Pectus Excavatum is Associated with a Higher Incidence of Primary Spontaneous Pneumothorax in a Young Population in Taiwan: A Nationwide Population-based Study

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Objectives: To investigate the risk of primary spontaneous pneumothorax among patients with pectus excavatum and to evaluate whether they have a higher risk of primary spontaneous pneumothorax than the general population.

Methods: Patient data from the Taiwan National Health Insurance Research Database from January 1, 2000 to December 31, 2013 were collected. A total of 1,652 patients with pectus excavatum and a retrospective matched comparison control cohort of 6,608 individuals were analyzed. Cox regression analyses were performed to determine the risk of primary spontaneous pneumothorax.

Results: The cumulative incidence rate of primary spontaneous pneumothorax was 0.36% in the study group and 0.15% in the control group. Cox regression analysis with adjustment for gender, age, income, urbanization level, and geographic region revealed that pectus excavatum patients were at significantly greater risk of developing primary spontaneous pneumothorax.

Conclusion: Patients with pectus excavatum have a higher risk of developing primary spontaneous pneumothorax. Surgeons should be aware of the risk of bilateral pneumothorax and carefully evaluate these patients before performing corrective surgery using the Nuss procedure. ***(Thorac Med 2019; 34: 47-57)***

Key words: pectus excavatum, spontaneous pneumothorax, funnel chest

Introduction

Pectus excavatum (PE), also known as "funnel chest", is the most common congenital chest wall deformity and manifests as a depression of the middle or lower sternum and associated costal cartilages. The incidence of PE is reported to be approximately 1:400 live births,

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and males are affected 3 times as often as females [1]. Surgical intervention is usually indicated for patients with cardiopulmonary distress or a Haller index >3.2. The minimally invasive Nuss technique has provided good outcomes in the past 2 decades [2-3].

Primary spontaneous pneumothorax (PSP) is usually caused by a rupture of apical subpleural blebs and air leakage into the pleural cavity. It is more prevalent in tall, thin, and young male populations [4]. Treatment of pneumothorax varies, and includes radiograph follow-up, drainage or surgery. The goal of surgical intervention is to prevent recurrence and life-threatening conditions such as tension pneumothorax. Resection of subpleural blebs and pleurodesis are often applied, but video-assisted thoracoscopic surgery (VATS) is the most common operation performed because it is minimally invasive [5]. In our daily thoracic surgery practice, we may observe a funnel chest and a high Haller index in some PSP patients. However, no studies in the literature have discussed the possible relationship between these 2 diseases. The purpose of this nationwide population-based cohort study was to investigate the association between PE and PSP.

Materials and Methods

Data sources

Taiwan's National Health Insurance Research Database (NHIRD) has been active since the establishment of Taiwan's health care system in 1995. This database includes the medical records of the entire population of approximately 23 million, and National Health Insurance (NHI) coverage was 99.6% in 2009. In our study, data were collected from the Longitudinal Health Insurance Database (LHID), which is a subset database of Taiwan's NHIRD that is released to the public for research purposes. The disease diagnosis codes are based on the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes. The Institutional Review Board of Tri-Service General Hospital approved this study and waived the requirement for written informed consent (TSGHIRB No. 2-105-05-082).

Study design and sampled participants

This was a retrospective cohort design study. Patients with newly diagnosed PE, using ICD-9 code 754.81 (Pectus excavatum), from January 1, 2000 to December 31, 2013, were selected. For the non-PE control cohort, we randomly selected patients without a past history of PE from insured cases. The PE cohort and non-PE control cohort were frequency-matched by age and gender. We chose patients aged between 16 and 40 years because spontaneous pneumothorax seldom occurs after 40 years of age, and the NHI claim code 67045B (Correction of adult chest wall deformity) is used for patients older than 16 years.

Outcome measures

All study participants were followed from the index date. PSP cases with ICD-9-CM code 512.0 (Spontaneous tension pneumothorax), 512 (Pneumothorax and air leak) or 512.81 (Primary spontaneous pneumothorax) were included. The exclusion codes were 512.82 (Secondary spontaneous pneumothorax), 860 (Traumatic pneumothorax), 011.71 (Tuberculous pneumothorax), and 759.82 (Marfan syndrome). The patients' data were reviewed for NHI claim codes 67045B (Correction of adult chest wall deformity), 67048B (Thoracoscopic pleurodesis), 67051B (Thoracoscopic wedge or partial resection of the lung), 56010B (Chest intubation) and 67006B (Closed drainage).

Variates included gender, age group (16-29, 30-39 years), geographical area of residence (north, center, south and east of Taiwan), urbanization level of residence (level 1 to 4), and monthly income (in New Taiwan Dollars [NTD]; <18,000, 18,000-34,999, and ≥35,000).

Statistical analysis

All analyses were performed using SPSS software version 22 (SPSS Inc., Chicago, Illinois, USA). The χ^2 and *t*-tests were used to evaluate differences between the groups with and without PE at baseline and at the study endpoint. The difference in the risk of PSP between the study and control groups was estimated using the Kaplan-Meier method, with the log-rank test to assess the occurrence of cumulative risk, and the results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A 2-tailed p-value <0.05 was considered to indicate statistical significance.

Results

A total of 3,946 patients with PE were identified in the NHIRD, which contains data on 1,978,496 individuals. All patients were between 16 and 40 years of age. After exclusion based on the above exclusion criteria and matching according to gender, age group and index year, there were 1,652 cases in the PE group, and 6,608 controls in the propensity score-matched non-PE group (Figure 1). The characteristic features of both groups at baseline and at the end of the study are listed in Tables 1 and 2. There were no significant differences in gender, age or insured premium. Compared with the controls, the PE group had a lower Charlson Comorbidity Index (CCI) (0.02 vs. 0.14, p<0.001) and more frequently lived in urbanized areas of northern Taiwan (p<0.001). The PE group tended to be diagnosed in the summer (44.6% vs 26.41%; p<0.001). The proportions of those living in northern Taiwan, in a higher urbanized area and with a better hospital level of care were higher in the PE group than in the non-PE group.

The cumulative incidence of PSP was 0.36% (6/1652) and 0.15% (10/6608), respectively, in the PE and non-PE groups. Using the Kaplan-Meier method, the cumulative risk of developing PSP differed significantly between the PE and non-PE groups (p<0.001) (Figure 2). Cox regression and controlling factors such as gender, age, season, urbanization level, and insured premium revealed that the PE group had a HR of 7.83 (p=0.002) of experiencing PSP, compared with the non-PE group. Using stratified variables, the PE 16-29-year-old age group had a HR of 7.969 of developing PSP compared to the non-PE group (Tables 3 and 4). Other factors showed no significant difference.

Discussion

In this population-based study, we observed that patients with PE had a 7.83-fold increased risk of developing PSP, and there was a positive correlation between PE and PSP. We assumed that PE is associated with a higher incidence of developing PSP. The case of a 17-year-old male who developed bilateral pneumothorax after undergoing the Nuss procedure was recently reported from Japan. The cause of the pneumothorax was found to be a bulla at the left apex of the lung with spontaneous rupture, and air went into the right pleural cavity through

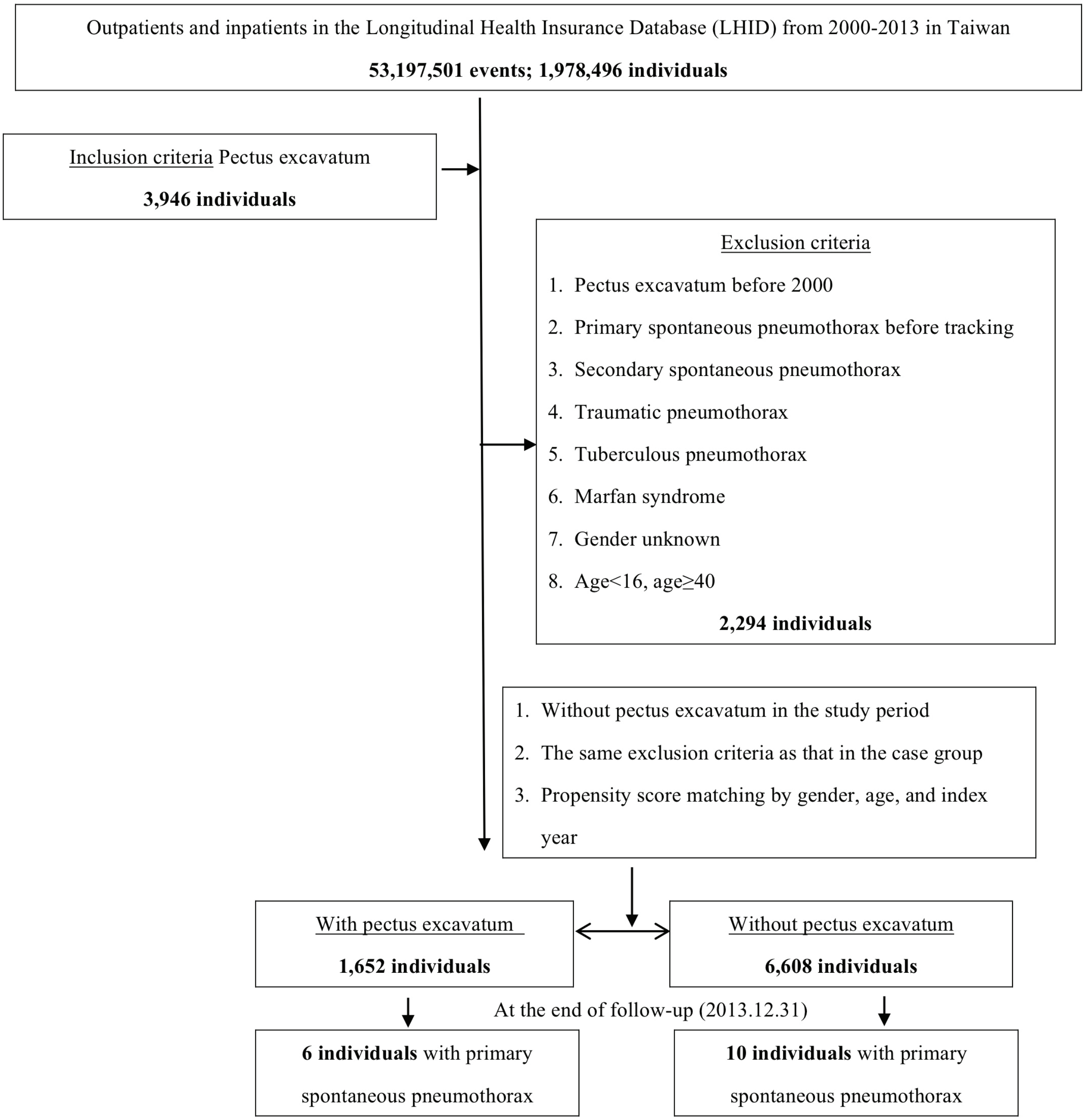

Fig. 1. Flowchart of study sample selection from the National Health Insurance Research Database in Taiwan
Pectus excavatum: ICD-9-CM 754.81; Primary spontaneous pneumothorax: ICD-9-CM 512.0, 512.8; Secondary spontaneous pneumothorax: ICD-9-CM 512.82; Traumatic pneumothorax: ICD-9-CM 860; Tuberculous pneumothorax: ICD-9-CM 011.71; Marfan syndrome: ICD-9-CM 759.82

the substernal tunnel created for the Nuss bar. Video-assisted thoracoscopic wedge resection was then performed without recurrence [6]. Although the exact mechanism regarding the relationship between PE and PSP is still unclear, some hypotheses have been proposed. Previous

Table 1. Baseline Patient Characteristics

Baseline patient characteristics							
Pectus excavatum	Total		With		Without		*P*
Variables	n	%	n	%	n	%	
Total	8,260		1,652	20.00	6,608	80.00	
Gender							0.999
Male	6,455	78.15	1,291	78.15	5,164	78.15	
Female	1805	21.85	361	21.85	1,444	21.85	
Age (years)	24.76±5.54		23.43±5.39		25.10±5.52		0.248
Age group (years)							0.999
16-29	7,090	85.84	1,418	85.84	5,672	85.84	
30-39	1,170	14.16	234	14.16	936	14.16	
Charlson Comorbidity Index (CCI)	0.11±0.68		0.02±0.20		0.14±0.75		<0.001
Season							<0.001
Spring	1,965	23.79	247	14.95	1,718	26.00	
Summer	2,483	30.06	739	44.73	1,744	26.39	
Autumn (September-November)	1,852	22.42	317	19.19	1,535	23.23	
Winter (December-February)	1,960	23.73	349	21.13	1,611	24.38	
Location							<0.001
Northern Taiwan	3,710	44.92	1,159	70.16	2,551	38.60	
Central Taiwan	2,304	27.89	242	14.65	2,062	31.20	
Southern Taiwan	1,848	22.37	223	13.50	1,625	24.59	
Eastern Taiwan + Outlying islands	398	4.82	28	1.69	370	5.60	
Urbanization level							<0.001
1	2,684	32.49	543	32.87	2,141	32.40	
2	3,488	42.23	858	51.94	2,630	39.80	
3	861	10.42	107	6.48	754	11.41	
4 (The lowest)	1,227	14.85	144	8.72	1,083	16.39	
Level of care							<0.001
Medical hospital	1,542	36.20	570	66.90	972	28.52	
Regional hospital	1,301	30.54	184	21.60	1,117	32.78	
Local hospital	1,417	33.26	98	11.50	1,319	38.70	
Insured premium (NT$)							0.302
<18,000	4,161	97.68	838	98.36	3,323	97.51	
18,000-34,999	56	1.31	7	0.82	49	1.44	
≥35,000	43	1.01	7	0.82	36	1.06	

P-value (categorical variables: Chi-square/Fisher's exact test; continuous variables: *t*-test)

Table 2. Patient Characteristics at the End of Follow-up

Patient characteristics at the end of follow-up							
Pectus excavatum	Total		With		Without		*P*
Variables	n	%	n	%	n	%	
Total	4,260		852	20.00	3,408	80.00	
Primary spontaneous pneumothorax							0.043
Without	4,252	99.81	849	99.65	3,403	99.85	
With	8	0.19	3	0.35	5	0.15	
Gender							0.999
Male	3,330	78.17	666	78.17	2,664	78.17	
Female	930	21.83	186	21.83	744	21.83	
Age (years)	27.20±6.61		24.01±5.39		27.99±6.65		0.053
Age group (years)							0.120
16-29	3,457	81.15	722	84.74	2,735	80.25	
30-39	803	18.85	130	15.26	673	19.75	
Charlson Comorbidity Index (CCI)	0.20±1.10		0.04±0.29		0.24±1.21		<0.001
Season							**<0.001**
Spring	940	22.07	121	14.20	819	24.03	
Summer	1,263	29.65	335	39.32	928	27.23	
Autumn (September-November)	1,057	24.81	201	23.59	856	25.12	
Winter (December-February)	1,000	23.47	195	22.89	805	23.62	
Location							<0.001
Northern Taiwan	1,942	45.59	591	69.37	1,351	39.64	
Central Taiwan	1,153	27.07	126	14.79	1,027	30.13	
Southern Taiwan	956	22.44	119	13.97	837	24.56	
Eastern Taiwan + Outlying islands	209	4.91	16	1.88	193	5.66	
Urbanization level							<0.001
1	1,374	32.25	288	33.80	1,086	31.87	
2	1,851	43.45	438	51.41	1,413	41.46	
3	435	10.21	46	5.40	389	11.41	
4 (The lowest)	600	14.08	80	9.39	520	15.26	
Insured premium (NT$)							0.120
<18,000	8,066	97.65	1,624	98.31	6,442	97.49	
18,000-34,999	109	1.32	14	0.85	95	1.44	
≥35,000	85	1.03	14	0.85	71	1.07	

P-value (categorical variables: Chi-square/Fisher's exact test; continuous variables: *t*-test)

data showed that patients with a lower BMI tended to develop PSP [7]. An associated hypothesis is that taller individuals have a higher distending pressure on the alveoli at the apex of the lung. This higher pressure could be related to the trapping of subpleural air and bleb forma-

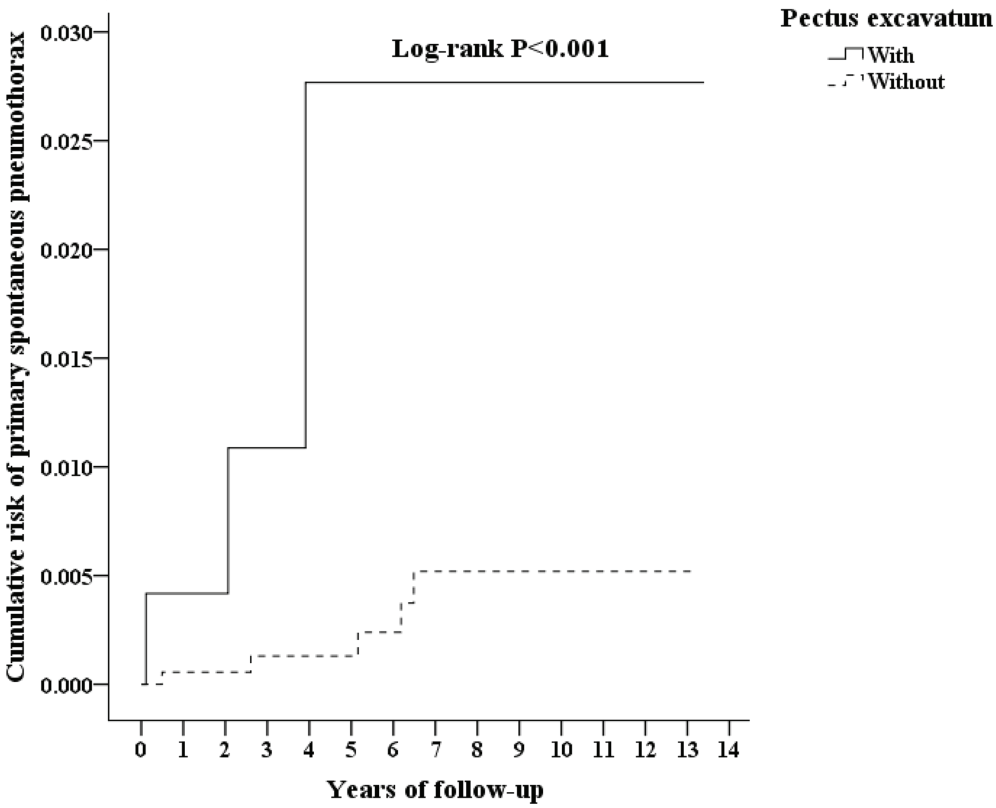

Fig. 2. Kaplan-Meier curve for the cumulative risk of primary spontaneous pneumothorax among patients aged 16-39 years stratified by pectus excavatum using a log-rank test

tion [7]. Casha *et al*. reported a biomechanical hypothesis regarding apical lung disease [8]. They used chest radiographs and computerized tomography images to investigate rib cage measurements in male pneumothorax patients and control groups. To assess pleural stress, a finite element analysis model was developed, which revealed a 20-fold increase in pleural stress in the apex of the chest, with a low thoracic index typical of spontaneous pneumothorax patients, and stress that was magnified by coughing in an antero-posteriorly flattened chest in individuals with a low BMI [9]. Park *et al*. performed a cross-sectional study on growth in PE patients [10]. Data on body measurements of height, weight, BMI and the Haller index were collected, and the findings showed that growth in PE patients is slowed compared with that in the normal population. After corrective surgery, weight and BMI remained low, but height was restored. Therefore, correction of the deformity may have some positive effects on growth.

We have some theories on the seasonal and geographic differences between the 2 groups in Tables 1 and 2, based on our thoracic surgery practice. Patients with PE often have a higher socioeconomic status and usually seek medical advice or surgical intervention during summer vacation. The above observation is compatible with our results.

Our study showed that young PE patients had a 7.83-fold increased risk of developing

Table 3. Primary Spontaneous Pneumothorax Factors at the End of Follow-up Using Cox Regression

Primary spontaneous pneumothorax factors at the end of follow-up using Cox regression								
Variables	Crude HR	95% CI	95% CI	*P*	Adjusted HR	95% CI	95% CI	*P*
Pectus excavatum								
Without	Reference				Reference			
With	12.313	3.955	38.336	<0.001	7.830	2.114	29.004	0.002
Gender								
Male	1.977	0.449	8.702	0.367	1.534	0.339	6.932	0.578
Female	Reference				Reference			
Age (years)	0.758	0.674	0.855	<0.001				
Age group (years)								
16-29	Reference				Reference			
30-39	0.373	0.132	1.050	0.062	0.552	0.232	3.023	0.328
Charlson Comorbidity Index (CCI)	1.211	1.055	1.391	0.006	1.265	0.303	3.871	0.007
Season								
Spring	Reference				Reference			
Summer	1.129	0.319	4.004	0.851	0.837	0.232	3.023	0.786
Autumn (September-November)	1.135	0.320	4.024	0.844	1.083	0.303	3.871	0.903
Winter (December-February)	0.000	-	-	0.958	0.000	-	-	0.961
Location					Had multicollinearity with urbanization level			
Northern Taiwan	Reference				Had multicollinearity with urbanization level			
Middle Taiwan	0.000	-	-	0.970	Had multicollinearity with urbanization level			
Southern Taiwan	0.224	0.051	0.986	0.048	Had multicollinearity with urbanization level			
Eastern Taiwan + Outlying islands	0.000	-	-	0.979	Had multicollinearity with urbanization level			
Urbanization level								
1	Reference				Reference			
2	0.710	0.267	1.893	0.494	0.900	0.325	2.490	0.839
3	0.000	-	-	0.981	0.000	-	-	0.981
4 (The lowest)	0.000	-	-	0.976	0.000	-	-	0.975
Insured premium (NT$)								
<18,000	Reference				Reference			
18,000-34,999	0.000	-	-	0.760	0.000	-	-	0.991
≥35,000	0.000	-	-	0.813	0.000	-	-	0.995

HR: hazard ratio, CI: confidence interval, Adjusted HR: Adjusted variables listed in the table

PSP. The possible reason may be that PE tends to lead to retarded growth and low BMI, which is correlated with higher pleural stress in the lung apex, which then causes blebs or bulla formation.

There are some limitations to our study. This was a retrospective study, and the NHIRD does not contain detailed information on pa-

Table 4. Primary Spontaneous Pneumothorax Factors at the End of Follow-up Stratified by Variables Listed in the Table Using Cox Regression

Primary spontaneous pneumothorax factors at the end of follow-up stratified by variables listed in the table using Cox regression											
Pectus excavatum		With			Without		Ratio	Adjusted HR	95%CI	95%CI	*P*
Variables	Event	PYs	Rate (per 105 PYs)	Event	PYs	Rate (per 105 PYs)					
Total	6	9,930.45	60.42	10	40,223.10	24.86	2.430	7.830	2.114	29.004	0.002
Gender											
Male	4	8,381.56	47.72	10	31,142.65	32.11	1.486	5.097	1.212	21.439	0.026
Female	2	1,548.89	129.12	0	9,080.45	0.00	-	-	-	-	-
Age group (years)											
16-29	6	8,354.97	71.81	4	14,533.74	27.52	2.609	7.969	1.578	40.240	0.012
30-39	0	1,575.48	0.00	6	25,689.36	23.36	0.000	0.000	-	-	0.990
Season											
Spring	0	1,714.54	0.00	4	8,598.21	46.52	0.000	0.000	-	-	0.996
Summer	4	3,286.00	121.73	2	11,136.82	17.96	6.778	3.851	0.638	23.248	0.142
Autumn (September-November)	2	2,565.71	77.95	4	11,549.04	34.63	2.251	7.567	0.764	74.947	0.084
Winter (December-February)	0	2,364.20	0.00	0	8,939.03	0.00	-	-	-	-	-
Urbanization level											
1	4	4,029.44	99.27	4	11,661.39	34.30	2.894	9.112	0.015	70.419	0.359
2	2	4,998.31	40.01	6	16,694.21	35.94	1.113	2.420	0.304	19.289	0.404
3	0	258.93	0.00	0	4,656.67	0.00	-	-	-	-	-
4 (The lowest)	0	643.77	0.00	0	7,210.83	0.00	-	-	-	-	-
Insured premium (NT$)											
<18,000	6	9,679.47	61.99	10	39,371.13	25.40	2.440	7.830	2.114	29.004	0.002
18,000-34,999	0	117.59	0.00	0	531.42	0.00	-	-	-	-	-
≥35,000	0	73.39	0.00	0	320.55	0.00	-	-	-	-	-

PYs: Person-years; Adjusted HR: Adjusted hazard ratio: Adjusted for the variables listed in the Cox regression table; CI: confidence interval

tients' weight, height, BMI or Haller index. Furthermore, patients with PE without symptoms or a lower Haller index may not be registered in this database. This may be related to the relatively small patient population. We also could not assess the imaging studies to verify lung conditions, including bleb formation. Further studies are required to clarify the relationship between PE and PSP.

We suggest that in the evaluation of a PE patient with a low BMI and a high Haller index based on a CT scan, bleb formation should be assessed at the apex. Surgeons should consider surgical intervention with correction of the deformity and bleb resection at the same time, due to the higher risk of PSP development and greater operative difficulty because of subsequent pleural adhesions or possible life-threatening bilateral pneumothorax after the Nuss procedure.

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漏斗胸與原發性自發性氣胸具有相關性：台灣健保資料庫研究

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漏斗胸（ICD-9-CM 754.81）是否較一般族群更容易增加自發性氣胸（ICD-9-CM 512.0 + ICD-9-CM 512.8）的風險。

臨床上偶而有男性瘦高病人因自發性氣胸來診發現有漏斗胸情形，或是因為漏斗胸來診於電腦斷層中發現異常肺泡組織（可能導致原發性自發性氣胸），以百萬歸人檔處理，希望可以看到其意義。

使用百萬歸人檔做回溯性分析，並以一比四做配對，可找出漏斗胸組 1,652 人及一般組 6,608 人，並使用迴歸分析來判斷發生自發性氣胸之風險。

結果：在累積自發性氣胸之發生率，可發現漏斗胸組為 0.36% 大於一般組的 0.15%，經過調整性別，年齡，投保級距及居住地都市化程度後，發現漏斗胸組別有較高風險發生自發性氣胸（Hazard ratio: 7.83, 95% CI 2.114-29.004, p=0.002）。

結論：漏斗胸族群與自發性氣胸之族群有高相關性，由於以納式微創矯正術治療可能導致雙側肋膜腔交通，若發生氣胸可能造成嚴重且致命的雙側氣胸，外科醫師在術前評估時，應考量有無原發性自發性氣胸的危險因素如斷層掃描發現異常肺泡等再行手術。***(胸腔醫學 2019; 34: 47-57)***

關鍵詞：漏斗胸，自發性氣胸

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