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Pleural Empyema and Aortic Aneurysm

A Retrospective National Population-Based Cohort Study

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Abstract: Pleural empyema (PE) may evolve into necrosis, fistula in the thorax, and sepsis; thus, it is also associated with high mortality.

We investigated and analyzed the risk of aortic aneurysm (AA) in a cohort study of patients with PE.

A total of 34,250 patients diagnosed with PE were identified as the PE cohort, and 137,000 patients without PE were selected randomly as the control group and matched by sex, age, and index year of PE diagnosis. Patients ages 20 years and younger with a history of AA were excluded. The risk of AA was analyzed using a Cox proportional hazards regression model.

Excess risk of AA development was 1.69-fold higher in PE patients (adjusted hazard ratio [aHR] = 1.69; 95% confidence interval [CI] = 1.39–2.05) compared with non-PE patients. The patients with PE exhibited a greater adjusted risk of AA (aHR = 2.01; CI = 1.44–2.81) even if they did not have any of the 9 comorbidities included in our analysis (diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, heart failure, cardiac artery disease, stroke, bacterial endocarditis, and rheumatic endocarditis). Compared with the patients without any of the 9 comorbidities or PE, the patients with only PE had a greater risk of developing AA (aHR = 2.00; CI = 1.43–2.79). The PE cohort had a significantly higher cumulative incidence of AA than the non-PE cohort did during 12 years of follow-up.

In a large-scale cohort, patients with PE are linked with an increased risk of AA.

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Abbreviations: AA = aortic aneurysm, aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, CVD = cardiovascular disease, HR = hazard ratio, IA = infectious aneurysm, ICD-9-CM = International Classification of Diseases 9th Revision Clinical Modification, IRB = Institutional Review Board, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = Taiwan National Health Insurance, NHIRD = National Health Insurance Research Database, PE = pleural empyema.

INTRODUCTION

Pleural empyema (PE), also known as empyema thoracis and pyothorax, is pus or bacteria in the pleural space.[1] Despite ever-advancing technology, PE remains endemic worldwide. PE may evolve into necrosis, fistula in the thorax, and sepsis; thus, it is also associated with high mortality. The mortality rate of patients with PE can be up to 20%,[2,3] even under strict therapeutic regimens. Moreover, the incidence of PE has increased worldwide in past years[1,3–5]; a review article stated that the rate of pneumococcal pneumonia in adults with empyema increased from 7.6% (1996–2001) to 14.9% (2005–2011).[6]

Aortic aneurysm (AA), a pathological dilation of the aortic wall, is typically classified as resulting from atherosclerotic processes, inflammatory courses, aortic dissection, infection, trauma, or a congenital etiology.[7] Confirmed risk factors of AA include smoking, hypertension, age, and hyperlipidemia.[8,9] The most common form of AA is abdominal AA (AAA). An American systematic review estimated that AAA affects up to 1.3% of women and up to 7.2% of men ages 50 years or older.[10] AAA also accounts for more than 10,000 deaths per year in the United States.[11]

A form of AA, infectious aneurysm (IA), also known as mycotic aneurysm, consists of dilatations caused by devastation of the aortic wall by organisms. The mechanisms of underlying IA include bacteremic seeding of existing atherosclerotic plaque or damaged intima (most common), septic emboli of the aortic vasa vasorum, and contiguous infective focus extending to the aortic wall (rare).[12] Diagnosing IA as early as possible is

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crucial because the natural course of untreated IA is fatal.[12,13] The factors predisposing arteries to IA are impaired immunity, infective endocarditis, congenital aortic anomalies, aortic trauma, and atherosclerosis.[12,14,15] Old age, non-*Salmonella* infection, location of the IA, and with/without operation have been identified as determinants of IA mortality.[12,16,17]

PE has been reported to be associated with IA. Thoracic IA resulting in death has been suspected to be caused by bilateral encapsulation of PE.[18] Sommer et al[19] also described a septic rupture of the aorta in a patient with PE. Atherosclerosis and preexisting aneurysms precipitate IA; therefore, further large-scale investigation is warranted to elucidate the relationship between PE and all types of AA. Thus, we conducted this retrospective nationwide cohort study by using a health insurance database representative of the population of Taiwan. We hypothesized that PE is linked with an increased risk of AA.

MATERIALS AND METHODS

Data Source

The Taiwan National Health Insurance (NHI) program is a mandatory, single-payer health insurance system in which all residents are required to participate. The NHI program was initiated by the Taiwan Government in 1995 and covers more than 99% of the 23 million residents of Taiwan.[20] The NHI Research Database (NHIRD) is a nationwide database of reimbursement claims data obtained from the NHI program and is maintained by the National Health Research Institutes (NHRI). The NHRI encrypts all patient identification numbers for the protection of privacy and provides researchers with anonymous numbers to link the relevant claims information such as patient sex, date of birth, medical claims and types of care, and medication prescriptions. For this cohort study, we used a subset of the NHIRD including files of inpatient claims and the Registry of Beneficiaries. Disease diagnosis was based on disease records according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Study Patients

Patients newly diagnosed with PE (ICD-9-CM codes 510, 510.0, 510.9) from 2000 to 2011 were identified from the inpatient claims data as a PE cohort. The date of the first admission for PE was used as the index date.

Patients diagnosed with AA (ICD-9-CM code 441) at the baseline, ages under 20 years, and with incomplete information on demographics were excluded. Four times as many control patients as PE patients were randomly selected from all NHI beneficiaries without PE, and the same exclusion criteria were applied. The non-PE cohort patients were frequency matched with the PE patients by age (in 5-year bands), sex, and the index year. All study patients were followed-up until they were diagnosed with AA, which was identified on the basis of hospitalization records. The follow-up period was the period from the index date to the date of AA diagnosis, withdrawal from the insurance system, death, or the end of 2011.

Comorbidities

The baseline comorbidities of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401405), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 491, 492, 496), heart failure (ICD-9-CM code 428), coronary artery disease (CAD) (ICD-9-CM codes 410–414), stroke (ICD-9-CM codes 430–438), bacterial endocarditis (ICD-9-CM code 421), and rheumatic endocarditis (ICD-9-CM codes 391.1, 394.0–397.9) were identified according to diagnoses in the hospitalization records prior to the index date.

Statistical Analysis

The baseline characteristics and comorbidities of the PE and non-PE cohorts were compared. Chi-squared and *t* tests were used to determine the differences in categorical and continuous variables, respectively, between the 2 cohorts. The AA cumulative incidence curves were estimated for both cohorts by using Kaplan–Meier analysis and a log-rank test. The overall, sex-, age-, comorbidity-, and follow-up-time-specific incidence density rates (per 1000 person-years) of AA were calculated for each cohort. Univariate and multivariate Cox proportional hazards regression analyses were used to assess the hazard ratio (HR) and 95% confidence interval (CI) of AA development associated with PE, compared with that of the non-PE cohort. The multivariate models were simultaneously adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, bacterial endocarditis, and rheumatic endocarditis, all of which showed a significant difference (Table 1). Further data analysis was performed to evaluate the joint effect for AA between PE and AA-associated risk factors. We used SAS software (version 9.4 for Windows; SAS Institute Inc., Cary, NC) for all data analyses. A P value < 0.05 was considered statistically significant.

RESULTS

This study consisted of 34,250 patients with PE and 137,000 patients without PE. Table 1 shows the characteristics of the study patients in the 2 cohorts; men (77.2%) and patients older than 65 years of age (49.0%) were predominant in both groups. The mean ages of the PE and non-PE cohorts were 62.5 ± 16.5 and 61.9 ± 16.6 years, respectively. Compared with the non-PE cohort, comorbidities were more prevalent in the PE cohort ($P < 0.001$). The mean follow-up periods were 3.27 ± 3.25 years in the PE cohort and 5.36 ± 3.10 years in the non-PE cohort ($P < 0.001$). The Kaplan–Meier analysis revealed that the cumulative incidence of AA was higher for the PE cohort than for the non-PE cohort (log-rank test, $P < 0.001$; Figure 1).

The overall incidence density rate of AA was 1.59-fold higher in the PE cohort than in the non-PE cohort (1.32 vs 0.83 per 1000 person-years), with an adjusted HR (aHR) of 1.69 (95% CI, 1.39–2.05) after controlling for age, sex, and comorbidities (diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, bacterial endocarditis, and rheumatic endocarditis; Table 2). Except for the patients ages $\geq$ 80 years, the patients with PE had a significantly higher risk of AA than the patients without PE did, stratified by sex (aHR = 2.22, 95% CI = 1.43–3.46 for women; aHR = 1.59, 95% CI = 1.28–1.97 for men), age group (aHR = 4.22, 95% CI = 2.24–7.95 for $\leq$49 years; aHR = 1.68, 95% CI = 1.08–2.63 for 50–64 years; aHR = 1.42, 95% CI = 1.06–1.89 for 65–79 years), and comorbidities (aHR = 2.01, 95% CI = 1.44–2.81 for comorbidities; aHR = 1.31, 95% CI = 1.03–1.65 for no comorbidities). The analysis stratified by follow-up duration revealed that the PE

TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Patient With and Without Pleural Empyema

	Pleural Empyema		
	No (N = 137,000)	**Yes (N = 34,250)**	***P* Value**
Gender			0.99
Women	31,276 (22.8)	7819 (22.8)	
Men	105,724 (77.2)	26,431 (77.2)	
Age stratified			0.99
≤49	33,976 (24.8)	8494 (24.8)	
50–64	35,948 (26.2)	8987 (26.2)	
65–79	46,046 (33.6)	11,506 (33.6)	
80+	21,030 (15.4)	5263 (15.4)	
Age, mean ± SD*	61.9 (16.6)	62.5 (16.5)	<0.001
Comorbidity			
Diabetes	10,861 (7.93)	10,326 (30.2)	<0.001
Hypertension	21,521 (15.7)	13,065 (38.2)	<0.001
Hyperlipidemia	4867 (3.55)	2481 (7.24)	<0.001
COPD	6557 (4.79)	7018 (20.5)	<0.001
Heart failure	3572 (2.61)	3552 (10.4)	<0.001
CAD	10,566 (7.71)	5364 (15.7)	<0.001
Stroke	10,012 (7.31)	7393 (21.6)	<0.001
Bacterial endocarditis	85 (0.06)	241 (0.70)	<0.001
Rheumatic endocarditis	1008 (0.74)	666 (1.94)	<0.001

Chi-squared test.
CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, SD = standard deviation.
* *t* test.

cohort had a higher risk than the non-PE cohort did during the 2 years of follow-up (aHR = 1.37, 95% CI = 1.04–1.80). PE patients with only bacterial endocarditis had the highest risk of AA (aHR = 32.7, 95% CI = 4.59–233.0), followed by those with only CAD (aHR = 2.04, 95% CI = 1.25–3.32), and those with only PE (aHR = 2.00, 95% CI = 1.43–2.79). Moreover, compared with the non-PE patients without these comorbidities, among patients with PE, those with 2 or more comorbidities were at a significantly increased risk of AA (aHR = 2.81, 95% CI = 2.17–3.63), followed by those with 1 comorbidity (aHR = 2.11, 95% CI = 1.49–2.98; Table 3).

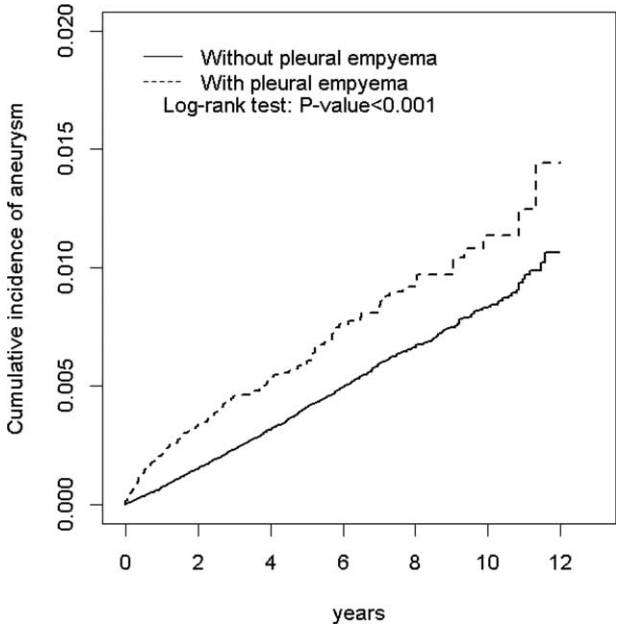

FIGURE 1. Cummulative incidence of aortic aneurysmin patients with pleural empyema and comparison patients.

DISCUSSION

We hypothesized that PE is independently associated with subsequent AA, regardless of the antecedent comorbidities. To elucidate the relationship between AA risk and PE, in this study, the interference of sex, age, and comorbidities was reduced as much as possible by statistically adjusting for the risk of AA in the PE group.

We investigated the AA incidence rate in 34,250 patients with PE by analyzing claims data from the NHIRD. The PE group exhibited a significantly higher risk (HR = 1.69; 95% CI = 1.39–2.05) of AA compared with the non-PE group. Our data revealed that the PE patients exhibited a higher risk of developing AA regardless of sex, and age seemed to exert a reversed effect on the risk of developing AA. The overall incidence of AA was 59% higher in the PE than in the non-PE group. A significantly higher risk of PAD was noted after the 2nd year until the end of the follow-up period.

Several factors may be considered surrogates for AA to explain the relationship between PE and AA. First, in this study, the patients with PE were older and had a higher incidence of comorbidities compared with the non-PE patients (Table 1). Patients with diabetes mellitus are not only at an increased risk of *Klebsiella pneumoniae*-related empyema[21] but also have a greater risk of atherosclerosis. Moreover, age, hypertension, hyperlipidemia, and COPD are risk factors for AA[8,22]; furthermore, patients with CAD or stroke have a higher risk of general atherosclerosis. In this study, the patients with these

TABLE 2. Comparison of Incidence Densities of Aneurysm Hazard Ratio Between With and Without Pleural Empyema by Gender, Age, Comorbidity, and Follow-Up Time

	Pleural Empyema							
	No			Yes				
	Event	PY	Rate	Event	PY	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
All	607	733,919	0.83	148	111,959	1.32	1.59 (1.33, 1.90)***	1.69 (1.39, 2.05)***
Gender								
Women	91	169,111	0.54	32	24,766	1.29	2.35 (1.57, 3.53)***	2.22 (1.43, 3.46)***
Men	516	564,808	0.91	116	87,192	1.33	1.45 (1.19, 1.78)***	1.59 (1.28, 1.97)***
Stratify age								
≤49	22	205,558	0.11	25	40,296	0.62	5.78 (3.26, 10.3)***	4.22 (2.24, 7.95)***
50–64	92	205,330	0.45	34	33,032	1.03	2.33 (1.57, 3.45)***	1.68 (1.08, 2.63)*
65–79	305	245,606	1.24	63	30,962	2.03	1.67 (1.27, 2.19)***	1.42 (1.06, 1.89)*
80+	188	77,425	2.43	26	7669	3.59	1.44 (0.95, 2.17)	1.26 (0.82, 1.94)
Comorbidity								
No	349	594,436	0.59	39	51,683	0.75	1.29 (0.93, 1.80)	2.01 (1.44, 2.81)***
Yes	258	139,483	1.85	109	60,276	1.81	0.97 (0.77, 1.21)	1.31 (1.03, 1.65)*
Follow-up time, y								
≤2	195	257,785	0.76	81	45,661	1.77	2.32 (1.79, 3.00)***	1.17 (0.90, 1.51)
>2	412	476,133	0.87	67	66,297	1.01	2.16 (1.63, 2.87)***	1.37 (1.04, 1.80)*

Adjusted HR = multiple analysis including age, gender, and co-morbidities of diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, bacterial endocarditis, and rheumatic endocarditis, CAD = coronary artery disease, CI = confidence interval, Comorbidity = patients with any 1 of the comorbidities diabetes, hypertension, hyperlipidemia, COPD, heart failure, CAD, stroke, bacterial endocarditis, and rheumatic endocarditis were classified as the comorbidity group, COPD = chronic obstructive pulmonary disease, Crude HR = relative hazard ratio, HR = hazard ratio, PY = person-years, Rate = incidence rate, per 1000 person-years, 80+ = people ages 80 years or more than 80 years.

* $P < 0.05$.

*** $P < 0.001$.

comorbidities tended to exhibit a greater risk of AA than did the patients without these comorbidities.

Second, IA is a form of AA; although considerably rare, an association between PE and IA has been proposed.[18,23] A case resulting in death indicated that bacterial extension of PE may cause fatal IA.[18] Moreover, there are outcomes of researches support a link between IA and PE: Dénes et al[24] stated that *Streptococcus pneumonia* infection intensifies atherosclerosis. Atherosclerosis is a crucial risk factor for aortic infection 15 and AA. Moreover, *S pneumonia* is a common pathogen of PE,[6,25] and it is also a pathogen of IA.[26–29] Thus, patients with *S pneumonia* empyema may be at a higher risk of AA. *Mycoplasma pneumonia*, a possible pathogen of PE,[30,31] is suspected to be associated with the development of subsequent AA

TABLE 3. Joint Effects for Aneurysm Between Pleural Empyema and Aortic Aneurysm-Associated Risk Factor

Variable	N	No. of Events	Rate	Adjusted HR	95% CI
None	103,884	349	0.59	1	Reference
Only pleural empyema	12,371	39	0.75	2.00	1.43, 2.79***
Only diabetes	2522	7	0.60	0.74	0.35, 1.56
Only hypertension	5618	44	1.72	1.58	1.15, 2.17**
Only hyperlipidemia	505	0	0.00	–	–
Only COPD	1540	7	1.05	0.75	0.35, 1.59
Only heart failure	249	2	1.94	1.64	0.41, 6.58
Only CAD	1510	17	2.19	2.04	1.25, 3.32**
Only stroke	1404	13	1.97	1.73	0.99, 3.02
Only bacterial endocarditis	18	1	13.1	32.7	4.59, 233.0***
Only rheumatic endocarditis	84	0	0.00	–	–
Pleural empyema with any 1 comorbidity	8164	35	1.24	2.11	1.49, 2.98***
Pleural empyema with more than 2 comorbidity	13,715	74	2.31	2.81	2.17, 3.63***

Adjusted HR = multivariable analysis including age, and gender, CAD = coronary artery disease, CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, Rate = per 1000 person-year.

** $p < 0.01$.

*** $p < 0.001$

because of cross-reactivity of the human heat shock protein with the immune response to bacterial antibodies[32] or because of increased adventitial inflammation, inhibition of TIMP-1 activity, and increased collagen degradation.[33] Methicillin-resistant *Staphylococcus aureus* (MRSA), a severe cause of empyema, was reported to be associated with atherosclerosis[34]; thus, patients with MRSA-induced empyema may be at a higher risk of AA. There are 2 potential mechanisms of PE inducing IA. First, extension of a contiguous infection (PE) can lead to an IA, and has been described.[35–38] The histological finding in a previous article even suggested that an IA of the thoracic aorta was caused by direct bacterial extension from PE.[18] However, further investigations of the pathogenesis including signal transduction pathway and gene regulation are required. Second possible mechanism of PE inducing IA: bacteremic seeding of an atherosclerotic lesion, existing intimal injury, or preexisting aneurysm. PE with concomitant bacteremia is not a rare event.[39,40] It is also well-known that the intima is normally resistant to infection; however, bacteria can pass through the intima into deeper layers of the arterial wall when the intima is diseased. Then, after focal suppuration and perforation, an IA occurs. Moreover, the aorta is the common location affected by primarily bacteremic seeding, since it is the common site of atherosclerosis.

The strength of our study is that it is the first cohort study focusing on AA in PE patients, using consistent data collection and a large sample size for meaningful analyses. However, the study also had several limitations. First, despite adjustment for confounding factors, we may not have completely avoided the confounding effects of the preexisting comorbidities of AA, potentially resulting in an imprecise estimation of the relationship between PE and AA. Second, NHIRD diagnoses are documented using ICD-9-CM codes, and data on environmental risk factors influencing AA and PE, such as smoking[1] and family history, could not be obtained. Third, the etiologic, anatomic, and pathologic characteristics of AA were unavailable in the NHIRD database. Thus, association of PE with different types of AA, in particular the IA or mycotic aneurysm, could not be analyzed. Finally, although the outcome of our research is consistent with the studies on the possible role of PE in increasing risk of AA, there is still a lack of experimental demonstration and biological plausibility. Further researches to unravel the pathogenesis between PE and AA are warranted.

In conclusion, patients with PE are linked with an increased risk of AA, regardless of preexisting comorbidities. AA in both infectious and noninfectious forms is life-threatening; therefore, we strongly suggest further investigation of expected possibility and frequency of AA may minimize its severe consequences.

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