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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

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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 hospitalised at any point during 2000–2010 (n=1 08 935). Each CVF patient was frequency-matched to a no-CVF hospitalised patients based on age, sex, index year and comorbidities (n=1 08 935). 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 vs 3.99, 119.1 vs 89.6, 283.3 vs 183.5 and 9.18 vs 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

- ► This is the first population-based, longitudinal cohort study to focus on the correlation between CVF and the subsequent risks of specific cardiopulmonary diseases.
- ► 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.
- ► 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.
- ► 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.
- ► Because of geographic and epidemiologic discrepancies, our results might not be applicable to other countries or regions.

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 unfavourable 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 ageing 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

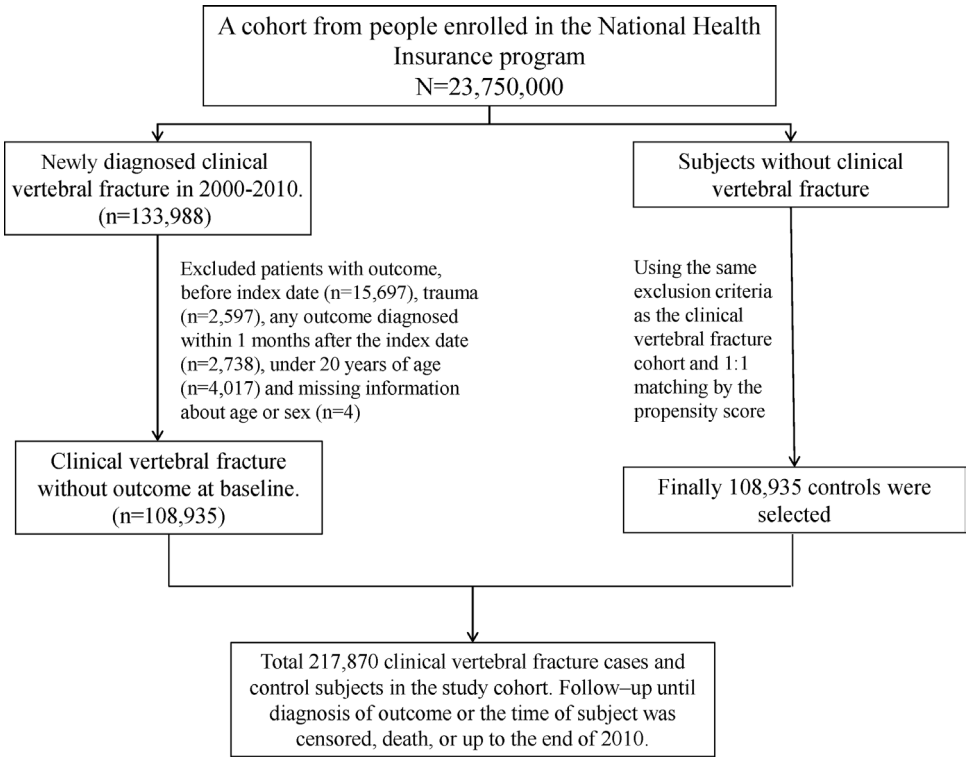

Figure 1 Derivation of our study cohort.

would die within 48 h[10]. Congestive heart failure (CHF) is the major cause of hospitalisation in old age, with more than 650 000 new cases confirmed annually in the United States, and more than 1 million people were hospitalised 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 characterised by diffuse hydrostatic pulmonary oedema, 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 standardised 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 (ischaemic or haemorrhagic) 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 hypothesised 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) programme in March 1995, and 99% of the 23.74 million residents were enrolled.[26] The details of the NHIRD and NHI programme 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 Hospital (CMUH-104-REC2-115-CR4).

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 to 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=2597); with any outcome event (AD, CHF, pneumonia and ARDS) diagnosed within 1 month after the index date (n=2738); those under 18 years of age (n=4017); 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 hospitalisation 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-specific, age-specific 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 analysed using univariable and multivariable Cox proportional hazard regression models and presented as HRs and 95% 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, North Carolina, 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.

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.

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

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

	Clinical vertebral fracture		
	Yes (n=108935)	No (n=108935)	
	n(%)	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)	
three or more	6437 (5.9)	5017 (4.6)	

*Chi-square test examined categorical data.
†T-test examined continuous.

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.

Figure 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 ageing 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 unfavourable 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 recognisable 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,

Table 2 Incidence and adjusted HR of outcome by sex, age and comorbidity for clinical vertebral fracture patients compared with controls

	Clinical vertebral fracture						Compared with control	
	Yes			No				
Variables	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 to 1.44)*	1.23 (1.03 to 1.45)*
Gender								
Female	149	322213	4.62	109	333909	3.26	1.42 (1.11 to 1.82)**	1.40 (1.09 to 1.79)**
Male	137	267703	5.12	136	280224	4.85	1.05 (0.83 to 1.33)	1.08 (0.85 to 1.37)
P for interaction								0.09
Age, years								
≤49	19	230604	0.82	8	229738	0.35	2.37 (1.04 to 5.40)*	2.37 (1.03 to 5.41)*
50–64	43	139107	3.09	30	143099	2.10	1.48 (0.93 to 2.36)	1.45 (0.91 to 2.31)
≥65	224	220204	10.2	207	241296	8.58	1.19 (0.99 to 1.44)	1.17 (0.97 to 1.42)
P for interaction								0.29
Comorbidity§								
No	117	411117	2.85	86	421520	2.04	1.40 (1.06 to 1.85)*	1.38 (1.04 to 1.83)*
Yes	169	178798	9.45	159	192612	8.25	1.15 (0.92 to 1.42)	1.14 (0.91 to 1.41)
P for interaction								0.28
Congestive heart failure								
All	6866	576513	119.1	5411	603639	89.6	1.33 (1.28 to 1.38)***	1.35 (1.30 to 1.40)***
Gender								
Female	4689	312775	149.9	3649	326705	111.7	1.34 (1.29 to 1.40)***	1.33 (1.27 to 1.39)***
Male	2177	263738	82.5	1762	276934	63.6	1.30 (1.22 to 1.38)***	1.38 (1.30 to 1.47)***
P for interaction								0.38
Age, years								
≤49	233	230058	10.1	142	229391	6.19	1.63 (1.33 to 2.01)***	1.64 (1.33 to 2.03)***
50–64	733	137433	53.3	577	141714	40.7	1.31 (1.18 to 1.47)***	1.31 (1.17 to 1.46)***
≥65	5900	209022	282.3	4692	232533	201.8	1.41 (1.35 to 1.46)***	1.38 (1.33 to 1.44)***
P for interaction								0.51
Comorbidity§								
No	2115	406910	52.0	1508	418712	36.0	1.45 (1.35 to 1.54)***	1.42 (1.33 to 1.52)***
Yes	4751	169603	280.1	3903	184927	211.1	1.33 (1.28 to 1.39)***	1.31 (1.26 to 1.37)***
P for interaction								0.04
Follow-up period								
<5 years	5193	194850	266.5	3753	197188	190.3	1.40 (1.34 to 1.46)***	1.07 (1.00 to 1.15)*
≧5 years	1673	166386	100.6	1658	177139	93.6	1.34 (1.29 to 1.40)***	1.17 (1.09 to 1.25)***
Pneumonia								
All	15912	561694	283.3	10929	595609	183.5	1.54 (1.51 to 1.58)***	1.57 (1.54 to 1.61)***
Gender								
Female	8740	306705	285.0	6126	323229	189.5	1.50 (1.46 to 1.55)***	1.49 (1.44 to 1.53)***
Male	7172	254989	281.3	4803	272380	176.3	1.59 (1.53 to 1.65)***	1.68 (1.62 to 1.75)***
P for interaction								0.02
Age, years								
≤49	1468	226184	64.9	557	228317	24.4	2.66 (2.41 to 2.93)***	2.56 (2.32 to 2.82)***
50–64	2018	134598	149.9	1330	140288	94.8	1.59 (1.48 to 1.70)***	1.57 (1.47 to 1.69)***

Continued

Table 2 Continued

Variables	Clinical vertebral fracture						Compared with control	
	Yes			No				
	Events n	PY	Rate†	Events n	PY	Rate†	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
≥65	12426	200912	618.5	9042	227004	398.3	1.56 (1.52 to 1.60)***	1.53 (1.49 to 1.58)***
P for interaction								<0.001
Comorbidity§								
No	6398	398499	160.6	3657	414829	88.2	1.82 (1.75 to 1.90)***	1.74 (1.67 to 1.82)***
Yes	9514	163195	583.0	7272	180780	402.3	1.45 (1.41 to 1.50)***	1.45 (1.41 to 1.50)***
P for interaction								<0.001
Follow-up period								
<5 years	11970	194479	615.5	7447	197003	378.0	1.63 (1.58 to 1.67)***	1.23 (1.18 to 1.29)***
≧5 years	3942	156975	251.1	3482	170874	203.8	1.55 (1.50 to 1.59)***	1.36 (1.30 to 1.42)***
Acute respiratory distress syndrome								
All	542	590138	9.18	257	614432	4.18	2.20 (1.89 to 2.55)***	2.21 (1.91 to 2.57)***
Gender								
Female	254	322312	7.88	115	333999	3.44	2.29 (1.84 to 2.85)***	2.25 (1.81 to 2.81)***
Male	288	267826	10.8	142	280433	5.06	2.12 (1.74 to 2.59)***	2.17 (1.78 to 2.66)***
P for interaction								0.62
Age, years								
≤49	74	230565	3.21	20	229743	0.87	3.69 (2.25 to 6.04)***	3.47 (2.11 to 5.70)***
50–64	60	139177	4.31	38	143117	2.66	1.63 (1.08 to 2.44)*	1.60 (1.07 to 2.41)*
≥65	408	220396	18.5	199	241572	8.24	2.26 (1.91 to 2.68)***	2.22 (1.88 to 2.64)***
P for interaction								0.17
Comorbidity§								
No	226	411197	5.50	93	421615	2.21	2.49 (1.96 to 3.18)***	2.42 (1.89 to 3.09)***
Yes	316	178941	17.7	164	192717	8.51	2.08 (1.72 to 2.51)***	2.08 (1.72 to 2.51)***
P for interaction								0.25

*p<0.05, **p<0.01, ***p<0.001.
† 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.
PY, person-years.

the most common aetiology 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 signalling pathways of bone remodelling 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, unfavourable 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 ischaemic 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

Table 3 Comparisons of incidence, and HR 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	108 935	245	3.99	1(Reference)	1(Reference)
Cervical spine	9938	12	2.15	0.54 (0.30 to 0.96)*	0.92 (0.51 to 1.65)
Thoracic	32 205	95	5.72	1.44 (1.13 to 1.82)**	1.20 (0.95 to 1.53)
Lumbar	70 723	220	5.77	1.45 (1.21 to 1.74)***	1.33 (1.11 to 1.60)**
Sacrum and coccyx	7523	6	1.28	0.32 (0.14 to 0.72)**	1.06 (0.47 to 2.41)
Without SCI	98 984	265	5.00	1.25 (1.05 to 1.49)*	1.25 (1.05 to 1.48)*
With SCI	13 209	30	3.75	0.93 (0.64 to 1.37)	1.10 (0.75 to 1.61)
Congestive heart failure					
No vertebral fracture	108 935	5411	89.6	1(Reference)	1(Reference)
Cervical spine	9938	278	50.4	0.56 (0.50 to 0.63)***	1.40 (1.24 to 1.58)***
Thoracic	32 205	2678	166.6	1.86 (1.78 to 1.95)***	1.43 (1.37 to 1.50)***
Lumbar	70 723	4986	134.1	1.50 (1.44 to 1.56)***	1.38 (1.33 to 1.43)***
Sacrum and coccyx	7523	144	31.0	0.35 (0.29 to 0.41)***	1.33 (1.12 to 1.57)***
Without SCI	98 984	6291	121.5	1.36 (1.31 to 1.41)***	1.34 (1.29 to 1.39)***
With SCI	13 209	834	106.5	1.19 (1.10 to 1.28)***	1.50 (1.39 to 1.61)***
Pneumonia					
No vertebral fracture	108 935	10 929	183.5	1(Reference)	1(Reference)
Cervical spine	9938	1106	208.4	1.14 (1.07 to 1.21)***	2.22 (2.08 to 2.36)***
Thoracic	32 205	5617	358.8	1.96 (1.90 to 2.02)***	1.59 (1.54 to 1.64)***
Lumbar	70 723	11 125	307.1	1.67 (1.63 to 1.72)***	1.56 (1.52 to 1.60)***
Sacrum and coccyx	7523	437	95.7	0.52 (0.47 to 0.57)***	1.76 (1.60 to 1.94)***
Without SCI	98 984	14 378	284.7	1.55 (1.51 to 1.59)***	1.56 (1.52 to 1.60)***
With SCI	13 209	2203	292.8	1.59 (1.52 to 1.67)***	1.91 (1.82 to 2.00)***
Acute respiratory distress syndrome					
No vertebral fracture	108 935	257	4.18	1(Reference)	1(Reference)
Cervical spine	9938	52	9.33	2.23 (1.65 to 3.00)***	3.42 (2.50 to 4.68)***
Thoracic	32 205	191	11.5	2.76 (2.29 to 3.33)***	2.35 (1.94 to 2.84)***
Lumbar	70 723	365	9.57	2.29 (1.95 to 2.69)***	2.11 (1.80 to 2.48)***
Sacrum and coccyx	7523	10	2.13	0.51 (0.27 to 0.95)*	1.51 (0.79 to 2.87)
Without SCI	98 984	478	9.02	2.16 (1.85 to 2.51)***	2.15 (1.84 to 2.50)***
With SCI	13 209	87	10.9	2.58 (2.03 to 3.29)***	2.97 (2.34 to 3.78)***

*p<0.05, **p<0.01, ***p<0.001.
†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 scoreICD-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.

demonstrated the strongest correlation between cervical CVF combined with SCI and risks of pneumonia and ARDS. In a 2year 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

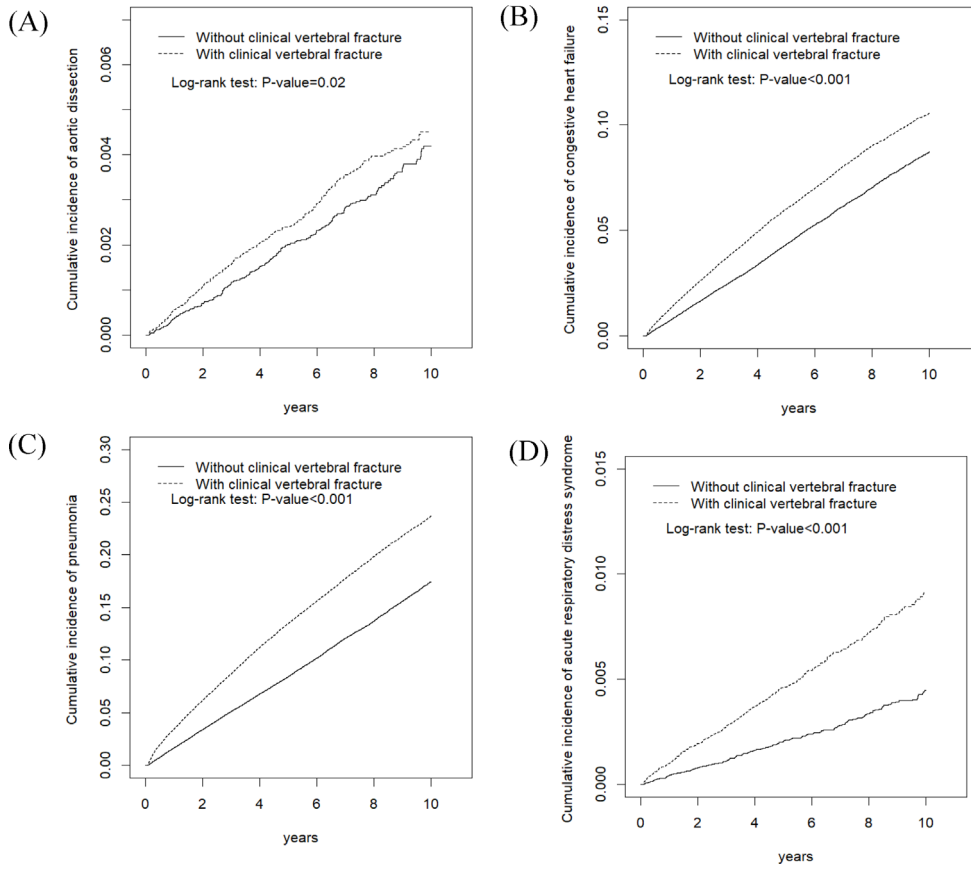

Figure 2 Cummulative incidence of aortic dissection (A), congestive heart failure (B), pneumonia (C) and acute respiratory distress syndrome (D) in patients with clinical vertebral fracture and comparison patients

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 scrutinised 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. Ageing 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.

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REFERENCES

1 Longo UG, Loppini M, Denaro L, *et al*. Conservative management of patients with an osteoporotic vertebral fracture: a review of the literature. *J Bone Joint Surg Br* 2012;94:152–7.
2 Longo UG, Loppini M, Denaro L, *et al*. Osteoporotic vertebral fractures: current concepts of conservative care. *Br Med Bull* 2012;102:171–89.
3 CW Y, Hsieh MK, Chen LH, *et al*. Percutaneous balloon kyphoplasty for the treatment of vertebral compression fractures. *BMC Surg* 2014;14.
4 Guo J-B, Zhu Y, Chen B-L, *et al*. Surgical versus non-surgical treatment for vertebral compression fracture with osteopenia: a systematic review and meta-analysis. *PLoS One* 2015;10:e0127145.
5 Bliuc D, Center JR. Determinants of mortality risk following osteoporotic fractures. *Curr Opin Rheumatol* 2016;28:413–9.
6 Chih YP, WT W, Lin CL, *et al*. Vertebral compression fracture related to pancreatic cancer with osteoblastic metastasis: a case report and literature review. *Medicine* 2016;95:e2670.
7 Lewiecki EM, Laster AJ. Clinical applications of vertebral fracture assessment by dual-energy X-ray absorptiometry. *J Clin Endocrinol Metab* 2006;91:4215–22.
8 Lindsay R*et al*. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001;285:320–3.
9 Park SB, Kim J, Jeong JH, *et al*. Prevalence and incidence of osteoporosis and osteoporotic vertebral fracture in Korea: nationwide epidemiological study focusing on differences in socioeconomic status. *Spine* 2016;41:328–36.
10 Tolenaar JL, van Bogerijen GHW, Eagle KA, *et al*. Update in the management of aortic dissection. *Curr Treat Options Cardiovasc Med* 2013;15:200–13.
11 Melvinsdottir IH, Lund SH, Agnarsson BA, *et al*. The incidence and mortality of acute thoracic aortic dissection: results from a whole nation study. *Eur J Cardiothorac Surg* 2016;50::ezw235.:1111–7.
12 Pacini D, Di Marco L, Fortuna D, *et al*. Acute aortic dissection: epidemiology and outcomes. *Int J Cardiol* 2013;167:2806–12.
13 Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;8:30–41.
14 Givertz MM, Teerlink JR, Albert NM, *et al*. Acute decompensated heart failure: update on new and emerging evidence and directions for future research. *J Card Fail* 2013;19:371–89.
15 Maze R, Haddad H. An update in the management of acute decompensated heart failure. *Curr Opin Cardiol* 2014;29:180–4.
16 Bender MT, Niederman MS. Improving outcomes in community-acquired pneumonia. *Curr Opin Pulm Med* 2016;22:235–42.
17 Marrie TJ, File TM. Bacterial pneumonia in older adults. *Clin Geriatr Med* 2016;32:459–77.
18 Kim W-Y, Hong S-B. Sepsis and acute respiratory distress syndrome: recent update. *Tuberc Respir Dis* 2016;79:53–7.
19 Koh Y. Update in acute respiratory distress syndrome. *j intensive care* 2014;2.
20 Chen Y-C, Wu J-C, Liu L, *et al*. Hospitalized osteoporotic vertebral fracture increases the risk of stroke: a population-based cohort study. *J Bone Miner Res* 2013;28:516–23.
21 Laroche M, Pecourneau V, Blain H, *et al*. Osteoporosis and ischemic cardiovascular disease. *Joint Bone Spine* 2016.
22 Silverman SL, Delmas PD, Kulkarni PM, *et al*. Comparison of fracture, cardiovascular event, and breast cancer rates at 3 years in postmenopausal women with osteoporosis. *J Am Geriatr Soc* 2004;52:1543–8.
23 Ni Mhuircheartaigh O, Crowson CS, Gabriel SE, *et al*. Fragility fractures are associated with an increased risk for cardiovascular events in women and men with rheumatoid arthritis: a population-based study. *J Rheumatol* 2017;44:558–64.
24 Kim B, Kim J, Jo YH, *et al*. Risk of pneumonia after vertebral compression fracture in women with low bone density: a population-based study. *Spine* 2018;43:E830–5.

25 Melton LJ, Kallmes DF. Epidemiology of vertebral fractures: implications for vertebral augmentation. *Acad Radiol* 2006;13:538–45.
26 Shou-Hsia C, Tung-Liang C. The effect of universal health insurance on health care utilization in Taiwan: results from a natural experiment. *JAMA : the journal of the American Medical Association* 1997;278:89–93.
27 Peng Y-C, Lin C-L, Yeh H-Z, *et al*. Diverticular disease and additional comorbidities associated with increased risk of dementia. *J Gastroenterol Hepatol* 2016;31:1816–22.
28 Chen Y-T, Su J-S, Tseng C-W, *et al*. Inflammatory bowel disease on the risk of acute pancreatitis: a population-based cohort study. *J Gastroenterol Hepatol* 2016;31:782–7.
29 Lee C-H, Hsu W-C, Ko J-Y, *et al*. Trends in the management of peritonsillar abscess in children: a nationwide population-based study in Taiwan. *Int J Pediatr Otorhinolaryngol* 2019;125:32–7.
30 JA S, Chang CC, Wang HM, *et al*. Antidepressant treatment and mortality risk in patients with dementia and depression: a nationwide population cohort study in Taiwan. *Ther Adv Chronic Dis* 2019;10.
31 Hong WJ, Chen W, Yeo KJ, *et al*. Increased risk of osteoporotic vertebral fracture in rheumatoid arthritis patients with new-onset cardiovascular diseases: a retrospective nationwide cohort study in Taiwan. *Osteoporos Int* 2019.
32 Huang KL, Yeh CC, SI W, *et al*. Risk of dementia among individuals with psoriasis: a nationwide population-based cohort study in Taiwan. *J Clin Psychiatry* 2019;80.
33 Lin C-E, Chung C-H, Chen L-F, *et al*. Risk of incident hypertension, diabetes, and dyslipidemia after first posttraumatic stress disorder diagnosis: a nationwide cohort study in Taiwan. *Gen Hosp Psychiatry* 2019;58:59–66.
34 Cheng C-L, Chien H-C, Lee C-H, *et al*. Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in national health insurance research database in Taiwan. *Int J Cardiol* 2015;201:96–101.
35 Cheng C-L, Kao Y-HY, Lin S-J, *et al*. Validation of the National health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf* 2011;20:236–42.
36 Cheng C-L, Lee C-H, Chen P-S, *et al*. Validation of acute myocardial infarction cases in the National health insurance research database in Taiwan. *J Epidemiol* 2014;24:500–7.
37 TW H, Ruan SY, Huang CT, *et al*. Validity of ICD9-CM codes to diagnose chronic obstructive pulmonary disease from national health insurance claim data in Taiwan. *Int J Chron Obstruct Pulmon Dis* 2018;13:3055–63.
38 Bouyer B, Vassal M, Zairi F, *et al*. Surgery in vertebral fracture: epidemiology and functional and radiological results in a prospective series of 518 patients at 1year's follow-up. *Orthopaedics & Traumatology: Surgery & Research* 2015;101:11–15.
39 Jackson SA, Tenenhouse A, Robertson L. Vertebral fracture definition from population-based data: preliminary results from the Canadian multicenter osteoporosis study (CaMos). *Osteoporosis International* 2000;11:680–7.
40 Kendler DL, Bauer DC, Davison KS, *et al*. Vertebral fractures: clinical importance and management. *Am J Med* 2016;129:221.e1–221.e10.
41 Yeh T-Y, Chen C-Y, Huang J-W, *et al*. Epidemiology and medication utilization pattern of aortic dissection in Taiwan. *Medicine* 2015;94:e1522.
42 Szulc P. Abdominal aortic calcification: a reappraisal of epidemiological and pathophysiological data. *Bone* 2016;84:25–37.10.1016/j.bone.2015.12.004
43 Thompson B, Towler DA. Arterial calcification and bone physiology: role of the bone-vascular axis. *Nat Rev Endocrinol* 2012;8:529–43.
44 Hassanein M, Abdelhamid M, Ibrahim B, *et al*. Gender differences in Egyptian patients hospitalized with heart failure: insights from the European Society of cardiology heart failure long-term registry. *ESC Heart Failure* 2018;5:1159–64.
45 Madan N, Itchhaporia D, Albert CM, *et al*. Atrial fibrillation and heart failure in women. *Heart Fail Clin* 2019;15:55–64.
46 Magnussen C, Niiranen TJ, Ojeda FM, *et al*. Sex-Specific epidemiology of heart failure risk and mortality in Europe: results from the BiomarCaRE Consortium. *JACC Heart Fail* 2019;7:204–13.
47 Lyons KJ, Majumdar SR, Ezekowitz JA. The unrecognized burden of osteoporosis-related vertebral fractures in patients with heart failure. *Circulation* 2011;4:419–24.10.1161/CIRCHEARTFAILURE.111.961185
48 Sennerby U*et al*. Cardiovascular diseases and risk of hip fracture. *JAMA* 2009;302:1666–73.
49 Aluoch AO, Jessee R, Habal H, *et al*. Heart failure as a risk factor for osteoporosis and fractures. *Curr Osteoporos Rep* 2012;10:258–69.
50 Larina VN, Bart BI, Raspopova TN. [Chronic heart failure and osteoporosis]. *Kardiologiia* 2013;53:76–84.
51 Farhat GN, Cauley JA. The link between osteoporosis and cardiovascular disease. *Clin Cases Miner Bone Metab* 2008;5:19–34.
52 Gerber Y, Melton LJ, Weston SA, *et al*. Osteoporotic fractures and heart failure in the community. *Am J Med* 2011;124:418–25.
53 Veronese N, Stubbs B, Crepaldi G, *et al*. Relationship between low bone mineral density and fractures with incident cardiovascular disease: a systematic review and meta-analysis. *J Bone Miner Res* 2017;32:1126–35.
54 Adelborg K, Schmidt M, Sundboll J, *et al*. Mortality risk among heart failure patients with depression: a nationwide population-based cohort study. *J Am Coll Cardiol* 2016;67:1318–18.
55 Fletcher DJ, Taddonio RF, Byrne DW, *et al*. Incidence of acute care complications in vertebral column fracture patients with and without spinal cord injury. *Spine* 1995;20:1136–46.
56 Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehabil* 1994;75:270–5.
57 Winslow C, Bode RK, Felton D, *et al*. Impact of respiratory complications on length of stay and hospital costs in acute cervical spine injury. *Chest* 2002;121:1548–54.
58 Cotton BA, Pryor JP, Chinwalla I, *et al*. Respiratory complications and mortality risk associated with thoracic spine injury. *J Trauma* 2005;59:1400–9.
59 Veeravagu A, Jiang B, Rincon F, *et al*. Acute respiratory distress syndrome and acute lung injury in patients with vertebral column fracture(s) and spinal cord injury: a nationwide inpatient sample study. *Spinal Cord* 2013;51:461–5.
60 Lieberman IH, Webb JK. Cervical spine injuries in the elderly. *J Bone Joint Surg Br* 1994;76-B:877–81.
61 Kado DM, Browner WS, Palermo L, *et al*. Vertebral fractures and mortality in older women: a prospective study. *Archives of internal medicine* 1999;159:1215–20.
62 Harrison RA, Siminoski K, Vethanayagam D, *et al*. Osteoporosis-related kyphosis and impairments in pulmonary function: a systematic review. *J Bone Miner Res* 2007;22:447–57.
63 Krege JH, Kendler D, Krohn K, *et al*. Relationship between vertebral fracture burden, height loss, and pulmonary function in postmenopausal women with osteoporosis. *J Clin Densitom* 2015;18:506–11.
64 Chen Y*et al*. Identification of risk factors for respiratory complications in upper cervical spinal injured patients with neurological impairment. *Acta Orthop Traumatol Turc* 2013;47:111–7.
65 Krassioukov A. Autonomic function following cervical spinal cord injury. *Respir Physiol Neurobiol* 2009;169:157–64.