title: Clinical Vertebral Fracture and Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome Risks

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Abstract

Objective: Studies on the association between clinical vertebral fractures (CVFs) and the subsequent risk of cardiopulmonary diseases, including aortic dissection (AD), congestive heart failure (CHF), pneumonia, and acute respiratory distress syndrome (ARDS), are scarce. Therefore, we used the National Health Insurance Research Database to investigate whether patients with CVF have a heightened risk of subsequent AD, CHF, pneumonia and ARDS.

Design: The National Health Insurance Research Database was used to investigate whether patients with CVFs have an increased risk of subsequent AD, CHF, pneumonia, and ARDS.

Participants: This cohort study comprised patients aged ≥ 18 years with a diagnosis of CVF and were hospitalized at any point during 2000–2010 (n = 108,935). Each CVF patient was frequency-matched to a non-CVF hospitalized patients based on age, sex, index year and comorbidities (n = 108,935). The Cox proportional hazard regressions model was used to estimate the adjusted effect of CVF on AD, CHF, pneumonia, and ARDS risk.

Results: The overall incidence of AD, CHF, pneumonia, and ARDS was higher in the CVF group than in the non-CVF group (4.82 versus 4.06, 118.7 versus 89.6, 282.8 versus 183.6, and 9.11 versus 4.18/10,000 person-years, respectively). After

adjustment for age, sex, comorbidities, and Charlson comorbidity index score, patients with CVF had a 1.20-fold higher risk of AD (95% CI = 1.02-1.42), 1.35-fold higher risk of CHF (95% CI = 1.30-1.40), 1.57-fold higher risk of pneumonia (95% CI = 1.54-1.61), and 2.20-fold higher risk of ARDS (95% CI = 1.90-2.55) than did those without CVF. Patients with cervical CVF and SCI were more likely to develop pneumonia and ARDS.

Conclusions: Our study demonstrates that CVFs are associated with an increased risk of subsequent cardiopulmonary diseases. Future investigations are encouraged to delineate the mechanisms underlying this association.

Strengths and limitations of this study:

1. This is the first population-based, longitudinal cohort study to focus on the correlation between CVF and the subsequent risks of specific cardiopulmonary diseases.

2. By sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, stable outcomes could be achieved with such adequate, representative samples.

3. All disease definitions and sample selection in our study were based on the ICD-9-CM coding. Therefore, miscoding or misclassification might exist, although it is considered rare.

4. In our study, sampled participants were retrieved from NHIRD from January 1, 2000, to December 31, 2010. Aging property of the data might not truly reflect the current medical conditions.

5. Because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Keywords: Clinical Vertebral fracture, aortic dissection, congestive heart failure, pneumonia, acute respiratory distress syndrome, National Health Insurance Research Database.

Introduction

Clinical Vertebral fractures (CVFs) constitute a major healthcare burden worldwide because of its high incidence and strong influence on individuals' quality of life, medical resource consumption, and direct or potential unfavorable impacts on socioeconomic development[1-3]. Approximately 1.4 million new cases of CVF are diagnosed globally every year[4], and among these, osteoporosis, trauma, and malignancy are the major etiologies[5-9]. Acute aortic dissection (AD) remains the major life-threatening vascular emergency, with a steadily increasing incidence because of population aging and the explosive growth of radiologic technology[10]. Without early recognition and timely treatment, the prognosis of AD would be extremely poor, and half the patients would die within 48 h[10]. Congestive heart failure (CHF) is the major cause of hospitalization in old age, with more than 650,000 new cases confirmed annually in the United States, and more than 1 million people were hospitalized for decompensated CHF, resulting in costs exceeding 39 billion[11-13]. Pneumonia is one of the most common infectious diseases in elderly adults and is also the leading cause of death in Americans older than 65 years[14 15]. Acute respiratory distress syndrome (ARDS) is a complex syndrome characterized by diffuse hydrostatic pulmonary edema, alveoli damage, and persistent hypoxemia, which are mainly triggered by infection, inflammation, trauma, or other etiologies. The

in-hospital mortality rate for this condition could reach 40% even when managed with the standardized lung protective ventilator strategy[16 17].

Studies have demonstrated that elderly patients with a history of osteoporotic vertebral fracture have an increased risk of cardiovascular events, including stroke (ischemic or hemorrhagic) and coronary heart disease[18-21]. Recently, Kim et al.[22] reported an association between isolated CVF and future development of pneumonia in women with low bone density. In addition, chronic, worsened and longstanding backache accompanied with CVF might result in a long-term increase of sympathetic tone, fatigue, stress reaction, low physical activity, depressive tendency, diminished pulmonary function, and, consequently a poor quality of life, which might be correlated with cardiopulmonary disease risk[3 5 7 8 23]. Therefore, we hypothesized that an association exists between CVF and the risk of cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS. Accordingly, we conducted a nationwide, population-based data analysis to verify this hypothesis and tried to provide essential evidence-based information for clinical practice.

Methods

Data Source

This retrospective cohort study used datasets from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National

Health Insurance (NHI) program in March 1995, and 99% of the 23.74 million residents were enrolled[24]. The details of the NHIRD and NHI program are well presented in previous studies[25-31]. The NHIRD records diseases according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Validation of the NHIRD with cardiovascular diseases were investigated and appeared to be a valid resource for population research[32-35]. This study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115).

Sampled Participants

Patients aged ≥18 years with newly diagnosed CVF (ICD-9-CM codes, 805 and 806) from January 1, 2000, to December 31, 2010, were identified as the CVF cohort. The location of CVF was defined in two ways as follows: (1) cervical spine (ICD-9-CM codes, 805.0-805.18 and 806.0-806.19), thoracic spine (ICD-9-CM codes, 805.2, 805.3, and 806.2-806.39), lumbar spine (ICD-9-CM codes, 805.4, 805.5, 806.4, and 806.5), and sacrum plus coccyx (ICD-9-CM codes, 805.6, 805.7, and 806.6-806.79) and (2) without spinal cord injury (SCI) (ICD-9-CM codes, 805-805.9), and with SCI (ICD-9-CM codes, 806-806.9). The date of first-time CVF diagnosis at admission was defined as the index date. Participants with prior AD (ICD-9-CM codes, 441.0, 441.00, 441.01, 441.02, and 441.03), CHF (ICD-9-CM code, 428), pneumonia (ICD-9-CM codes, 480-488), and ARDS (ICD-9-CM codes, 518.82 and

518.5) before the index date (n=15,697); with the diagnosis of trauma (ICD-9-CM codes, 800-959 except 805-806) during the same period (n=2,597); with any outcome event (AD, CHF, pneumonia, and ARDS) diagnosed within 1 month after the index date (n=2,738); those under 18 years of age (n=4,017); and those with missing information about age or sex (n=4) in both the CVF and non-CVF cohorts; were excluded. For each CVF patient, a non-CVF participant was frequency-matched by the index year of CVF diagnosis, age (every 5-year span), sex, and comorbidities of diabetes (ICD-9-CM code, 250), hypertension (ICD-9-CM codes, 401-405), hyperlipidemia (ICD-9-CM code, 272), atrial fibrillation (ICD-9-CM code, 427.31), chronic kidney disease (CKD; ICD-9-CM codes, 580-589), and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes, 491, 492, and 496) (Figure 1). Coexisting comorbidities were identified before the index date, with at least one time of principal or secondary diagnoses documented in hospitalizations during the period 2000 to 2010. We have also added Charlson comorbidity index (CCI) score as a confounding factor. Summary of ICD-9-CM codes applied for disease definition are presented in online supplementary table 1.

Outcome

The main outcome was hospitalization with a new diagnosis of AD, CHF, pneumonia, or ARDS during the follow-up period. Both the CVF and non-CVF

cohorts were followed up until the diseases appeared or they were censored because of loss to follow-up, death, or the end of December 31, 2011, whichever occurred first.

Statistical analysis

A chi-square test and Student's *t*-test were used to evaluate the differences in the distribution of categorical and continuous variables, respectively, between the CVF and non-CVF cohorts. The overall, sex-, age-, and comorbidity-specific incidence densities of AD, CHF, pneumonia, and ARDS were estimated for each cohort. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. The results showed that there was no significant relationship between Schoenfeld residuals for CVF and follow-up time (p-value = 0.06) in the model evaluating the AD risk and Schoenfeld residuals for CVF and follow-up time (p-value = 0.18) in the model evaluating the ARDS risk. In the model evaluating the CHF and pneumonia risk throughout overall follow-up period, the results of the test revealed a significant relationship between Schoenfeld residuals for CVF and follow-up time, suggesting the proportionality assumption was violated. The relative risks of AD, CHF, pneumonia, and ARDS in the CVF cohort compared with the non-CVF cohort were analyzed using univariable and multivariable Cox proportional hazard regression models and presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable models were

simultaneously adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD. We further tested the interaction between gender and VCF; between age and VCF; and between comorbidity and VCF by including a cross-product term in the model. Further analysis was performed to assess whether the association of CVF with AD, CHF, pneumonia, and ARDS varied according to the levels of CVF. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA), and we set the significance level at less than 0.05 for two-sided testing of P-values.

Patient and public involvement

There was no patient or public involvement in this study.

Results

In this study, 108,935 CVF patients and 108,935 matched non-CVF participants with similar distributions of age, sex, and comorbidities were assessed (Table 1). In the CVF cohort, ≥ 44.3% of patients were aged ≥ 65 years, and 55.3% of the patients were women (Table 1). The mean age of the patients was 58.8 ± 18.8 years in the CVF cohort and 58.3 ± 18.8 years in the non-CVF cohort. Both cohorts had a medical history of hypertension (26.0%), diabetes (15.2%), COPD (5.3%), hyperlipidemia (5.2%), atrial fibrillation (1.2%), and CKD (3.5%). Patients of CVF cohort were more prevalent with CCI than non-CVF cohort.

Table 1. Comparison of demographics and comorbidity between clinical vertebral fracture patients and controls

	Clinical vertebral fracture		
	Yes (N=108935) n(%)	No (N=108935) n(%)	*p*-value
Age, years[&]			0.99
≤49	36313(33.3)	36310(33.3)	
50-64	24341(22.3)	24345(22.4)	
≥65	48281(44.3)	48280(44.3)	
Mean (SD) [†]	58.8(18.8)	58.3(18.8)	<0.001
Gender[&]			0.99
Female	60216(55.3)	60218(55.3)	
Male	48719(44.7)	48717(44.7)	
Comorbidity[&]			
Hypertension	28339(26.0)	28338(26.0)	0.99
Diabetes	16553(15.2)	16554(15.2)	0.99
Hyperlipidemia	5692(5.2)	5695(5.2)	0.98
Atrial fibrillation	1381(1.2)	1377(1.2)	0.94
CKD	3810(3.5)	3814(3.5)	0.96
COPD	5865(5.3)	5867(5.3)	0.98
CCI score[&]			<0.001
0	77930(71.5)	82878(76.1)	
1	17489(16.1)	15662(14.4)	
2	7079(6.5)	5378(4.9)	
3 or more	6437(5.9)	5017(4.6)	

[&]Chi-square test examined categorical data; [†]T-test examined continuous;

Overall, the incidence of AD was 1.19 -fold higher in the CVF cohort than in the non-CVF cohort (4.82 vs. 4.06 per 10,000 person-years), with an adjusted HR (aHR) of 1.20 (95% CI = 1.02-1.42) (Table 2). The aHR of AD among women was significantly higher in the CVF cohort than in the non-CVF cohort (aHR = 1.40, 95%

CI = 1.10-1.79). The age-specific relative hazard of AD in the CVF cohort was higher than that in the non-CVF cohort for age ≤ 49 group. The relative hazard of AD was higher in the CVF cohort than in the non-CVF cohort for patients without comorbidities (aHR = 1.35, 95% CI = 1.02–1.77). In all stratifications, the risk of CHF, pneumonia, and ARDS remained higher in the CVF cohort than in the non-CVF cohort.

Table 2. Incidence and adjusted hazard ratio of outcome by sex, age and comorbidity for clinical vertebral fracture patients compared to controls

Variables	Clinical vertebral fracture						Compared to Control	
	Yes			No				
	Events n	PY	Rate#	Events n	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
Aortic dissection								
All	291	603307	4.82	255	628390	4.06	1.19(1.01, 1.41)*	1.20(1.02, 1.42)*
Gender								
Female	152	329203	4.62	111	341326	3.25	1.42(1.11, 1.82)**	1.40(1.10, 1.79)**
Male	139	274104	5.07	144	287063	5.02	1.01(0.80, 1.27)	1.04(0.82, 1.31)
P for interaction								0.049
Age, years								
≤49	20	237557	0.84	9	236602	0.38	2.21(1.01, 4.86)*	2.22(1.01, 4.88)*
50-64	43	142476	3.02	33	146642	2.25	1.35(0.86, 2.12)	1.32(0.84, 2.08)
≥65	228	223274	10.2	213	245146	8.69	1.18(0.98, 1.43)	1.16(0.97, 1.40)
P for interaction								0.41
Comorbidity§								
No	92	432848	2.13	121	422004	2.87	1.35(1.03, 1.77)*	1.35(1.02, 1.77)*
Yes	163	195541	8.34	170	181303	9.38	1.13(0.91, 1.40)	1.12(0.90, 1.38)
P for interaction								0.31
Congestive heart failure								

All	6997	589382	118.7	5529	617386	89.6	1.33(1.28, 1.37)***	1.35(1.30, 1.40)***
Gender								
Female	4781	319413	149.7	3731	333763	111.8	1.34(1.28, 1.40)***	1.33(1.27, 1.39)***
Male	2216	269969	82.1	1798	283622	63.4	1.29(1.21, 1.38)***	1.38(1.30, 1.47)***
P for interaction								0.38
Age, years								
≤49	244	236960	10.3	151	236214	6.39	1.61(1.31, 1.97)***	1.62(1.32, 1.99)***
50-64	760	140709	54.0	596	145151	41.1	1.32(1.19, 1.47)***	1.31(1.18, 1.46)***
≥65	5993	211713	283.1	4782	236020	202.6	1.40(1.35, 1.46)***	1.38(1.33, 1.44)***
P for interaction								0.47
Comorbidity§								
No	2177	417566	52.1	1564	429827	36.4	1.43(1.34, 1.53)***	1.41(1.32, 1.51)***
Yes	4820	171816	280.5	3965	187559	211.4	1.33(1.28, 1.39)***	1.31(1.26, 1.37)***
P for interaction								0.06
Follow-up period								
<5 years	5193	194850	266.5	3753	197188	190.3	1.40(1.34, 1.46)***	1.34(1.29, 1.40)***
≧5 years	1804	176596	102.2	1776	188594	94.2	1.09(1.02, 1.16)*	1.19(1.11, 1.27)***
Pneumonia								
All	16226	573845	282.8	11179	608895	183.6	1.54(1.50,1.58)***	1.57(1.54, 1.61)***
Gender								
Female	8931	312978	285.4	6273	330078	190.1	1.50(1.46, 1.55)***	1.49(1.44, 1.54)***
Male	7295	260866	279.7	4906	278818	176.0	1.58(1.53, 1.64)***	1.68(1.62, 1.74)***
P for interaction								0.02
Age, years								
≤49	1526	232820	65.5	588	235046	25.0	2.62(2.38, 2.88)***	2.53(2.30, 2.78)***
50-64	2076	137694	150.8	1365	143617	95.0	1.59(1.48, 1.70)***	1.58(1.48, 1.69)***
≥65	12624	203330	620.9	9226	230233	400.7	1.56(1.52, 1.60)***	1.53(1.49, 1.57)***
P for interaction								<0.001
Comorbidity§								
No	6589	408667	161.2	3782	425656	88.9	1.82(1.75, 1.89)***	1.74(1.67, 1.81)***
Yes	9637	165178	583.4	7397	183239	403.7	1.45(1.40, 1.49)***	1.45(1.41, 1.50)***
P for interaction								<0.001
Follow-up period								
<5 years	4335	194479	222.9	2959	197003	150.2	1.49(1.42, 1.56)***	1.40(1.34, 1.47)***
≧5 years	266	169126	157.4	2570	148161	139.6	1.13(1.07, 1.20)***	1.28(1.21, 1.35)***
Acute respiratory distress syndrome								
All	550	603537	9.11	263	628708	4.18	2.18(1.88, 2.52)***	2.20(1.90, 2.55)***

Gender								
Female	260	329305	7.90	118	341422	3.46	2.29(1.84, 2.84)***	2.25(1.81, 2.80)***
Male	290	274232	10.6	145	287285	5.05	2.09(1.72, 2.56)***	2.15(1.76, 2.62)***
P for interaction								0.57
Age, years								
≤49	75	237516	3.16	20	236607	0.85	3.74(2.28, 6.12)***	3.52(2.15, 5.78)***
50-64	63	142550	4.42	39	146664	2.66	1.67(1.12, 2.48)*	1.65(1.10, 2.45)*
≥65	412	223472	18.4	204	245437	8.31	2.23(1.89, 2.64)***	2.19(1.85, 2.60)***
P for interaction								0.15
Comorbidity§								
No	231	422088	5.47	96	432950	2.22	2.47(1.95, 3.13)***	2.40(1.89, 3.05)***
Yes	319	181449	17.6	167	195758	8.53	2.06(1.71, 2.49)***	2.06(1.71, 2.49)***
P for interaction								0.25

PY, person-years; Rate#, incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio;
Adjusted HR†: adjusted hazard ratio controlling for age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, COPD, and CCI score
Comorbidity§: Patients with any one of the comorbidities hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD were classified as the comorbidity group
*p<0.05, **p<0.01, ***p<0.001

Compared with patients without CVF, the risk of AD was 1.32-fold (95% CI = 1.10-1.58) higher in CVF-lumbar patients and was 1.22-fold (95% CI = 1.03-1.45) higher in CVF patients without SCI (Table 3). The risk of CHF and pneumonia remained higher in patients with various levels of CVF than in patients without CVF. Table 3 also shows that patients with various levels of CVF, except for those with sacrum or coccyx fractures, had a significantly higher risk of ARDS than did patients without CVF.

Table 3. Comparisons of Incidence, and Hazard Ratios of outcome by subtypes of clinical vertebral fracture

Variables	N	Event	Rate[#]	Crude HR (95% CI)	Adjusted HR[†] (95% CI)
Aortic dissection					
No vertebral fracture	108935	255	4.06	1(Reference)	1(Reference)
Cervical spine	9938	12	2.10	0.52(0.29, 0.92)*	0.86(0.48, 1.55)
Thoracic	32205	96	5.66	1.40(1.11, 1.77)**	1.18(0.93, 1.49)
Lumbar	70723	225	5.77	1.42(1.19, 1.70)***	1.32(1.10, 1.58)***
Sacrum and coccyx	7523	6	1.25	0.30(0.14, 0.68)**	1.01(0.44, 2.28)
Without SCI	98984	270	4.98	1.23(1.04, 1.46)*	1.22(1.03, 1.45)**
With SCI	13209	30	3.65	0.89(0.61, 1.30)	1.05(0.71, 1.53)
Congestive heart failure					
No vertebral fracture	108935	5529	89.6	1(Reference)	1(Reference)
Cervical spine	9938	283	50.1	0.56(0.50, 0.63)***	1.39(1.23, 1.57)***
Thoracic	32205	2729	166.5	1.86(1.78, 1.95)***	1.43(1.37, 1.50)***
Lumbar	70723	5083	133.8	1.49(1.44, 1.55)***	1.38(1.33, 1.43)***
Sacrum and coccyx	7523	150	31.4	0.35(0.30, 1.41)***	1.35(1.14, 1.59)***
Without SCI	98984	6410	121.2	1.35(1.30, 1.40)***	1.34(1.30, 1.39)***
With SCI	13209	854	106.2	1.18(1.10, 1.27)***	1.49(1.39, 1.61)***
Pneumonia					
No vertebral fracture	108935	11179	183.6	1(Reference)	1(Reference)
Cervical spine	9938	1135	208.7	1.14(1.07, 1.21)***	2.22(2.08, 2.36)***
Thoracic	32205	5718	358.3	1.96(1.90, 2.02)***	1.59(1.54, 1.64)***
Lumbar	70723	11338	306.5	1.67(1.63, 1.71)***	1.56(1.52, 1.60)***
Sacrum and coccyx	7523	451	96.2	0.52(0.47, 0.57)***	1.77(1.60, 1.94)***
Without SCI	98984	14645	284.0	1.55(1.51, 1.58)***	1.55(1.52, 1.59)***
With SCI	13209	2265	293.5	1.59(1.52, 1.67)***	1.92(1.83, 2.00)***
Acute respiratory distress syndrome					
No vertebral fracture	108935	263	4.18	1(Reference)	1(Reference)
Cervical spine	9938	52	9.10	2.17(1.61, 2.93)***	3.35(2.45, 4.58)***
Thoracic	32205	195	11.5	2.76(2.29, 3.32)***	2.35(1.95, 2.83)***
Lumbar	70723	369	9.46	2.26(1.93, 2.65)***	2.09(1.79, 2.45)***
Sacrum and coccyx	7523	10	2.08	0.49(0.26, 0.93)*	1.47(0.77, 2.79)
Without SCI	98984	482	8.89	2.13(1.83, 2.47)***	2.12(1.82, 2.46)***
With SCI	13209	91	11.1	2.63(2.07, 3.34)***	2.97(2.33, 3.78)***

Rate[#], incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio;

Adjusted HR†: adjusted hazard ratio controlling for age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, COPD, and CCI score ICD-9-CM: Cervical spine: 805.0-805.18, 806.0-806.19; Thoracic: 805.2, 805.3, 806.2-806.39; Lumbar: 805.4, 805.5, 806.4, 806.5; Sacrum and coccyx: 805.6, 805.7, 806.6-806.79; SCI involved or Not: Without SCI: 805-805.9 & With SCI: 806-806.9 *p<0.05, **p<0.01, ***p<0.001

Figures 2A–2D show that the CVF cohort had a significantly higher cumulative proportion of AD (P = 0.001; Figure 2A), CHF (P < 0.001; Figure 2B), pneumonia (P < 0.001; Figure 2C), and ARDS (P < 0.001; Figure 2D) than did the non-CVF cohort.

Discussion

To the best of our knowledge, this is the first population-based, longitudinal cohort study to focus on the correlation between CVF and the subsequent risks of specific cardiopulmonary diseases. The main results demonstrated that CVF is significantly associated with an increased risk of several specific cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS. In our study, patients older than 65 years and females accounted for the majority of participants. The incidence and prevalence of vulnerable fractures, accompanied with population aging and subsequent frequently occurring home accidents, are steadily rising[36]. In addition, CVF in women is constantly a consequence of postmenopausal bone loss[5 7 8]. According to recent studies, the prevalence of women older than 50 years who

experienced at least one CVF event was 23% - 26%, which was higher than that of men (21.5%)[37 38]. It is noteworthy that young adults aged ≤ 49, though represented the minority of CVF patients, bore a significant heightened risk of developing adverse cardiopulmonary outcomes. We speculate that CVF could have more prominent influence on the outcome diseases without the interaction of multiple potential comorbidities and unknown confounders. Moreover, CVF is less frequent in a young, healthy population; it could be more severe, especially for hospitalized trauma victims and therefore, strengthening the correlations between the investigated diseases.

AD represents a complicated, life-threatening emergency and is associated with high morbidity and mortality[39 40]. In our analysis, with or without CVF, the incidence of AD was higher in men, elderly patients older than 65 years, and those with coexisting comorbidities; this finding is in line with previous epidemiological investigations[39-41]. Notably, most studies examining the incidence of AD have been confined to specific geographic regions or focused on inpatients; thus, the true incidence is hard to be reflected[39]. Moreover, compared with patients without CVF, CVF patients, especially female patients, younger population (age ≤49) and those without comorbidities, bore a higher risk of subsequent AD development. Studies that have focused on this correlation are scarce, and the current literature describes only a few cases of aortic injury following thoracolumbar spine fractures in polytrauma

victims[42-46]. Interestingly, prior studies have provided evidence for the strong correlation between abdominal aortic calcifications and poor bone health with major fragility fracture[47 48]. With the progressive destruction of intima-media layer accompanied with new bone-like tissue deposition in the aortic wall, aneurysm or dissection might tend to occur. Other potential explanations we suppose include the intractable pain induced by fractures, accompanied with increments in sympathetic tone, stress, hypertension, and the impact on the vascular wall, as well as an unfavorable sedentary life style could all contribute to the formation of AD.

Our study indicated one counterintuitive result that women bore a higher overall incidence of CHF than men did. However, previous investigations of sex-specific epidemiology of CHF have demonstrated that women with atrial fibrillation have a higher incidence of heart failure with preserved ejection fraction, especially in very old age compared with men[49-51]. In this study, CVF was associated with an increased risk of CHF, and the results remained statistically significant across various age and sex strata, as well as with or without comorbidities. In a cross-sectional analysis, Lyons et al.[52] demonstrated that more than one-tenth of heart failure patients had radiologic recognizable vertebral fracture, and among those, multiple vertebral fractures accounted for one half, indicating the close correlation between these two diseases. Moreover, Sennerby et al.[53] conducted a twin population study and proposed

that specific genes involved in cellular mechanisms that shared by the vasculature and bone might connect the close relationship between cardiovascular diseases and fractures. Additionally, the most common etiology of CVF, osteoporosis, together with CHF, are conventionally deemed to be independent diseases. However, recent investigations have indicated that the two diseases share common risk factors, including advantaged age, female sex, hypovitaminosis D, renal insufficiency, diabetes, and a smoking habit, as well as the same etiologic mechanisms, including activation of the renin-angiotensin-aldosterone system, hypersecretion of parathyroid hormones, and oxidative / nitrosative stress[21 52 54-57]. In a meta-analysis, Veronese et al.[58] provided evidence that low bone mineral density and fractures were modestly associated with increased risk of cardiovascular diseases. The authors speculated that alterations in signaling pathways of bone remodeling and arterial calcifications, low-grade inflammation, higher prevalence of vascular calcifications, and low estrogen levels could all contributed to the higher cardiovascular risk. Indeed, diffuse vascular calcifications which is strongly associated with bone loss, including abdominal aorta and coronary arteries, could result in a higher afterload on the left ventricle, leading to subsequent left ventricular hypertrophy and finally, congestive heart failure[47 48]. Furthermore, unfavorable outcomes following fracture, including a loss of functional and social activities, dependency with poor quality of life, higher

serum cortisol levels accompanied with depressive disorder, higher inflammatory markers, lower drug and diet compliance, a sedentary life style, and arrhythmia or cardiac ischemic events caused by high sympathetic activity, might all contribute to the deterioration of heart function[55 59].

Our study results reveal that patients with CVF bore a significantly heightened risk of subsequent pneumonia and ARDS across all strata of age and sex and irrespective of the presence of comorbidities. Further analyses demonstrated the strongest correlation between cervical CVF combined with SCI and risks of pneumonia and ARDS. In a 2-year retrospective multicenter trauma registry analysis, Fletcher et al.[60] noted that 16% of elderly patients older than 65 years with cervical spine trauma ultimately developed pneumonia. Other studies have revealed the incidence of pulmonary complications following cervical spine trauma to be 35% - 95%[61 62], and among these complications, the most common type was pneumonia and atelectasis, although ARDS was the most severe type and represented the predominant contributor to morbidity and mortality[63-65]. There are several possible explanations. First, deformity of the vertebral body or even kyphosis might decrease the lung capacity and therefore impair the pulmonary function. Prior studies have indicated that a single vertebral fracture would decrease the predicted forced vital capacity by 9%, increase the risk of restrictive lung disease, and lead to a 3-fold risk of mortality[1]

[2 66]. Harrison et al.[67] conducted a systemic review of 4 case-control studies and reported that women with osteoporotic vertebral fractures or kyphosis were associated with decreased predicted vital capacity, as well as total lung capacity. Furthermore, Krege et al.[68] estimated that spine fracture burden was correlated with reduced lung volume, but not flow; indicating that spine fracture burden is linked with restrictive, but not obstructive lung disease. The authors further concluded that patients with marginally compensated pulmonary function may not tolerate the superimposed lung restrictive change resulting from vertebral fractures and thus, leading to a further compromised pulmonary function and subsequent lung diseases. Second, cervical CVF combined with SCI might cause paralysis of the diaphragm and hypoactivity of the respiratory accessory muscles, which results in hypoventilation. In addition, the imbalance of sympathetic-parasympathetic interactions would result in an elevated airway tone, bronchorrhea, and poor clearance, which are all associated with the development of various pulmonary complications[69 70]. Third, Chen et al.[69] proposed that in upper cervical spine trauma and SCI patients, hypoalbuminemia would not only indicate nutrition status but would also impair the function of respiratory muscles, leading to respiratory complications. However, additional investigations are necessary for verification before definite conclusions are established. Fourth, patients with SCI are prone to develop aspiration and subsequent pulmonary infection due to impaired

neuromuscular transmission. Finally, similar to rib fractures, worsening pain related to CVF might impair cough and secretion clearance, leading to atelectasis and subsequent lung infection[22].

The major strength of our study is sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, and stable outcomes could be achieved with such adequate, representative samples. However, the inevitable limitations should be discussed. First, all disease definitions and sample selection in our study were based on the ICD-9-CM coding, which has been rigorously scrutinized and peer-reviewed by clinical physicians, the declaration unit of medical institutions and finally the NHI administration. However, miscoding or misclassification might still exist, although it is considered rare. Similarly, diagnostic criteria applied, as well as physician's ability to diagnose the investigated diseases might vary among different hospitals and areas. Second, retrospective dataset analysis results cannot be used to determine causal relationships. Third, several crucial variables could not be obtained from our dataset, including family history, education and socioeconomic status, information of life style and physical activity, body weight, smoking habits, disease severity, laboratory results, radiologic reports, and estimated pain scores, which are potential confounders that might have affected the results. Fourth, a considerable portion of vertebral fracture patients with slight or no symptoms might not have been

diagnosed or might have even been overlooked in clinical settings; thus, the true incidence of CVF and the inferred association between CVF and cardiopulmonary diseases could be underestimated. Fifth, patients with CVF might have one or more overlapping etiologies include osteoporosis, trauma and malignancies, etc. Therefore, it was technically infeasible to simply divide the CVF patients into several subgroups for sub-analysis based on the coding of etiologies. Sixth, our sampled participants were retrieved from NHIRD from January 1, 2000, to December 31, 2010. Aging property of the data might not truly reflect the current medical conditions. Finally, because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Conclusion

In conclusion, our study results support the hypothesis that CVF is associated with subsequent risks of AD, CHF, pneumonia, and ARDS. Future studies are warranted to delineate the actual pathophysiologic mechanisms underlying this correlation and to develop optimal strategies for reducing the heath care burden of CVF and its complications. Based on our results, we suggest that patients with CVF should be targeted for further screening and preventive interventions for cardiopulmonary diseases.

Abbreviations:

CVFs: clinical vertebral fractures; AD: aortic dissection; CHF: congestive heart failure; ARDS: acute respiratory distress syndrome; NHIRD: National Health Insurance Research Database; NHI: National Health Insurance; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; SCI: spinal cord injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; aHRs: adjusted hazard ratios; CI: confidence interval; SD: standard deviation.

Declarations:

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Ethics approval and consent to participate

This study was approved by the Ethics Review Board of China Medical University and Hospital, Taiwan (CMUH-104-REC2-115). The IRB waived the consent requirement.

Availability of data and materials

Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Owing to the Personal Information Protection Act, these cannot be made publicly available (http://nhird .nhri.org.tw).

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

The authors' individual contributions are outlined as follows. Conception and design: F-Y.L. and T.-Y.Y. Administrative support: T.-Y.Y. Data collection and organization: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Data analysis and interpretation: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Manuscript writing: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Final approval of the manuscript: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L.

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Figure Legends

Figure 1. Derivation of our study cohort

Figure 2. Cumulative incidence of aortic dissection (A), congestive heart failure (B), pneumonia (C) and acute respiratory distress syndrome (D) in patients with clinical vertebral fracture and comparison patients

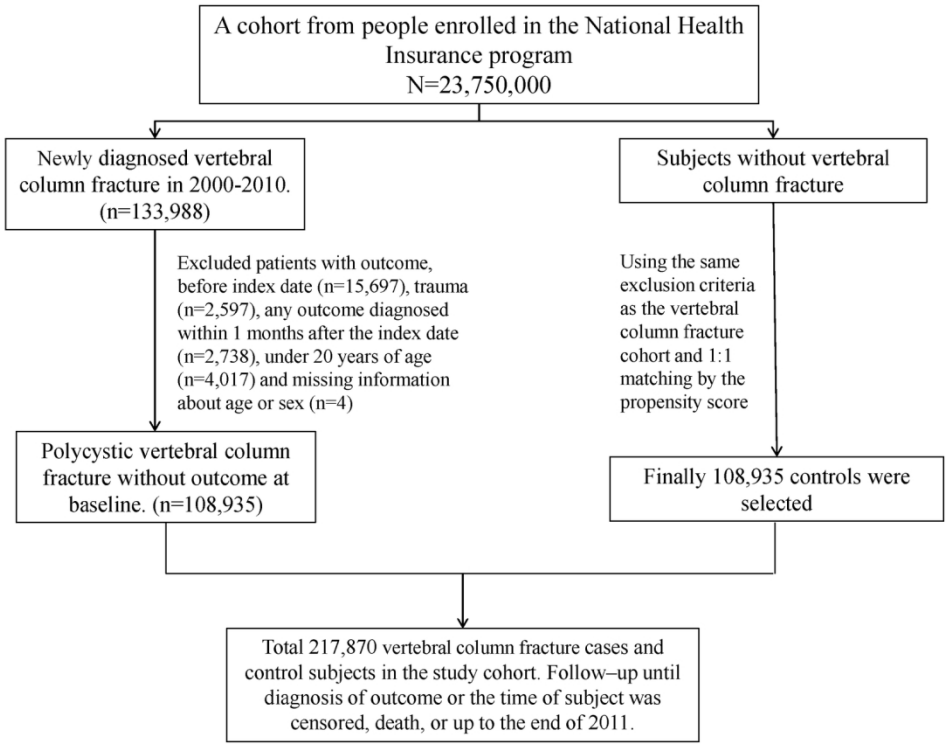

Figure 1. Derivation of our study cohort

146x109mm (300 x 300 DPI)

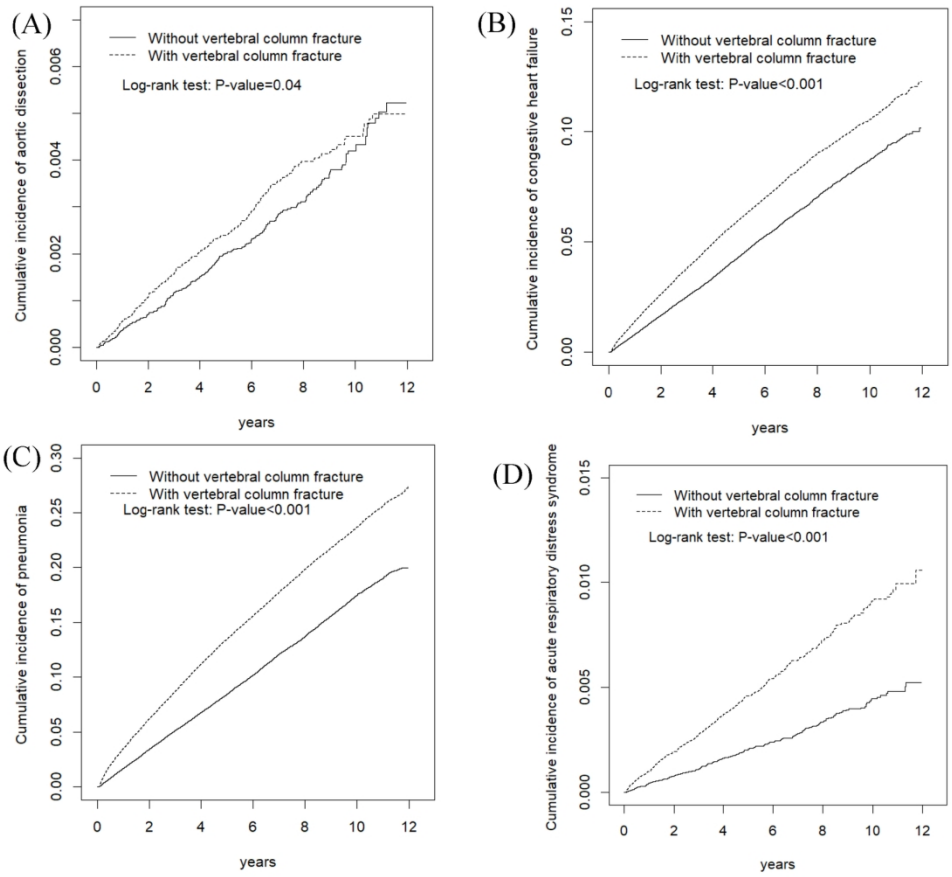

Figure 2. Cumulative incidence of aortic dissection (A), congestive heart failure (B), pneumonia (C) and acute respiratory distress syndrome (D) in patients with clinical vertebral fracture and comparison patients

160x141mm (300 x 300 DPI)

Supplemental Table 1. Summary of the ICD-9-CM codes used for disease definition and their matching diseases

Diseases	ICD-9-CM codes
Clinical vertebral fracture (CVF)	805, 806
Cervical spine CVF	805.0-805.18, 806.0-806.19
Thoracic spine CVF	805.2, 805.3, 806.2-806.39
Lumbar spine CVF	805.4, 805.5, 806.4, 806.5
Sacrum plus coccyx CVF	805.6, 805.7, 806.6-806.79
CVF without spinal cord injury (SCI)	805-805.9
CVF with spinal cord injury (SCI)	806-806.9
Aortic dissection (AD)	441.0, 441.00, 441.01, 441.02, 441.03
Congestive heart failure (CHF)	428
Pneumonia	480-488
Acute respiratory distress syndrome (ARDS)	518.82, 518.5
Comorbidities	
Hypertension	401–405
Diabetes mellitus	250
Hyperlipidemia	272
Atrial fibrillation	427.31
Chronic kidney disease	580-589
Chronic obstructive pulmonary disease	491,492,496

*Defined by administration code. ICD-9-CM, Clinical Modification of ICD-9.

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Risk of Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome in Patients with Clinical Vertebral Fracture: A Nationwide Population-based Cohort Study in Taiwan

Running title: Clinical Vertebral Fracture and Aortic Dissection, Congestive Heart Failure, Pneumonia, and Acute Respiratory Distress Syndrome Risks

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Abstract

Objective: Studies on the association between clinical vertebral fractures (CVFs) and the subsequent risk of cardiopulmonary diseases, including aortic dissection (AD), congestive heart failure (CHF), pneumonia, and acute respiratory distress syndrome (ARDS), are scarce. Therefore, we used the National Health Insurance Research Database to investigate whether patients with CVF have a heightened risk of subsequent AD, CHF, pneumonia and ARDS.

Design: The National Health Insurance Research Database was used to investigate whether patients with CVFs have an increased risk of subsequent AD, CHF, pneumonia, and ARDS.

Participants: This cohort study comprised patients aged ≥ 18 years with a diagnosis of CVF and were hospitalized at any point during 2000–2010 (n = 108,935). Each CVF patient was frequency-matched to a no-CVF hospitalized patients based on age, sex, index year and comorbidities (n = 108,935). The Cox proportional hazard regressions model was used to estimate the adjusted effect of CVF on AD, CHF, pneumonia, and ARDS risk.

Results: The overall incidence of AD, CHF, pneumonia, and ARDS was higher in the CVF group than in the no-CVF group (4.85 versus 3.99, 119.1 versus 89.6, 283.3 versus 183.5, and 9.18 versus 4.18/10,000 person-years, respectively). After

adjustment for age, sex, comorbidities, and Charlson comorbidity index score, patients with CVF had a 1.23-fold higher risk of AD (95% CI = 1.03-1.45), 1.35-fold higher risk of CHF (95% CI = 1.30-1.40), 1.57-fold higher risk of pneumonia (95% CI = 1.54-1.61), and 2.21-fold higher risk of ARDS (95% CI = 1.91-2.57) than did those without CVF. Patients with cervical CVF and SCI were more likely to develop pneumonia and ARDS.

Conclusions: Our study demonstrates that CVFs are associated with an increased risk of subsequent cardiopulmonary diseases. Future investigations are encouraged to delineate the mechanisms underlying this association.

Strengths and limitations of this study:

1. This is the first population-based, longitudinal cohort study to focus on the correlation between CVF and the subsequent risks of specific cardiopulmonary diseases.

2. By sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, stable outcomes could be achieved with such adequate, representative samples.

3. All disease definitions and sample selection in our study were based on the ICD-9-CM coding. Therefore, miscoding or misclassification might exist, although it is considered rare.

4. In our study, sampled participants were retrieved from NHIRD from January 1, 2000, to December 31, 2010. Aging property of the data might not truly reflect the current medical conditions.

5. Because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Keywords: Clinical Vertebral fracture, aortic dissection, congestive heart failure, pneumonia, acute respiratory distress syndrome, National Health Insurance Research Database.

Introduction

Clinical Vertebral fractures (CVFs) constitute a major healthcare burden worldwide because of its high incidence and strong influence on individuals' quality of life, medical resource consumption, and direct or potential unfavorable impacts on socioeconomic development[1-3]. Approximately 1.4 million new cases of CVF are diagnosed globally every year[4], and among these, osteoporosis, trauma, and malignancy are the major etiologies[5-9]. Acute aortic dissection (AD) remains the major life-threatening vascular emergency, with a steadily increasing incidence because of population aging and the explosive growth of radiologic technology[10-12]. Without early recognition and timely treatment, the prognosis of AD would be extremely poor, and half the patients would die within 48 h[10]. Congestive heart failure (CHF) is the major cause of hospitalization in old age, with more than 650,000 new cases confirmed annually in the United States, and more than 1 million people were hospitalized for decompensated CHF, resulting in costs exceeding 39 billion[13-15]. Pneumonia is one of the most common infectious diseases in elderly adults and is also the leading cause of death in Americans older than 65 years[16 17]. Acute respiratory distress syndrome (ARDS) is a complex syndrome characterized by diffuse hydrostatic pulmonary edema, alveoli damage, and persistent hypoxemia, which are mainly triggered by infection, inflammation, trauma, or other etiologies. The

in-hospital mortality rate for this condition could reach 40% even when managed with the standardized lung protective ventilator strategy[18 19].

Studies have demonstrated that elderly patients with a history of osteoporotic vertebral fracture have an increased risk of cardiovascular events, including stroke (ischemic or hemorrhagic) and coronary heart disease[20-23]. Recently, Kim et al.[24] reported an association between isolated CVF and future development of pneumonia in women with low bone density. In addition, chronic, worsened and longstanding backache accompanied with CVF might result in a long-term increase of sympathetic tone, fatigue, stress reaction, low physical activity, depressive tendency, diminished pulmonary function, and, consequently a poor quality of life, which might be correlated with cardiopulmonary disease risk[3 5 7 8 25]. Therefore, we hypothesized that an association exists between CVF and the risk of cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS. Accordingly, we conducted a nationwide, population-based data analysis to verify this hypothesis and tried to provide essential evidence-based information for clinical practice.

Methods

Data Source

This retrospective cohort study used datasets from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National

Health Insurance (NHI) program in March 1995, and 99% of the 23.74 million residents were enrolled[26]. The details of the NHIRD and NHI program are well presented in previous studies[27-33]. The NHIRD records diseases according to International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Validation of the NHIRD with cardiovascular diseases were investigated and appeared to be a valid resource for population research[34-37]. This study was approved by the Institutional Review Board of China Medical University (CMUH-104-REC2-115).

Sampled Participants

Patients aged ≥18 years with newly diagnosed CVF (ICD-9-CM codes, 805 and 806) from January 1, 2000, to December 31, 2010, were identified as the CVF cohort. Study subjects with the diagnosis of vertebral fracture from 1996-1999 were excluded at the baseline. The location of CVF was defined in two ways as follows: (1) cervical spine (ICD-9-CM codes, 805.0-805.18 and 806.0-806.19), thoracic spine (ICD-9-CM codes, 805.2, 805.3, and 806.2-806.39), lumbar spine (ICD-9-CM codes, 805.4, 805.5, 806.4, and 806.5), and sacrum plus coccyx (ICD-9-CM codes, 805.6, 805.7, and 806.6-806.79) and (2) without spinal cord injury (SCI) (ICD-9-CM codes, 805-805.9), and with SCI (ICD-9-CM codes, 806-806.9). The date of first-time CVF diagnosis at admission was defined as the index date. Participants with prior AD (ICD-9-CM codes, 441.0, 441.00, 441.01, 441.02, and 441.03), CHF (ICD-9-CM code, 428),

pneumonia (ICD-9-CM codes, 480-488), and ARDS (ICD-9-CM codes, 518.82 and 518.5) before 1999 and before the index date (n=15,697); with the diagnosis of trauma (ICD-9-CM codes, 800-959 except 805-806) during the same period (n=2,597); with any outcome event (AD, CHF, pneumonia, and ARDS) diagnosed within 1 month after the index date (n=2,738); those under 18 years of age (n=4,017); and those with missing information about age or sex (n=4) in both the CVF and no-CVF cohorts; were excluded. For each CVF patient, a no-CVF participant was frequency-matched by the index year of CVF diagnosis, age (every 5-year span), sex, and comorbidities of diabetes (ICD-9-CM code, 250), hypertension (ICD-9-CM codes, 401-405), hyperlipidemia (ICD-9-CM code, 272), atrial fibrillation (ICD-9-CM code, 427.31), chronic kidney disease (CKD; ICD-9-CM codes, 580-589), and chronic obstructive pulmonary disease (COPD; ICD-9-CM codes, 491, 492, and 496) (Figure 1). Coexisting comorbidities were identified before the index date, with at least one time of principal or secondary diagnoses documented in hospitalizations during the period 2000 to 2010. We have also added Charlson comorbidity index (CCI) score as a confounding factor. Summary of ICD-9-CM codes applied for disease definition are presented in online supplementary table 1.

Outcome

The main outcome was hospitalization with a new diagnosis of AD, CHF,

pneumonia, or ARDS during the follow-up period. Both the CVF and no-CVF cohorts were followed up until the diseases appeared or they were censored because of loss to follow-up, death, or the end of December 31, 2010, whichever occurred first.

Statistical analysis

A chi-square test and Student's *t*-test were used to evaluate the differences in the distribution of categorical and continuous variables, respectively, between the CVF and no-CVF cohorts. The overall, sex-, age-, and comorbidity-specific incidence densities of AD, CHF, pneumonia, and ARDS were estimated for each cohort. To address the concern of constant proportionality, we examined the proportional hazard model assumption using a test of scaled Schoenfeld residuals. The results showed that there was no significant relationship between Schoenfeld residuals for CVF and follow-up time (p-value = 0.06) in the model evaluating the AD risk and Schoenfeld residuals for CVF and follow-up time (p-value = 0.18) in the model evaluating the ARDS risk. In the model evaluating the CHF and pneumonia risk throughout overall follow-up period, the results of the test revealed a significant relationship between Schoenfeld residuals for CVF and follow-up time, suggesting the proportionality assumption was violated. The relative risks of AD, CHF, pneumonia, and ARDS in the CVF cohort compared with the no-CVF cohort were analyzed using univariable and multivariable Cox proportional hazard regression models and presented as hazard ratios (HRs) and 95% confidence intervals (CIs). The multivariable models were

simultaneously adjusted for age, sex, and comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD. We further tested the interaction between gender and VCF; between age and VCF; and between comorbidity and VCF by including a cross-product term in the model. Further analysis was performed to assess whether the association of CVF with AD, CHF, pneumonia, and ARDS varied according to the levels of CVF. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA), and we set the significance level at less than 0.05 for two-sided testing of P-values.

Patient and public involvement

There was no patient or public involvement in this study.

Results

Demographics and comorbidity

In this study, 108,935 CVF patients and 108,935 matched no-CVF participants with similar distributions of age, sex, and comorbidities were assessed (Table 1). In the CVF cohort, ≥ 44.3% of patients were aged ≥ 65 years, and 55.3% of the patients were women (Table 1). The mean age of the patients was 58.8 ± 18.8 years in the CVF cohort and 58.3 ± 18.8 years in the no-CVF cohort. Both cohorts had a medical history of hypertension (26.0%), diabetes (15.2%), COPD (5.3%), hyperlipidemia (5.2%), atrial fibrillation (1.2%), and CKD (3.5%). Patients of CVF cohort were more

prevalent with CCI than no-CVF cohort.

Table 1. Comparison of demographics and comorbidity between clinical vertebral fracture patients and controls

	Clinical vertebral fracture		
	Yes (N=108935) n(%)	No (N=108935) n(%)	*p*-value
Age, years[&]			0.99
≤49	36313(33.3)	36310(33.3)	
50-64	24341(22.3)	24345(22.4)	
≥65	48281(44.3)	48280(44.3)	
Mean (SD) [†]	58.8(18.8)	58.3(18.8)	<0.001
Gender[&]			0.99
Female	60216(55.3)	60218(55.3)	
Male	48719(44.7)	48717(44.7)	
Comorbidity[&]			
Hypertension	28339(26.0)	28338(26.0)	0.99
Diabetes	16553(15.2)	16554(15.2)	0.99
Hyperlipidemia	5692(5.2)	5695(5.2)	0.98
Atrial fibrillation	1381(1.2)	1377(1.2)	0.94
CKD	3810(3.5)	3814(3.5)	0.96
COPD	5865(5.3)	5867(5.3)	0.98
CCI score[&]			<0.001
0	77930(71.5)	82878(76.1)	
1	17489(16.1)	15662(14.4)	
2	7079(6.5)	5378(4.9)	
3 or more	6437(5.9)	5017(4.6)	

[&]Chi-square test examined categorical data; [†]T-test examined continuous;

Primary outcomes

Overall, the incidence of AD was 1.22 -fold higher in the CVF cohort than in the no-CVF cohort (4.85 vs. 3.99 per 10,000 person-years), with an adjusted HR (aHR) of

1.23 (95% CI = 1.03-1.45) (Table 2). The aHR of AD among women was significantly higher in the CVF cohort than in the no-CVF cohort (aHR = 1.40, 95% CI = 1.09-1.79). The age-specific relative hazard of AD in the CVF cohort was higher than that in the no-CVF cohort for age ≤ 49 group. The relative hazard of AD was higher in the CVF cohort than in the no-CVF cohort for patients without comorbidities (aHR = 1.38, 95% CI = 1.04–1.83). In all stratifications, the risk of CHF, pneumonia, and ARDS remained higher in the CVF cohort than in the no-CVF cohort.

Table 2. Incidence and adjusted hazard ratio of outcome by sex, age and comorbidity for clinical vertebral fracture patients compared to controls

Variables	Clinical vertebral fracture						Compared to Control	
	Yes			No				
	Events n	PY	Rate#	Events n	PY	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
Aortic dissection								
All	286	589915	4.85	245	614133	3.99	1.22(1.02, 1.44)*	1.23(1.03, 1.45)*
Gender								
Female	149	322213	4.62	109	333909	3.26	1.42(1.11, 1.82)**	1.40(1.09, 1.79)**
Male	137	267703	5.12	136	280224	4.85	1.05(0.83, 1.33)	1.08(0.85, 1.37)
P for interaction								0.09
Age, years								
≤49	19	230604	0.82	8	229738	0.35	2.37(1.04, 5.40)*	2.37(1.03, 5.41)*
50-64	43	139107	3.09	30	143099	2.10	1.48(0.93, 2.36)	1.45(0.91, 2.31)
≥65	224	220204	10.2	207	241296	8.58	1.19(0.99, 1.44)	1.17(0.97, 1.42)
P for interaction								0.29
Comorbidity§								
No	117	411117	2.85	86	421520	2.04	1.40(1.06, 1.85)*	1.38(1.04, 1.83)*

Yes	169	178798	9.45	159	192612	8.25	1.15(0.92, 1.42)	1.14(0.91, 1.41)
P for interaction								0.28
Congestive heart failure								
All	6866	576513	119.1	5411	603639	89.6	1.33(1.28, 1.38)***	1.35(1.30, 1.40)***
Gender								
Female	4689	312775	149.9	3649	326705	111.7	1.34(1.29, 1.40)***	1.33(1.27, 1.39)***
Male	2177	263738	82.5	1762	276934	63.6	1.30(1.22, 1.38)***	1.38(1.30, 1.47)***
P for interaction								0.38
Age, years								
≤49	233	230058	10.1	142	229391	6.19	1.63(1.33, 2.01)***	1.64(1.33, 2.03)***
50-64	733	137433	53.3	577	141714	40.7	1.31(1.18, 1.47)***	1.31(1.17, 1.46)***
≥65	5900	209022	282.3	4692	232533	201.8	1.41(1.35, 1.46)***	1.38(1.33, 1.44)***
P for interaction								0.51
Comorbidity§								
No	2115	406910	52.0	1508	418712	36.0	1.45(1.35, 1.54)***	1.42(1.33, 1.52)***
Yes	4751	169603	280.1	3903	184927	211.1	1.33(1.28, 1.39)***	1.31(1.26, 1.37)***
P for interaction								0.04
Follow-up period								
<5 years	5193	194850	266.5	3753	197188	190.3	1.40(1.34, 1.46)***	1.07(1.00, 1.15)*
≧5 years	1673	166386	100.6	1658	177139	93.6	1.34(1.29, 1.40)***	1.17(1.09, 1.25)***
Pneumonia								
All	15912	561694	283.3	10929	595609	183.5	1.54(1.51, 1.58)***	1.57(1.54, 1.61)***
Gender								
Female	8740	306705	285.0	6126	323229	189.5	1.50(1.46, 1.55)***	1.49(1.44, 1.53)***
Male	7172	254989	281.3	4803	272380	176.3	1.59(1.53, 1.65)***	1.68(1.62, 1.75)***
P for interaction								0.02
Age, years								
≤49	1468	226184	64.9	557	228317	24.4	2.66(2.41, 2.93)***	2.56(2.32, 2.82)***
50-64	2018	134598	149.9	1330	140288	94.8	1.59(1.48, 1.70)***	1.57(1.47, 1.69)***
≥65	12426	200912	618.5	9042	227004	398.3	1.56(1.52, 1.60)***	1.53(1.49, 1.58)***
P for interaction								<0.001
Comorbidity§								
No	6398	398499	160.6	3657	414829	88.2	1.82(1.75, 1.90)***	1.74(1.67, 1.82)***
Yes	9514	163195	583.0	7272	180780	402.3	1.45(1.41, 1.50)***	1.45(1.41, 1.50)***
P for interaction								<0.001
Follow-up period								
<5 years	11970	194479	615.5	7447	197003	378.0	1.63(1.58, 1.67)***	1.23(1.18, 1.29)***

≧5 years	3942	156975	251.1	3482	170874	203.8	1.55(1.50, 1.59)***	1.36(1.30, 1.42)***
Acute respiratory distress syndrome								
All	542	590138	9.18	257	614432	4.18	2.20(1.89, 2.55)***	2.21(1.91, 2.57)***
Gender								
Female	254	322312	7.88	115	333999	3.44	2.29(1.84, 2.85)***	2.25(1.81, 2.81)***
Male	288	267826	10.8	142	280433	5.06	2.12(1.74, 2.59)***	2.17(1.78, 2.66)***
P for interaction								0.62
Age, years								
≤49	74	230565	3.21	20	229743	0.87	3.69(2.25, 6.04)***	3.47(2.11, 5.70)***
50-64	60	139177	4.31	38	143117	2.66	1.63(1.08, 2.44)*	1.60(1.07, 2.41)*
≥65	408	220396	18.5	199	241572	8.24	2.26(1.91, 2.68)***	2.22(1.88, 2.64)***
P for interaction								0.17
Comorbidity§								
No	226	411197	5.50	93	421615	2.21	2.49(1.96, 3.18)***	2.42(1.89, 3.09)***
Yes	316	178941	17.7	164	192717	8.51	2.08(1.72, 2.51)***	2.08(1.72, 2.51)***
P for interaction								0.25

PY, person-years; Rate#, incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio;
Adjusted HR†: adjusted hazard ratio controlling for age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, COPD, and CCI score
Comorbidity§: Patients with any one of the comorbidities hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, and COPD were classified as the comorbidity group
*p<0.05, **p<0.01, ***p<0.001

Subtypes analysis

Compared with patients without CVF, the risk of AD was 1.33-fold (95% CI = 1.11-1.60) higher in CVF-lumbar patients and was 1.25-fold (95% CI = 1.05-1.48) higher in CVF patients without SCI (Table 3). The risk of CHF and pneumonia remained higher in patients with various levels of CVF than in patients without CVF. Table 3 also shows that patients with various levels of CVF, except for those with sacrum or coccyx fractures, had a significantly higher risk of ARDS than did patients

without CVF.

Table 3. Comparisons of Incidence, and Hazard Ratios of outcome by subtypes of clinical vertebral fracture

Variables	N	Event	Rate#	Crude HR (95% CI)	Adjusted HR† (95% CI)
Aortic dissection					
No vertebral fracture	108935	245	3.99	1(Reference)	1(Reference)
Cervical spine	9938	12	2.15	0.54(0.30, 0.96)*	0.92(0.51, 1.65)
Thoracic	32205	95	5.72	1.44(1.13, 1.82)**	1.20(0.95, 1.53)
Lumbar	70723	220	5.77	1.45(1.21, 1.74)***	1.33(1.11, 1.60)**
Sacrum and coccyx	7523	6	1.28	0.32(0.14, 0.72)**	1.06(0.47, 2.41)
Without SCI	98984	265	5.00	1.25(1.05, 1.49)*	1.25(1.05, 1.48)*
With SCI	13209	30	3.75	0.93(0.64, 1.37)	1.10(0.75, 1.61)
Congestive heart failure					
No vertebral fracture	108935	5411	89.6	1(Reference)	1(Reference)
Cervical spine	9938	278	50.4	0.56(0.50, 0.63)***	1.40(1.24, 1.58)***
Thoracic	32205	2678	166.6	1.86(1.78, 1.95)***	1.43(1.37, 1.50)***
Lumbar	70723	4986	134.1	1.50(1.44, 1.56)***	1.38(1.33, 1.43)***
Sacrum and coccyx	7523	144	31.0	0.35(0.29, 0.41)***	1.33(1.12, 1.57)***
Without SCI	98984	6291	121.5	1.36(1.31, 1.41)***	1.34(1.29, 1.39)***
With SCI	13209	834	106.5	1.19(1.10, 1.28)***	1.50(1.39, 1.61)***
Pneumonia					
No vertebral fracture	108935	10929	183.5	1(Reference)	1(Reference)
Cervical spine	9938	1106	208.4	1.14(1.07, 1.21)***	2.22(2.08, 2.36)***
Thoracic	32205	5617	358.8	1.96(1.90, 2.02)***	1.59(1.54, 1.64)***
Lumbar	70723	11125	307.1	1.67(1.63, 1.72)***	1.56(1.52, 1.60)***
Sacrum and coccyx	7523	437	95.7	0.52(0.47, 0.57)***	1.76(1.60, 1.94)***
Without SCI	98984	14378	284.7	1.55(1.51, 1.59)***	1.56(1.52, 1.60)***
With SCI	13209	2203	292.8	1.59(1.52, 1.67)***	1.91(1.82, 2.00)***
Acute respiratory distress syndrome					
No vertebral fracture	108935	257	4.18	1(Reference)	1(Reference)
Cervical spine	9938	52	9.33	2.23(1.65, 3.00)***	3.42(2.50, 4.68)***
Thoracic	32205	191	11.5	2.76(2.29, 3.33)***	2.35(1.94, 2.84)***
Lumbar	70723	365	9.57	2.29(1.95, 2.69)***	2.11(1.80, 2.48)***

Sacrum and coccyx	7523	10	2.13	0.51(0.27, 0.95)*	1.51(0.79, 2.87)
Without SCI	98984	478	9.02	2.16(1.85, 2.51)***	2.15(1.84, 2.50)***
With SCI	13209	87	10.9	2.58(2.03, 3.29)***	2.97(2.34, 3.78)***

Rate[#], incidence rate, per 10,000 person-years; Crude HR: relative hazard ratio; Adjusted HR[†]: adjusted hazard ratio controlling for age, sex, comorbidities of hypertension, diabetes, hyperlipidemia, atrial fibrillation, CKD, COPD, and CCI score ICD-9-CM: Cervical spine: 805.0-805.18, 806.0-806.19; Thoracic: 805.2, 805.3, 806.2-806.39; Lumbar: 805.4, 805.5, 806.4, 806.5; Sacrum and coccyx: 805.6, 805.7, 806.6-806.79; SCI involved or Not: Without SCI: 805-805.9 & With SCI: 806-806.9
*p<0.05, **p<0.01, ***p<0.001

Figures 2A–2D show that the CVF cohort had a significantly higher cumulative proportion of AD (P = 0.02; Figure 2A), CHF (P < 0.001; Figure 2B), pneumonia (P < 0.001; Figure 2C), and ARDS (P < 0.001; Figure 2D) than did the no-CVF cohort.

Discussion

To the best of our knowledge, this is the first population-based, longitudinal cohort study to focus on the correlation between CVF and the subsequent risks of specific cardiopulmonary diseases. The main results demonstrated that CVF is significantly associated with an increased risk of several specific cardiopulmonary diseases, including AD, CHF, pneumonia, and ARDS.

Demographics and comorbidity

In our study, patients older than 65 years and females accounted for the majority of participants. In fact, the incidence and prevalence of vulnerable fractures,

accompanied with population aging and subsequent frequently occurring home accidents, are steadily rising[38]. In addition, CVF in women is constantly a consequence of postmenopausal bone loss[5 7 8]. According to recent studies, the prevalence of women older than 50 years who experienced at least one CVF event was 23% - 26%, which was higher than that of men (21.5%)[39 40]. It is noteworthy that young adults aged ≤ 49, though represented the minority of CVF patients, bore a significant heightened risk of developing adverse outcomes in the following analyses. We speculate that CVF in young adults could have more prominent influence on the outcome diseases without the interaction of multiple potential comorbidities and unknown confounders. Another explanation is that CVF is less frequent in a young, healthy population; it could be more severe and detrimental, strengthening the correlations between the investigated diseases.

Clinical vertebral fracture and aortic dissection

In our analysis, with or without CVF, the incidence of AD was higher in men, elderly patients older than 65 years, and those with coexisting comorbidities; this finding is in line with previous epidemiological investigations[11 12 41]. Moreover, compared with patients without CVF, CVF patients, especially female patients, younger population (age ≤49) and those without comorbidities, bore a higher risk of subsequent AD development. Studies that have focused on this correlation are scarce.

Interestingly, prior studies have provided evidence for the strong correlation between poor bone health with major fragility fracture and abdominal aortic calcifications[42 43]. With the progressive destruction of intima-media layer accompanied with new bone-like tissue deposition in the aortic wall, aneurysm or dissection might tend to occur. Other potential explanations we suppose include the intractable pain induced by fractures, accompanied with increments in sympathetic tone, stress, hypertension, and the impact on the vascular wall, as well as an unfavorable sedentary life style could all contribute to the formation of AD.

Clinical vertebral fracture and congestive heart failure

Our study indicated one counterintuitive result that women bore a higher overall incidence of CHF than men did. However, previous investigations of sex-specific epidemiology of CHF have demonstrated that women with atrial fibrillation have a higher incidence of heart failure with preserved ejection fraction, especially in very old age compared with men[44-46]. In this study, CVF was associated with an increased risk of CHF, and the results remained statistically significant across various age and sex strata, as well as with or without comorbidities. In a cross-sectional analysis, Lyons et al.[47] demonstrated that more than one-tenth of heart failure patients had radiologic recognizable vertebral fracture, and among those, multiple vertebral fractures accounted for one half, indicating the close correlation between these two

diseases. Moreover, Sennerby et al.[48] conducted a twin population study and proposed that specific genes involved in cellular mechanisms that shared by the vasculature and bone might connect the close relationship between cardiovascular diseases and fractures. Additionally, the most common etiology of CVF, osteoporosis, together with CHF, share common risk factors and etiologic mechanisms, including advantaged age, female sex, hypovitaminosis D, renal insufficiency, diabetes, a smoking habit, activation of the renin-angiotensin-aldosterone system, hypersecretion of parathyroid hormones, and oxidative / nitrosative stress[23 47 49-52]. In a meta-analysis, Veronese et al.[53] concluded that alterations in signaling pathways of bone remodeling and arterial calcifications could contributed to the higher cardiovascular risk. Indeed, diffuse vascular calcifications accompanied with bone loss could result in a higher afterload on the left ventricle, leading to subsequent left ventricular hypertrophy and finally, congestive heart failure[42 43]. Furthermore, unfavorable outcomes following fracture, including a loss of functional and social activities, dependency with poor quality of life, higher serum cortisol levels accompanied with depressive disorder, higher inflammatory markers, lower drug and diet compliance, a sedentary life style, and arrhythmia or cardiac ischemic events caused by high sympathetic activity, might all contribute to the deterioration of heart function[50 54].

Clinical vertebral fracture and pneumonia, acute respiratory distress syndrome,

and subtypes analysis

Our study results reveal that patients with CVF bore a significantly heightened risk of subsequent pneumonia and ARDS across all strata of age and sex and irrespective of the presence of comorbidities. Further analyses demonstrated the strongest correlation between cervical CVF combined with SCI and risks of pneumonia and ARDS. In a 2-year retrospective multicenter trauma registry analysis, Fletcher et al.[55] noted that 16% of elderly patients older than 65 years with cervical spine trauma ultimately developed pneumonia. Other studies have revealed the incidence of pulmonary complications following cervical spine trauma to be 35% - 95%[56 57], and among these complications, the most common type was pneumonia and atelectasis, although ARDS was the most severe type[58-60]. There are several possible explanations. First, deformity of the vertebral body or even kyphosis might decrease the lung capacity and therefore impair the pulmonary function. Prior studies have indicated that a single vertebral fracture would decrease the predicted forced vital capacity by 9%, increase the risk of restrictive lung disease[1 2 61]. Harrison et al.[62] conducted a systemic review of 4 case-control studies and reported that women with osteoporotic vertebral fractures or kyphosis were associated with decreased predicted vital capacity, as well as total lung capacity. Furthermore, Krege et al.[63] estimated that spine fracture burden is linked with restrictive, but not obstructive lung disease. The

authors further concluded that patients with marginally compensated pulmonary function may not tolerate the superimposed lung restrictive change resulting from vertebral fractures and thus, leading to a further compromised pulmonary function and subsequent lung diseases. Second, cervical CVF combined with SCI might cause paralysis of the diaphragm and hypoactivity of the respiratory accessory muscles, which results in hypoventilation. In addition, the imbalance of sympathetic-parasympathetic interactions would result in an elevated airway tone, bronchorrhea, and poor clearance, which are all associated with the development of various pulmonary complications[64 65]. Third, patients with SCI are prone to develop aspiration and subsequent pulmonary infection due to impaired neuromuscular transmission. Finally, similar to rib fractures, worsening pain related to CVF might impair cough and secretion clearance, leading to atelectasis and subsequent lung infection[24].

Limitations

The major strength of our study is sampling from a large nationwide database, which covers nearly 100% of all residents in Taiwan, and stable outcomes could be achieved with such adequate, representative samples. However, the inevitable limitations should be discussed. First, all disease definitions and sample selection in our study were based on the ICD-9-CM coding, which has been rigorously scrutinized

and peer-reviewed by clinical physicians, the declaration unit of medical institutions and finally the NHI administration. However, miscoding or misclassification might still exist, although it is considered rare. Similarly, diagnostic criteria applied, as well as physician's ability to diagnose the investigated diseases might vary among different hospitals and areas. Second, retrospective dataset analysis results cannot be used to determine causal relationships. Third, several crucial variables could not be obtained from our dataset, including family history, education and socioeconomic status, information of life style and physical activity, body weight, smoking habits, disease severity, laboratory results, radiologic reports, and estimated pain scores, which are potential confounders that might have affected the results. Fourth, a considerable portion of vertebral fracture patients with slight or no symptoms might not have been diagnosed or might have even been overlooked in clinical settings; thus, the true incidence of CVF and the inferred association between CVF and cardiopulmonary diseases could be underestimated. Fifth, patients with CVF might have one or more overlapping etiologies include osteoporosis, trauma and malignancies, etc. Therefore, it was technically infeasible to simply divide the CVF patients into several subgroups for sub-analysis based on the coding of etiologies. Sixth, our sampled participants were retrieved from NHIRD from January 1, 2000, to December 31, 2010. Aging property of the data might not truly reflect the current medical conditions. Finally,

because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

Conclusion

In conclusion, our study results support the hypothesis that CVF is associated with subsequent risks of AD, CHF, pneumonia, and ARDS. Future studies are warranted to delineate the actual pathophysiologic mechanisms underlying this correlation and to develop optimal strategies for reducing the heath care burden of CVF and its complications. Based on our results, we suggest that patients with CVF should be targeted for further screening and preventive interventions for cardiopulmonary diseases.

Abbreviations:

CVFs: clinical vertebral fractures; AD: aortic dissection; CHF: congestive heart failure; ARDS: acute respiratory distress syndrome; NHIRD: National Health Insurance Research Database; NHI: National Health Insurance; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; SCI: spinal cord injury; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; aHRs: adjusted hazard ratios; CI: confidence interval; SD:

standard deviation.

Declarations:

Acknowledgements

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Ethics approval and consent to participate

This study was approved by the Ethics Review Board of China Medical University and Hospital, Taiwan (CMUH-104-REC2-115-CR4). The IRB waived the consent requirement.

Availability of data and materials

Data are available from the NHIRD published by Taiwan National Health Insurance Bureau. Owing to the Personal Information Protection Act, these cannot be made publicly available (http://nhird.nhri.org.tw).

Competing interests

The authors declare that they have no competing interests.

Authors' Contributions

The authors' individual contributions are outlined as follows. Conception and design: F-Y.L. and T.-Y.Y. Administrative support: T.-Y.Y. Data collection and organization: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Data analysis and interpretation: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Manuscript writing: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L. Final approval of the manuscript: F.-Y.L., W.-K.C., C.-C.L., C.-H. K., T.-Y.Y.& C.-Y.L.

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Figure Legends

Figure 1. Derivation of our study cohort

Figure 2. Cummulative incidence of aortic dissection (A), congestive heart failure (B), pneumonia (C) and acute respiratory distress syndrome (D) in patients with clinical vertebral fracture and comparison patients

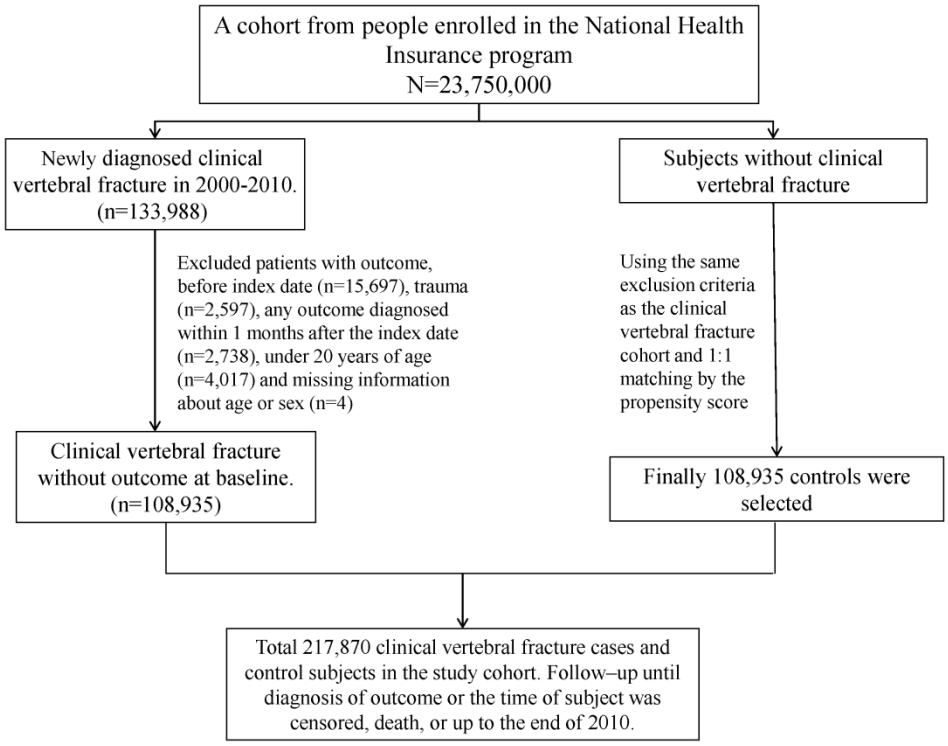

Figure 1. Derivation of our study cohort

254x190mm (300 x 300 DPI)

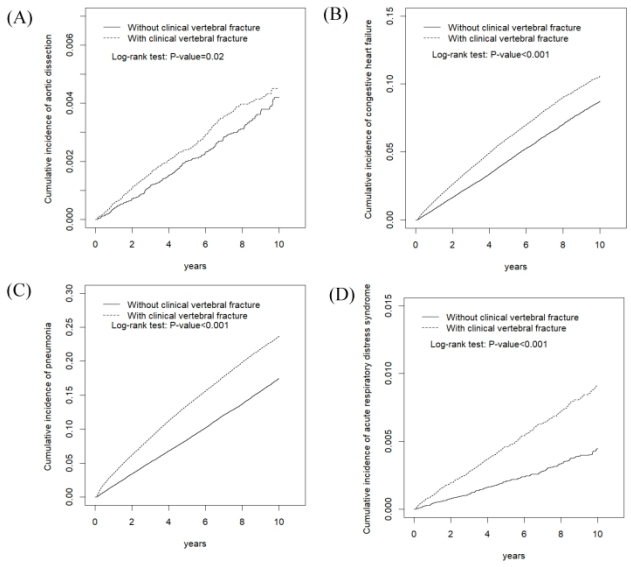

Figure 2. Cummulative incidence of aortic dissection (A), congestive heart failure (B), pneumonia (C) and acute respiratory distress syndrome (D) in patients with clinical vertebral fracture and comparison patients.

338x190mm (300 x 300 DPI)

Supplemental Table 1. Summary of the ICD-9-CM codes used for disease definition and their matching diseases

Diseases	ICD-9-CM codes
Clinical vertebral fracture (CVF)	805, 806
Cervical spine CVF	805.0-805.18, 806.0-806.19
Thoracic spine CVF	805.2, 805.3, 806.2-806.39
Lumbar spine CVF	805.4, 805.5, 806.4, 806.5
Sacrum plus coccyx CVF	805.6, 805.7, 806.6-806.79
CVF without spinal cord injury (SCI)	805-805.9
CVF with spinal cord injury (SCI)	806-806.9
Aortic dissection (AD)	441.0, 441.00, 441.01, 441.02, 441.03
Congestive heart failure (CHF)	428
Pneumonia	480-488
Acute respiratory distress syndrome (ARDS)	518.82, 518.5
Comorbidities	
Hypertension	401–405
Diabetes mellitus	250
Hyperlipidemia	272
Atrial fibrillation	427.31
Chronic kidney disease	580-589
Chronic obstructive pulmonary disease	491,492,496

*Defined by administration code. ICD-9-CM, Clinical Modification of ICD-9.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2-5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	17-22
Study size	10	Explain how the study size was arrived at	11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11-13
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-17

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	13-17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-17
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	22-24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	8
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.