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## **ORIGINAL ARTICLE**



# Shoulder Pain and Risk of Developing Hypertension and Cardiovascular Disease: A Nationwide Population-Based Cohort Study in Taiwan

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**Background:** Shoulder pain is a common complaint across the population. It is associated with co-morbidities such as depression, diabetes mellitus, musculoskeletal disorders or cancer. However, there has been no study on the association of shoulder symptoms with future development of diseases. This nationwide population-based study aimed to investigate and clarify this association. **Materials and Methods:** A total of 76,304 patients with shoulder symptoms during 2000 and 2013 were selected from the National Health Insurance Research Database in Taiwan. Clinical endpoints such as hypertension (HTN) and cardiovascular disease (CVD) were evaluated by hazard ratio (HR) with 95% confidence interval (CI) after adjusting any confounding factors in Cox regression analysis. **Results:** Among the registered subjects, 16,570 (21.72%) and 8,453 (11.08%) patients developed HTN and CVD, respectively. After adjusting gender, age, household income, catastrophic illness, season, urbanization level and level of care, patients with shoulder symptoms aged ≥65 years had the highest risk of HTN (adjusted HR = 5.806, 95% CI = 5.464-6.169, P < 0.001), and CVD (adjusted HR = 4.371, 95% CI = 4.047-4.721, P < 0.001), with reference to younger age group of 22-44. The association of older age persisted in other cardiovascular problems (P < 0.001). **Conclusions:** Shoulder symptoms were associated with HTN and CVD. Future studies are required to elucidate the clinicopathogenesis.

Key words: Shoulder symptoms, hypertension, cardiovascular disease, national health insurance research database, Taiwan

#### INTRODUCTION

Shoulder pain is a common complaint across the general population. The lifetime prevalence of shoulder pain ranges from 7% to 67%, with incidence of about 1.5% per year. 1.2 The most common cause of shoulder pain has been reported to be rotator cuff disorders, acromioclavicular joint disease and glenohumeral joint disorders. 3 Other causes are mostly nonspecific and there lacks reliable tools for clinical assessment. 3 Therefore, the research of shoulder pain etiology is limited. Furthermore, due to its chronic characteristics,

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the complaint is often overlooked. However, the neck and shoulder pain can have a significant impact on the life quality and might be associated with some underlying diseases. 4.5 Further understanding of the underlying etiology and comorbidities that are potentially related to the shoulder pain is crucial for diagnosis and optimal treatment. Nevertheless, there have been few studies addressing this problem, and only some studies using small cohorts. In the United States, Vogt *et al.* showed that shoulder pain was associated with mental disorders, low back pain, osteoarthritis, history of

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heart attack and angina in the elderly.<sup>5</sup> Similar results for younger population were reported in Finland.<sup>4,6</sup> Another larger, cross-sectional, retrospective study was conducted in the United States and identified that shoulder symptoms were associated with diabetes mellitus, depressive disorder, pulmonary, cardiovascular, other musculoskeletal problems and cancer, as well as pain, aching or stiffness at other sites.<sup>7</sup>

In Taiwan, hypertension (HTN) and cardiovascular disease (CVD) contribute significant medical burden and costs. Therefore, early diagnosis and management is of vital importance. Based on the mentioned evidence, we hypothesize that shoulder pain is an early sign of HTN and CVD because of referred pain. The purpose of this study is to clarify the clinicopathological association of shoulder pain with other underlying conditions, we carried out this study using National Health Insurance Research Database (NHIRD) in Taiwan.

#### MATERIALS AND METHODS

#### **Ethics**

Our study was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB 2-104-05-035).

#### Data source

NHIRD in Taiwan covered more than 99% of the entire population. The research database is released from the Bureau of National Health Insurance, which is affiliated to over 93% medical institutions such as medical centers and local hospitals. The NHIRD contains the annual registration files and all claims data for reimbursement. Personal information is encrypted for individual privacy. There have been many studies addressing the accuracy and validity of the use of the database. Therefore, NHIRD was adopted as the data source in this retrospective study. Moreover, the Longitudinal Health Insurance Database (LHID), a subset of the NHIRD that randomly selects one million insured individuals, was used to investigate the association between shoulder pain and HTN and CVD over a 14-year period (2000–2013).

### Study design and sampled participants

This study was a population-based cohort design. Patients with shoulder pain that had at least three outpatient or inpatient visits were retrieved from the LHID from January 1, 2000, to December 31, 2013 according to diagnosis of shoulder pain, strains or sprains (ICD-9-CM 719.41, 719.42, 840). Patients with shoulder symptoms before index date were excluded, and the patients having HTN and CVD before tracing were also excluded. All patients aged <20 years old and with unknown gender were excluded from this study. In the end, a total of 76,304 registered patients were included [Figure 1].

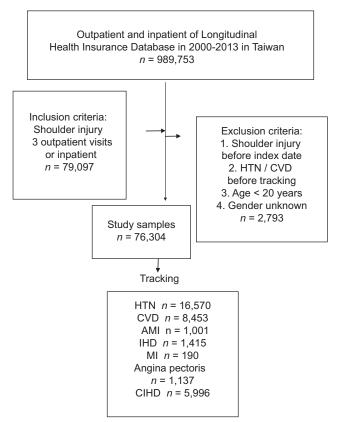


Figure 1: Flowchart of the study samples from the National Health Insurance Research Database in Taiwan

The covariate factors in our study included gender, age group (20–44, 45–64 and ≥65 years), income, catastrophic illness, seasons, geographical area of residence (north, middle, south, east and outlet islands of Taiwan), urbanization level (level 1-4), and level of care (hospital center, regional hospital and local hospital). The urbanization levels of residence were defined by the population and various factors associated with level of development. Population of > 1,250,000, with specific political, economic, cultural and metropolitan development was defined as level 1. Regions with population between 500,000 and 1,249,999, and having important role in the politics, economy, and culture were defined as urbanization level 2. Urbanization level 3 was defined for those with population between 149,999 and 499,999, and regions with urbanization level 4 had the lowest population (<149,999). The hospital level factors consisted of the level of care determined by the Standard of Medical Staff and Facilities Requirement of Hospital and Hospital Accreditation, and Urbanization level.

The clinical endpoints were HTN (in ICD-9-CM codes, 401–405) and CVD (410–414). The subsets of CVD included acute myocardial infarction (AMI, 410), other acute and subacute forms of ischemic heart disease (IHD, 411), old

myocardial infarction (MI, 412), angina pectoris (413) and other forms of chronic ischemic heart disease (CIHD, 414).

#### **Outcome measures**

All participants in the study were followed from the index date to the onset of HTN and CVD, withdrawal from the NHI program or at the end of 2013.

## Statistical analysis

All statistical analyses were performed using SPSS, version 22.0 (IBM Corp., Armonk, NY). Chi-square and t-tests were used to evaluate the distributions of the categorical and continuous variables, respectively, with a Fischer exact examination. The results were presented as adjusted hazard ratio (HR) with a 95% confidence interval (CI). Differences in the risk of clinical endpoints between the study and control groups were estimated using the Kaplan–Meier method with the log-rank test. A two-tailed P < 0.05 was considered to indicate the statistical significance.

#### **RESULTS**

## Baseline characteristics of the study population

The baseline characteristics of the study population are depicted in Table 1. The average age with shoulder symptoms was  $49.71 \pm 16.62$  in our study, with more patients in the age group of 20–44 (39.26%) and 45–64 (40.7%) years. Most of the patients do not have low-income threshold and were not inflicted with catastrophic illness (98.21% and 94%). Northern Taiwan accounted for the most patient source (37.36%), followed by the middle Taiwan (27.54%). Patients were more likely to reside in towns with level II urbanization level (42.4%), and had more chance to be cared in the regional hospital (40.3%).

## Shoulder pain associated with HTN

Of the study population, 16,570 (21.7%) developed HTN in the 13-year follow-up. Female and elderly patients were prone to develop HTN (P = 0.002 and < 0.001, respectively) [Table 2]. Patients with lower household income and catastrophic illness were more likely to develop HTN within the follow-up years. Those who lived in urbanization level 4 and sought medical help in regional hospital were also associated with HTN (P < 0.001 for both).

In the Cox regression analysis, male subjects were shown to have higher risk of HTN with reference to female ones (adjusted HR = 1.106, 95% CI = 1.073–1.141, P < 0.001) [Table 3]. Patients in the age group of 45–64 and  $\geq$ 65 years had higher risk of HTN (adjusted HR = 3.187 and 5.806, respectively, P < 0.001 for both). Moreover, diagnosis

Table 1: Characteristics of study in the baseline

Variables	n (%)
Overall	76,304
Gender	
Male	42,079 (55.15)
Female	34,225 (44.85)
Age (years)	49.71±16.62
Age group (years)	
20-44	29,955 (39.26)
45-64	31,055 (40.70)
≧65	15,294 (20.04)
Low-income household	
Without	74,937 (98.21)
With	1367 (1.79)
Catastrophic illness	
Without	71,728 (94.00)
With	4,576 (6.00)
Season	
Spring	19,642 (25.74)
Summer	19,898 (26.08)
Autumn	19,357 (25.37)
Winter	17,407 (22.81)
Location	
Northern taiwan	28,510 (37.36)
Middle taiwan	21,016 (27.54)
Southern taiwan	20,451 (26.80)
Eastern taiwan	5851 (7.67)
Outlets islands	476 (0.62)
Urbanization level	
1 (the highest)	22,228 (29.13)
2	32,351 (42.40)
3	7,934 (10.40)
4 (the lowest)	13,791 (18.07)
Level of care	
Hospital center	19,409 (25.44)
Regional hospital	30,750 (40.30)
Local hospital	26,145 (34.26)

of shoulder pain in winter was not associated with HTN risk (adjusted HR = 0.969, 95% CI = 0.928–1.012, P = 0.151). With reference of level 4 urbanization, patients residing in lower urbanization level showed nonsignificantly lower risk of HTN. On the other hand, subjects seeking higher level of care had lower risk of HTN (adjusted HR = 0.868 for hospital center and 0.870 for regional hospital, with reference to local hospital, P < 0.001 for both).

Table 2: Characteristics and development of hypertension

Variables	Total, <i>n</i> (%)	With, n (%)	Without, $n$ (%)	P
Overall	76,304	16,570 (21.72)	59,734 (78.28)	
Gender				
Male	42,079 (55.15)	8961 (54.08)	33,118 (55.44)	0.002
Female	34,225 (44.85)	7609 (45.92)	26,616 (44.56)	
Age (years)	52.99±17.40	66.18±13.38	49.33±16.59	< 0.001
Age group (years)				
20-44	25,718 (33.70)	1183 (7.14)	24,535 (41.07)	< 0.001
45-64	30,345 (39.77)	6030 (36.39)	24,315 (40.71)	
≧65	20,241 (26.53)	9357 (56.47)	10,884 (18.22)	
Low-income household				
Without	74,684 (97.88)	16,095 (97.13)	58,589 (98.08)	< 0.001
With	1620 (2.12)	475 (2.87)	1145 (1.92)	
Catastrophic illness				
Without	68,228 (89.42)	14033 (84.69)	54,195 (90.73)	< 0.001
With	8076 (10.58)	2537 (15.31)	5539 (9.27)	
Season				
Spring	18,377 (24.08)	4266 (25.75)	14,111 (23.62)	< 0.001
Summer	19,452 (25.49)	4055 (24.47)	15,397 (25.78)	
Autumn	20,889 (27.38)	4171 (25.17)	16,718 (27.99)	
Winter	17,586 (23.05)	4078 (24.61)	13,508 (22.61)	
Location				
Northern taiwan	28,991 (37.99)	5739 (34.63)	23,252 (38.93)	< 0.001
Middle taiwan	21,008 (27.53)	4909 (29.63)	16,099 (26.95)	
Southern taiwan	20,430 (26.77)	4460 (26.92)	15,970 (26.74)	
Eastern taiwan	5494 (7.20)	1394 (8.41)	4100 (6.86)	
Outlets islands	381 (0.50)	68 (0.41)	313 (0.52)	
Urbanization level				
1 (the highest)	22,462 (29.44)	4509 (27.21)	17,953 (30.05)	< 0.001
2	33,304 (43.65)	7286 (43.97)	26,018 (43.56)	
3	7017 (9.20)	1388 (8.38)	5629 (9.42)	
4 (the lowest)	13,521 (17.72)	3387 (20.44)	10,134 (16.97)	
Level of care				
Hospital center	22,442 (29.41)	4795 (28.94)	17,647 (29.54)	< 0.001
Regional hospital	33,585 (44.01)	7599 (45.86)	25,986 (43.50)	
Local hospital	20,277 (26.57)	4176 (25.20)	16,101 (26.95)	

HTN=Hypertension

## Shoulder pain associated with CVD

A total of 8,453 subjects developed CVD. Of those patients, CHID accounts for 70.58%, followed by IHD (16.74%) and angina pectoris (13.45%), respectively [Table 4]. Male patients were more likely to be associated with CVD (P<0.001). Similar to HTN, patients who had CVD were elder (P<0.001), with 58.23% of subjects in the age group of  $\geq$ 65 years (P<0.001).

Subjects having low household income and catastrophic illness were associated with CVD (P < 0.001 and P = 0.037). Diagnosis of shoulder pain in summer and winter also showed association with CVD (P < 0.001). Subjects living in the level 1 urbanization and received care in the medical center were less likely to have CVD within the 13 years of follow-up (P < 0.001 for both).

Table 3: Factors of hypertension by using cox regression

		HTN		
Variables	Adjusted HR	95% CI Lower	95% CI Upper	P
Gender				
Male	1.106	1.073	1.141	< 0.001
Female	Reference			
Age group (years)				
20-44	Reference			
45-64	3.187	2.994	3.392	< 0.001
≧65	5.806	5.464	6.169	< 0.001
Low-income household				
Without	Reference			
With	1.166	1.063	1.278	0.001
Catastrophic illness				
Without	Reference			
With	0.956	0.916	0.998	0.038
Season				
Spring	Reference			
Summer	0.900	0.863	0.940	< 0.001
Autumn	0.820	0.785	0.855	< 0.001
Winter	0.969	0.928	1.012	0.151
Urbanization level				
1 (the highest)	0.984	0.936	1.035	0.535
2	0.961	0.920	1.003	0.068
3	0.917	0.861	0.976	0.007
4 (the lowest)	Reference			
Level of care				
Hospital center	0.868	0.828	0.910	< 0.001
Regional hospital	0.870	0.837	0.904	< 0.001
Local hospital	Reference			

HTN=Hypertension; HR=Hazard ratio; CI=Confidence interval

The Cox regression analysis further confirmed that male, elderly patients, with catastrophic illness were associated with higher risk for any CVD (AMI, IHD, MI, angina pectoris and CIHD, P < 0.05 for all) [Table 5]. Age remains the highest risk (adjusted HR = 4.371, 95% CI = 4.047–4.721, P < 0.001). The factor of season in the regression analysis revealed discrepant results across the subsets of CVD, as was the urbanization level and the level of care.

#### **DISCUSSION**

In this population-based cohort study, we investigated the association of shoulder symptoms, including pain, strain and sprains with the development of HTN and CVD from 2000

to 2013. We also examined the covariates of age, gender, household income, catastrophic illness, seasons, geographical residence, level of urbanization and level of care. After adjusting the above factors, we found that male patients, older age and lower household income were significantly associated with HTN and CVD (P < 0.05). Patients with catastrophic illness had lower risk of developing HTN and CVD, showing possible masking effect by the coding of catastrophic illness. In terms of season, although shoulder pain in winter was expected to correlate with HTN and CVD, our study did not confirm this association. In the subgroup analysis, shoulder pain diagnosed in winter only contributed to higher risk of AMI, emphasizing the correlation of shoulder discomfort with this lethal illness in winter. Patients in the lower urbanization level had lower risk of HTN. This might indicate that those patients had shoulder symptoms caused by other reasons. However, the leveling effect of urbanization level was not observed in the association with CVD. Moreover, patients who sought medical care in the hospital center or regional hospital had lower risk of HTN. It suggested that those subjects might have more medical intervention than those who were cared in the local hospital. Nevertheless, this finding was not seen in the subgroup analysis for AMI and MI, in which patients with higher level of care had higher risk of getting these two diseases. It might be explained by the fact that those patients had more severe shoulder discomfort and were managed in hospitals with higher level of care. In addition, it also suggested that severe shoulder symptom might be associated with underlying cardiovascular problems.

Several studies have investigated the association of CVD with musculoskeletal conditions. However, there were few studies describing the relation with shoulder.<sup>5,10</sup> In Johnson County Osteoarthritis Project, the authors demonstrated significant association between cardiovascular problems (stroke, heart attack, heart trouble, and circulation problems) and moderate to severe shoulder symptoms after adjusting the covariates.<sup>7</sup> The authors in the study also pointed out this clinically relevant association may limit recommended physical activity and general rehabilitation.

In fact, cancers are known to be associated with local and generalized musculoskeletal symptoms.<sup>7</sup> Pain or discomfort induced under such circumstance should not be overlooked because such disturbing illness can affect the quality of life and a patient's surviving willingness.<sup>11,12</sup> In the study carried out by Wright *et al.*, cancer was associated with neck and shoulder symptoms.<sup>7</sup> However, there has been no study implicating the association of shoulder symptoms with future development of cancer. Our study identified significant association between shoulder pain and cancer arising from the esophagus and

Table 4: Characteristics and development of cardiovascular disease

Variables	Total, $n$ (%)	With, <i>n</i> (%)	Without, $n$ (%)	P
Overall	76,304	8453 (11.08)	67,851 (88.92)	
Subgroup				
AMI		1001 (11.84)		
IHD		1415 (16.74)		
MI		190 (2.25)		
Angina pectoris		1137 (13.45)		
CIHD		5966 (70.58)		
Gender				
Male	42,079 (55.15)	4878 (57.71)	37,201 (54.83)	< 0.001
Female	34,225 (44.85)	3575 (42.29)	30,650 (45.17)	
Age (years)	52.98±17.52	66.45±14.52	51.31±17.14	< 0.001
Age group (years)				
20-44	25,907 (33.95)	752 (8.90)	25,155 (37.07)	< 0.001
45-64	30,174 (39.54)	2779 (32.88)	27,395 (40.38)	
≧65	20,223 (26.50)	4922 (58.23)	15,301 (22.55)	
Low-income household				
Without	74,626 (97.80)	8125 (96.12)	66,501 (98.01)	< 0.001
With	1678 (2.20)	328 (3.88)	1350 (1.99)	
Catastrophic illness				
Without	68,093 (89.24)	7487 (88.57)	60,606 (89.32)	0.037
With	8211 (10.76)	966 (11.43)	7245 (10.68)	
Season				
Spring	18,102 (23.72)	2130 (25.20)	15,972 (23.54)	< 0.001
Summer	19,510 (25.57)	2173 (25.71)	17,337 (25.55)	
Autumn	21,281 (27.89)	2120 (25.08)	19,161 (28.24)	
Winter	17,411 (22.82)	2030 (24.02)	15,381 (22.67)	
Location				
Northern taiwan	28,858 (37.82)	2932 (34.69)	25,926 (38.21)	< 0.001
Middle taiwan	21,005 (27.53)	2407 (28.48)	18,598 (27.41)	
Southern taiwan	20,482 (26.84)	2310 (27.33)	18,172 (26.78)	
Eastern taiwan	5576 (7.31)	778 (9.20)	4798 (7.07)	
Outlets islands	383 (0.50)	26 (0.31)	357 (0.53)	
Urbanization level				
1 (the highest)	22,374 (29.32)	2052 (24.28)	20,322 (29.95)	< 0.001
2	33,453 (43.84)	4068 (48.12)	29,385 (43.31)	
3	6,949 (9.11)	607 (7.18)	6342 (9.35)	
4 (the lowest)	13,528 (17.73)	1726 (20.42)	11,802 (17.39)	
Level of care				
Hospital center	22,318 (29.25)	2293 (27.13)	20,025 (29.51)	< 0.001
Regional hospital	33,743 (44.22)	3888 (46.00)	29,855 (44.00)	
Local hospital	20,243 (26.53)	2272 (26.88)	17,971 (26.49)	

CVD=Cardiovascular disease; AMI=Acute myocardial infarction; IHD=Ischemic heart disease; MI=Myocardial infarction; CIHD=Chronic ischemic heart disease

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		CVD	_			AMI				=				Ξ			Angina	Angina pectoris			CIHD
Variables	Adjusted HR	- 95% 95% CI CI Lower Upper	95% CI Upper	Ь	Adjusted HR	95% 95% CI CI Lower Upper	95% CI Upper	P A	Adjusted HR	95% 95% CI CI Lower Upper		P Adju	Adjusted 95% HR CI Lower	95% 95% CI CI Lower Upper	% P	Adjusted HR	ted 95% CI Lower	6 95% CI er Upper	P 4	Adjusted HR	95% 95% <i>P</i> CI CI Lower Upper
Gender																					
Male	1.294	1.239	1.239 1.351 <0.001		1.862	1.633	2.123 <	<0.001	1.623	1.455	1.810<0.001		2.056 1.5	1.514 2.792	92 <0.001	01 1.205		1.071 1.356	0.002	1.254	1.191 1.321 <0.001
Female	Reference			т.	Reference			R	Reference			Refe	Reference			Reference	nce		×	Reference	
Age group (years)																					
20-44	Reference			i.z.	Reference			×	Reference			Refe	Reference			Reference	nce		×	Reference	
45-64	2.295	2.116	2.487 <	<0.001	2.014	1.608	2.524 <	<0.001	1.239	1.068	1.437 0.005		7.585 3.2	3.291 17.482	482 <0.001	01 2.303	3 1.873	2.831	<0.001	3.567	3.177 4.003 < 0.001
≥65	4.371	4.047	4.721 <	<0.001	3.807	3.073 4	4.716 <	<0.001	1.657	1.434	1.914<0.001		13.711 6.03	6.026 31.1	31.193 <0.001	01 3.480	0 2.848	4.252	<0.001	7.193	6.434 8.042 <0.001
Low-income household																					
Without	Reference			ix.	Reference			R	Reference			Refe	Reference			Reference	nce		R	Reference	
With	1.314	1.175	1.175 1.470 <0.001		0.803	0.529	1.218 (	0.301	1.448	1.133	1.851 0.003		1.089 0.4	0.479 2.4	2.475 0.840	1.439	9 1.085	5 1.908	0.012	1.197	1.039 1.378 0.013
Catastrophic illness																					
Without	Reference			124	Reference			ĸ	Reference			Refe	Reference			Reference	nce		R	Reference	
With	0.649	909.0	0.606 0.694 <0.001		0.659	0.547 (	0.795 <	<0.001	0.601	0.506	0.714 < 0.001		0.507 0.315	15 0.817	17 0.005	0.521		0.425 0.638	<0.001	0.586	0.539 0.636 < 0.001
Season																					
Spring	Reference			Ľ	Reference			R	Reference			Refe	Reference			Reference	nce		×	Reference	
Summer	0.934	0.880	0.991	0.025	996.0	0.806	1.158 (	0.708	0.991	0.855	1.149 0.907		0.649 0.433	33 0.973	73 0.036	1.036	6 0.881	1 1.219	699.0	0.910	0.848 0.977 0.009
Autumn	0.770	0.725	0.818 <	<0.001	0.831	0.694	0.996	0.045	0.851	0.734 (	0.986 0.032		0.705 0.483		1.029 0.070	0.772	2 0.652	2 0.913	0.003	0.742	0.691 0.797 < 0.001
Winter	0.937	0.882	966.0	0.037	1.253	1.053	1.492 (	0.011	0.970	0.834	1.129 0.694		0.735 0.493		1.095 0.130	11.011	0.856	6 1.194	668.0	0.905	0.842 0.972 0.006
Urbanization level																					
1 (the highest)	0.929	0.865	0.998	0.044	0.743	0.603	0.916 (	0.005	0.892	0.754	1.057 0.187		0.982 0.595		1.621 0.944	1.003	3 0.832	2 1.209	0.978	0.977	0.897 1.065 0.602
2	1.074	1.012	1.140	0.018	0.840	0.703	1.003 (	0.054	0.894	0.775	1.031 0.123		1.156 0.752		1.779 0.508	0.987	7 0.843	3 1.155	0.871	1.156	1.076 1.242 < 0.001
3	0.782	0.713	> 658.0	<0.001	0.629	0.466 (	0.849 (	0.002	0.730	0.586	0.911 0.005		0.982 0.5	0.513 1.8	1.879 0.957	0.790	0 0.621	1 1.004	0.054	0.856	0.767 0.956 0.006
4 (the lowest)	Reference			¥	Reference			R	Reference			Refei	Reference			Reference	nce		×	Reference	
Level of care																					
Hospital center	0.815	0.763	0.870 <0.001	<0.001	2.083	1.682	2.581 <	<0.001	0.881	0.748	1.038 0.129		1.585 1.004		2.502 0.048	18 0.632	2 0.526	6 0.760 <0.001	<0.001	0.829	0.766 0.896 < 0.001
Regional hospital	0.830	0.787	0.875 <	<0.001	1.595	1.325	1.921	<0.001	0.926	0.813	1.055 0.250		1.164 0.782		1.734 0.454	54 0.849	9 0.738	8 0.976	0.022	0.852	0.800 0.908 < 0.001
Local hospital Reference	Reference			124	Reference			R	Reference			Refe	Reference			Reference	ace		R	Reference	

lung, suggesting that cancer is not only associated with musculoskeletal symptoms at the time of cancer diagnosis and management, but also with the previous episodes of symptomatic onset.

There were many limitations in this population-based study. First, the data on severity, impact of the life quality, and specific anatomic location were not available, and the association of different shoulder symptoms with the clinical endpoints could not be investigated. Second, drug treatment for the shoulder discomfort were not analyzed, which would mask the effects of pharmacological regimen on HTN and CVD. Third, although we evaluated several socio-economic conditions such as income, urbanization level and level of care, we did not include education and marital status. Forth, in this retrospective study, the risk factors for HTN and CVD could not be adjusted. Therefore, our findings only suggested association but not causation. Fifth, the diagnosis of shoulder pain is based on NHIRD, which may not be precise.

#### **CONCLUSION**

The patients with shoulder symptoms were associated with the development of HTN and CVD, though the causative relationship could not be determined due to the inability of adjusting all risk factors in a prospective manner. Therefore, future studies are required to elucidate the underlying clinicopathogenesis.

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## **Conflicts of interest**

There are no conflicts of interest.

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