中 國 醫 藥 大 學
臨床醫學研究所
碩士學位論文

肺炎鏈球菌感染增加急性冠心症的風險

Pneumococcal Pneumonia and the Risk of Acute Coronary Syndrome

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碩士班 學位考試

論文題目

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本論文係 王駿丞 於中國醫藥大學臨床醫學研究所完成之碩士論文，經考試委員審查及口試合格，特此證明。

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中華民國　一〇二　年　7　月　10　日

Abstract

Introduction

A link between infection and the incidence of acute coronary syndrome (ACS) has been suggested. The reason of infection leading to ACS maybe explained by increased inflammation, hemoconcentration, imbalance between oxygen demand and supply. Of all bacterial infections, pneumonia is mostly associated with the development of ACS.Streptococcus pneumonia is the most common causative pathogen of community acquired pneumonia, and Streptococcus pneumonia infection is asscociated with clinically severe form of pneumonia. However, relatively few studies have specifically discussed the association between pneumococcal pneumonia and ACS. This study focuses on investigating the association between pneumococcal pneumonia and the development of ACS. This is an important research topic, because it may provide a rationale for implementing pneumococcal vaccination in preventing ACS, especially in Asian populations.

Materials and methods

We conducted a longitudinal cohort study from the Taiwan National Health Institute Research Database (NHIRD). The study sample consisted of 20111 patients who received the first diagnoses of pneumococcal pneumonia between 1997 and 2010. We age and sex-matched these participants with 80444 control patients without a previous diagnosis of either pneumococcal pneumonia or ACS. We first compared the differences of baseline demographics between the two groups with chi-square test.We consider hypertension,

diabetes, hyperlipidemia, and chronic obstructive pulmonary disease as potential covariates. We used the follow-up person-years to assess the incidence density rates until ACS was either identified or censored.We used Poisson regression models to evaluate the ratios of the pneumococcal pneumonia cohort to the controls (relative risk) and 95% confidence intervals (CI). We used the Cox proportional-hazards model to investigate whether pneumococcal pneumonia is independently associated with ACS after adjusting for all potential risk factors. We then used Kaplan-Meier analysis and the log-rank test to compare the cumulative risk of developing ACS between the 2 groups.

Results

The incidence of ACS was 43.1 per 10000 person-years in the pneumococcal pneumonia and 22.4 per 10000 person-years in the control group.(Incidence rate ratio: 1.92; 95% confidence interval: 1.70-2.17). Higher proportions of hypertension, diabetes, hyperlipidemia and chronic obstructive pulmonary disease are noted in the pneumococcal pneumonia group. After adjusting for age, sex, and comorbidities, we found that the risk of ACS was 47% higher in the pneumococcal pneumonia group than in the control group (95% confidence interval: 1.24-1.73). We divided the time lag into 3 periods, (≤ 3 mo, 3 mo to 1 y and >1 y), and found that the highest relative risk of incidence of ACS between the 2 groups was within the first 3 months after infection with pneumococcal pneumonia (Incidence rate ratio: 3.90; 95% confidence interval: 2.46-6.18). The Kaplan-Meier survival curve showed that the risk of ACS was higher in the pneumococcal pneumonia group than in the control group (Log-rank test, $P<0.0001$).

Conclusion

Pneumococcal pneumonia is associated with an increased incidence of ACS, and the relative risk of incidence of ACS between the two groups is highest within the first three months. Our study implied that pneumococcal vaccination may be considered as an option for prevention of incidence of ACS.

中文摘要:

簡介:

臨床上感染與急性冠心症之間的關聯過去的研究已被提及。感染會造成急性冠心症的病理機轉包含發炎反應，血液容積濃縮，與氧氣供需的失衡。在所有感染中，肺炎感染與急性冠心症之間最為相關肺炎鏈球菌是社區性肺炎最好發的致病菌，且往往造成臨床上表現較嚴重的社區性肺炎。然而, 肺炎鏈球菌的感染與急性冠心症的關聯則較少被提及。我們的研究主要目的是探討肺炎鏈球菌的感染與急性冠心症的關聯。我們的研究可以提供一個想法，就是肺炎鏈球菌疫苗可能減少未來得到急性冠心症的風險。

研究方法:

我們利用台灣健保資料庫作一個回溯性世代研究。我們搜索從民國 86 年至民國 99 年共 20111 位病人初次診斷為肺炎鏈球菌感染，且之前未曾患有急性冠心症的病人。對照組則是 80444 位過去未曾診斷有任何形式肺炎或是急性冠心症的病人。肺炎鏈球菌組與對照組的樣本是依 1:4 的比例且分別依年齡與性別去配對。兩組的基本資料我們用卡方分析作比較，我們考慮高血壓、糖尿病、高血脂及慢性呼吸道阻塞疾病當作共變項。我們使用 Cox-Proportional Hazard model 來評估經過多變項分析，肺炎鏈球菌感染是否是得到急性冠心症的一個危險因子。我們用 Kaplan-Meier curve 與 log-rank test 來探討肺炎鏈球菌組與對照組長期得到急性冠心症的風險是否有所不同。

研究結果:

在肺炎鏈球菌組中得到急性冠心症的發生率是 43.1/10000 人年，在對照組中得到急性冠心症的發生率是 22.4/10000 人年。(發生率比例為 1.92,95%信賴區間為 1.70-2.17) 經過年紀、性別與其它共變項的校正後，肺炎鏈球菌組長期得到急性冠心症的風險仍比對照組增加 47%，且其風險的增加呈統計上有意義相關。(95%信賴區間為 1.24-1.73)

我們把臨床上從感染肺炎鏈球菌到得到急性冠心症的時間分為三個時段(小於 3 個月, 3 個月至 1 年, 及大於一年)，我們發現肺炎鏈球菌組在感染的前三個月得到急性冠心症的相對風險與對照組比較起來增加最多。(發生率比例為 3.9, 95%信賴區間為 2.46-6.18)

我們用 Kaplan-Meier curve 比較兩組發生急性冠心症, 肺炎鏈球菌組得到急性冠心症的風險仍顯著的比對照組高。(Log-rank test, P<0.0001)

結論:

肺炎鏈球菌感染會增加得到急性冠心症的風險。病人在得到肺炎鏈球菌感染的前三個月得到急性冠心症的相對風險最高。我們的研究也建議未來發展合適的疫苗可能可以減少得到急性冠心症的風險。

誌　　謝

時光飛逝, 兩年的碩士班學業已結束。回首這兩年,每星期往來於學校與醫院,實驗室間,常忙得不可開交。然而, 從師長的手中拿下畢業證書,內心著實有一種苦盡甘來之感觸。今日能如願畢業, 首先需感謝中國醫藥大學臨床醫學研究所汪貴珍教授與醫學系高嘉鴻教授,感謝他們對我論文的指導。感謝中國醫藥大學公共衛生學系,感謝他們對統計方面的幫忙與分析。另外,感謝台中慈濟醫院人體試驗委員會與研究部,感謝他們對我碩士研究的支持。感謝台中慈濟醫院心臟內科林茂仁主任對我唸研究所的大力支持,以及科內同仁幫忙分擔科內臨床與行政事物。也感謝中國醫藥大學藥學系吳介信主任,台中榮民總醫院核醫科林萬鈺主任,彰賓秀傳核醫科洪光威主任,感謝他們百忙中撥空擔任我的碩士口試委員,並給予寶貴的建議。最後,感謝我的家人能體量我兼顧學業與工作的辛苦,幫我許多生活上的事,讓我無後顧之憂。

王駿丞　　謹誌

中華民國　102 年 7 月 24 日

目　　錄

Introduction:

Study Background

Previous research has proposed an association between acute bacterial infection and an increased incidence of acute coronary syndrome (ACS).[1] The reason of infection leading to ACS may be explained by increased inflammation, hemoconcentration, and imbalance betweeb oxygen demand and supply. Of all acute bacterial infections, acute bacterial pneumonia is most widely discussed. Pneumonia is still the leading cause of death in Western countries and the mortality rate of community acquired pneumonia(CAP) remains high at approximately 5%-15%.[2] Pneumonia may cause a ventilation-perfusion mismatch, hypoxemia, or hemodynamic compromise, aggravating the imbalance between the oxygen supply and demand of the myocardium. Several studies have proposed an association between CAP and an increased incidence of ACS. The most common pathogen of CAP is Streptococcus pneumonia. Streptococcus pneumonia may cause severe form of CAP and often required hospitalization. Though the association of CAP and ACS has been discussed before, few studies have focused on the specific bacterial agents that cause pneumonia. This is an important research topic because vaccination against specific infectious agents may improve cardiovascular outcomes if the association between acute cardiovascular events and the specific bacterial infection can be established.

Study Purpose

Limited publications have suggested an association between pneumococcal pneumonia and the incidence of ACS.[6,7]In addition, the results of pneumococcal vaccination for prevention

of incidence of cardiovascular outcomes published before are controversial. Therefore, we attempted to use large database from the Taiwan National Health Institute Research Database (NHIRD) to investigate if pneumococcal pneumonia is associated with risk of ACS, especially in the Taiwan population.

Materials and Methods

Data source

We established a longitudinal cohort study based on data from the Taiwan National Health Institute Research Database (NHIRD), which is the largest and most comprehensive population-based medical benefit claims. Taiwan launched a single-payer compulsory national health insurance (NHI) program in the beginning of 1995. This program covered over 99% of Taiwan's entire 23 million residents.[8,9] All of the NHI data sets can be interlinked throughde-identifications of people, making the NHI reimbursement data suitable for public academicresearch. The information in the NHIRD, such aspatient identification number,sex, birthday, and discharge date, have been thoroughly described in various studies.[10,11]The accuracy and validity of diagnosis identified in the NHIRD has been strictly implemented and certificated.[12,13]This study was exempted by the Institutional Review Board of China Medical University (CMU-REC-101-012).

Study design

Patients with pneumococcal pneumonia.

The International Classification of Disease, Ninth Revision (ICD-9) was used for the diagnosis. We selected all adult pneumococcal pneumonia (ICD-9 code 481) patients (≥20 years old), identifying 20111patients with a first-time diagnosis of pneumococcal pneumonia and with at least one health care admission from 1997 to 2010. The index date was the date of pneumococcal pneumonia registration. We excluded patients with a history of ACS before the index date, and those with incomplete age or sex information. We then

randomly selected patients without a history of pneumonia (ICD-9 codes 480-487) or ACS in the NHIRD. To increase the statistical power, we created four comparison controls(80444) for each case, and frequency- matched the patients based on age 5 years each, sex, and index year of enrollment. We followed all study patients were until the date at which they were diagnosed with ACS.

Identification of acute coronary syndrome cases.

We linked study patients to the admission claims datato identify the first episode of ACS (ICD-9-CM codes410, 411.1) after pneumococcal pneumonia. Thepatients newly diagnosed with ACS were confirmed by the cardiology specialistand the index date was the date of ACS registration. After providing comprehensive supporting information anda rigorous cardiology assessments, we enrolled patients who met the criteria for diagnoses.

Variables of exposure.

We identified potentially confounding factors based on established risk factors, and performed an analysis to establish whether these variables were substantially associated with ACS. Baseline comorbidities – including hypertension (ICD-9 codes 401-405), diabetes mellitus (DM, ICD-9 code 250), hyperlipidemia (ICD-9-CM 272), and chronic obstructive pulmonary disease (COPD) – are important factors affecting ACS episodes. Therefore, we assessed patients for the factors at the startof pneumococcal pneumonia. Hypertension, diabetes, and hyperlipidemia are conventional risk factors of ACS.[12,13,14,15] In addition, COPD, which is characterized by a chronic airway inflammatory process, has been linked to ACS.[16]

Statistical Analysis

We used the chi-square test to examine and compare the distributions of the categorical characteristics between the pneumococcal pneumonia group and the control group. We calculated the follow-up person-years to assess the incidence density rates until ACS was either identified or censored. We used Poisson regression models to evaluate the ratios of the pneumococcal pneumonia cohort to the controls(relative risk) and 95% confidence intervals (CI). To estimate the effect of age on the absolute and relative risk of ACS, we divided the study patients in categories based on age (20-40 years old, 40-54 years old, 55-64 years old, and ≥65 years old) at the index date of pneumococcal pneumonia. We also used Cox proportional-hazards analysis to investigate the association between pneumococcal pneumonia and the risk of developing ACS over time, and adjusted for any cofactors significantly related to pneumococcal pneumonia. A further analysis was performed to assess whether the association of ACS varied according to the length of the follow-up period after pneumococcal pneumonia was diagnosed. We divided the time lag into the following 3 periods: ≤ 3 months, 3 months to 1 year and >1 years. We performed all statistical analyses using the SAS package (Version 9.1 for Windows; SAS institute, Inc., Cary, NC, USA). We adopted a two-tailed *P* value lower than .05 as the statistical significance level.

Study Results

Descriptive statistical analysis

Table 1 shows the demographic characteritics of the study sample.More male patienta were present in our study, and almost 75% of the patients were more than 55 years old (mean age 65.0±17.8 years and 64.9±17.6 years in controls, respectively). The prevalence of comorbidities was greater in the pneumococcal pneumonia group.

Statistical analysis inference

Table 2 shows the incidence rate ratio (IRR, or relative risk) and adjusted hazard ratio (aHR, or absolute risk) between the pneumococcal pneumonia group and the controls.The overall incidence rate of ACS was 92% higher in the pneumococcal pneumonia group than in the controls (43.1vs22.4 per 10000 person-years) with an aHR of 1.47 (95% CI = 1.24-1.73) in the following 14 years.For women, the incidence densities of the 2 groups are 39.3 and 19.0 per 10000 person-years, with a 2.07-fold relative risk of developing ACS (95% CI = 1.68-2.54). Men have a significantly higher absolute risk (18%) of developing ACS compared to women (95% CI = 1.02-1.37). When stratified by age, the incidence density rates of ACS increase with age, and are the highest in the oldest patients of both groups (70.2 and 35.0, respectively, per 10000 person-years). The 40-54 year-old group had a 3.52-fold relative risk of developing ACS (95% CI = 2.32-5.35) in the pneumococcal pneumonia group than in the controls. However, in the 20-40 year-old age group, the relative risk of developing ACS in the pneumococcal pneumonia group than in the controls is not significantly increased. After adjusting for cofactors, the risk of developing ACS

increased with age (patients 20-40 years of age were the reference group) with an aHR of 24.7 (95% CI = 12.5-48.5). We calculated the aHR according to the length of the follow-up period after pneumococcal pneumonia diagnosis. The relative risk of developing ACS decreased over the follow-up period. We found a 3.90-fold greater relative risk of developing ACS (the highest value) within the first 3-months follow-up period (95% CI = 2.46-6.18).

Table 3 shows the specific analysis of the comorbidities of the IRRs and aHRs between the pneumococcal pneumonia group and the controls. In patients without any conventional cardiovascular risk factors, the incidence rate of ACS was 29%higher in the pneumococcal pneumonia group than in the controls (95% CI = 1.03–1.60).When stratified by comorbidites, patients with hypertension, DM, and hyperlipidemia had statistically significantly higher absolute risks of developing ACS compared to those without (aHR = 2.07,95% CI = 1.77-2.41 in hypertension; aHR = 1.77,95% CI = 1.48-2.11 in DM; aHR = 2.14,95% CI = 1.70-2.68 in hyperlipidemia).

Table 4 shows the comorbidity effects (joint effects) on ACS. For example, pneumococcal pneumonia patients who had hyperlipidemia in their medical history have a 4.8-fold increased risk of developing ACS than patients without any comorbidities. The Kaplan-Meier survival analysis showed that patients with pneumococcal pneumonia had significantly higher ACS rates than the controls (Log-rank test, $P<0.0001$) (Fig 1).

Discussion:

Discussion of the study results

The result of this study show that patients infected with pneucoccal pneumonia have increased risk of ACS in the long-term follow up.

We noted that patients infected with pneumococcal pneumonia had the highest hazard ratio of cumulative incidence of ACS than patients without pneumococcal pneumonia in the first 3 months. The hazard ratio of cumulative incidence of ACS gradually decreased after 3 months but the risk was persistently significantly higher in pneumococcal pneumonia patients. Relatively few studies have discussed the long-term association between patients with pneumococcal pneumonia and ACS. Smeeth et al. presented a within-person comparison by using a case-series method and proposed that patients had an increased risk of acute myocardial infarction (AMI) and stroke within 90 days of the exposure period after an acute respiratory tract infection compared to the baseline period.[17] Using the same method, Corrales-Medina et al. proposed that the risk of ACS increased significantly within 15 days of the exposure period after infection with CAP compared to the baseline period.[6] However, we showed that patients infected with pneumococcal pneumonia have a persistently higher risk of a cumulative incidence of ACS than the control group even longer than 1 year after exposure. Using a meta-analysis method, Corrales-Medina VF et al. proposed that patients had an increased risk of incidence of ACS within 30 days of CAP diagnosis.[18] Our explaination is that after the antibiotics treatment of the acute infection, the streptococcus pneumonia may still reside within the nasopharynx and lead to asymptomatic

persistence of infection.[19]Johnstone et al. conducted a retrospective cohort study to investigate long-term outcomes of patients hospitalized for CAP and concluded that up to 5.4 years of follow-up, approximately 31% of patients died of cardiovascular disease.[20] Although this study did not compare the cohort of CAP patients with a control group, the result implied that CAP patients may have an increased risk of cardiovascular events even after an acute infectious stage. Our data showed that the cumulative risk of ACS in patients with pneumococcal pneumonia is persistently significantly higher in the long-term follow up compared to the control group.

Several studies have discussed the association between CAP and ACS.[6,17,19,21,22,23]However, few of these studies have focused on the association between pneumococcal pneumonia and ACS,[6,7,24] and most of them are limited by a relatively small sample size. This prevents any definite conclusion regarding the association between pneumococcal pneumonia and ACS. Therefore, we used a subset of thedatabase from the reimbursement claims authorized by the National Health Research Institute (NHRI) in Taiwan, which encompasses a larger sample size, to investigate this association. The results of this study are justifiable because of several reasons.

First, Streptococcus is the most common pathogen in CAP.[3-5] Second, several studies had pointed out that patients with severe form of CAP might have increased risk of ACS.[23] Sahuquillo-Arce et al. proposed that Streptococcus pneumonia infection produces higher serum procalcitonin levels and had a higher inflammatory expression than other atypical pathogen.[25] Therefore, streptococcus pneumonia is likely associated with the severe form of

CAP and with ACS.

In our study, we do not find any significant difference between the two groups regarding the risk of developing ACS in the 20-40 year-old subgroup. This may be explained by the fact that patients of young age are more immunocompetent and have less comorbidities. Therefore, the severity of the pneumococcal pneumonia in the 20-40 year-old age group may be less severe and less likely to complicate with developing ACS.

Discussion of other associated aspects

This study has important clinical implications because it primarily focuses on a specific pathogen instead of the broader spectrum of CAP. If we cannot validate that streptococcus pneumonia is associated with an increased risk of ACS, then pneumococcal vaccination might not be effective in preventing ACS. Previous studies have produced controversial results regarding the effectiveness of pneumococcal vaccination in reducing the cumulative incidence of ACS.[26-29] The different results of these studies might be due to various study designs. Thus, in order to identify whether pneumococcal vaccination actually reduces the incidence of ACS, we need to consider two aspects. First, we need to establish the association between pneumococcal pneumonia and ACS. In our study, we used a large retrospective cohort database to validate this hypothesis. Second, we need to discuss the effectiveness of the current pneumococcal vaccination in patients with high cardiovascular risk factors. Animal models show that pneumococcal vaccination can reduce atherosclerosis through molecular mimicry between streptococcus pneumonia and oxidized low-density lipoprotein. However, the current 23-valent pneumococcal vaccine offers incomplete

protection and has poor immunogenicity in immunocompromised patients or patients with multiple comorbidities. Therefore, a new generation of a pneumococcal vaccine that could provide good immunogenicity in patients with high cardiovascular risk awaits.[18]

Study limitations

This study has limitations. First, the NHI database did not disclose patients' personal histories such as smoking, which is associated with both an increased risk of pneumococcal pneumonia and ACS. However, we attempted to control for this potential confounder by including the COPD covariate because the cause-effect relationship between smoking and COPD had been well validated. Pneumococcal pneumonia is still associated with an increased risk of ACS after adjusting the covariate COPD. In addition, the smoking confounder cannot explain the temporal relationship of the higher hazard ratio of cumulative risk of ACS within 3 months of exposure to pneumococcal pneumonia. Second, previous studies have proposed that in approximately 10% CAP cases, the causative pathogens are mixed. We could not exclude the possibility that some patients in the pneumococcal pneumonia group had a coexistent influenza virus infection. Influenza pneumonia has been linked to an increased risk of ACS. However, viral infection is not routinely checked in daily practice, and we do not know the numbers of cases in our study cohort with both streptococcus pneumonia and influenza virus infection. Third, the evidence derived from a retrospective cohort study is generally lower in statistical quality than that from randomized trials because of potential biases related to adjustments for confounding variables. Fourth, all data in the NHIRD are anonymous. Thus, relevant

clinical variables, such as blood pressure, imaging results, pathology findings, serum laboratory data, and inflammatory markers (especially C-reactive protein), were unavailable for our study cohort.

Conclusion and Commentary

Conclusion

In conclusion, our study demonstrates that pneumococcal pneumonia is associated with an increased risk of a cumulative incidence of ACS in the long-term follow up, and the hazard ratio is the highest within the first 3 months after exposure to pneumococcal pneumonia. Our study result implied that pneumococcal vaccination might be used as an option in preventing the occurrence of ACS.

Commentary

1. For future studies, we planned to use the same large database to compare if patients with pneumococcal vaccination could reduce the risk of ACS compared with patients without pneumococcal vaccination.
2. We plan to check some inflammatory marker that is associated with the occurrence of ACS in patients with active pneumococcal pneumonia infection and compare with patients without active infection. In addition, we plan to check inflammatory markers in patients with active infection and compare with the convalescent period.

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Table1. Demographic characteristics and co-morbidity in patients with and without pneumococcal pneumonia

Variables	Pneumococcal pneumonia				p-value†
	No (N=80444)		Yes (N=20111)		
	n	%	n	%	
Sex					1.00
Male	52640	65.4	13160	65.4	
Female	27804	34.6	6951	34.6	
Age, years					1.00
20-40	9856	12.3	2646	12.3	
40-54	10668	13.3	2667	13.3	
55-64	11408	14.2	2852	14.2	
≥65	48512	60.3	121218	60.3	
Hypertension					<0.0001
Yes	12501	15.5	7858	39.1	
No	47943	84.5	12253	60.9	
Diabetes mellitus					<0.0001
Yes	6213	7.7	5090	25.3	
No	74231	92.3	15021	74.7	
Hyperlipidemia					<0.0001
Yes	2327	2.9	1438	7.1	
No	78117	97.1	18673	92.9	
COPD					<0.0001
Yes	2819	3.5	3773	18.8	
No	77625	96.5	16338	81.2	

†Chi-square test; occupation missing n=29481

Table 2. Incidence rate ratio and HR of acutecoronary syndrome and pneumococcal pneumoniacohort to non-pneumococcal pneumonia cohort

Variables	Pneumococcal pneumonia						IRR[a] (95% CI)	aHR[b] (95% CI)
	No (N=80444)			Yes (N=20111)				
	event	Person years	rate[†]	event	Person years	rate[†]		
Total	1044	465272	22.4	332	77056	43.1	1.92 (1.70-2.17)***	1.47 (1.24-1.73)***
Sex								
Male	716	292892	24.5	209	45789	45.6	1.86 (1.60-2.18)***	1.18 (1.02-1.37)*
Female	328	172381	19.0	123	31267	39.3	2.07 (1.68-2.54)***	reference
Age, years								
20-40	7	68255	1.0	5	16316	3.1	2.99 (0.95-9.41)	reference
40-54	54	71888	7.5	37	13987	26.5	3.52 (2.32-5.35)***	8.07 (4.03-16.2)***
55-64	114	76538	14.9	53	12974	40.9	2.74 (1.98-3.80)***	10.6 (5.28-21.3)***
≥65	869	248591	35.0	237	33780	70.2	2.01 (1.74-2.32)***	24.7 (12.5-48.5)***
Follow up period								
Within 3 months	39	19861	19.6	34	4441	76.6	3.90 (2.46-6.18)***	-
Within 1 year	111	73965	15.0	52	14264	36.5	2.43 (1.75-3.38)***	-
> 1 year	894	389278	23.0	246	61643	40.0	1.74 (1.51-2.00)***	-

Rate[†] per 10000 person-year; IRR[a] represented incidence rate ratio; aHR[b]represented adjusted hazard ratio: mutually adjusted for age, gender, comorbidities in Cox proportional hazard regression;CI, confidence interval;*P<0.05, **P<0.01, ***P<0.001

Table 3. Incidence rate ratio and HR of acutecoronary syndrome and pneumococcal pneumoniacohort to non-pneumococcal pneumonia cohort stratify by comorbidity

Variables	Pneumococcal pneumonia						IRR[a] (95% CI)	aHR[b] (95% CI)
	No (N=231,832)			Yes (N=57,958)				
	event	Person years	rate[†]	event	Person years	rate[†]		
None[§]	632	400098	15.8	92	45226	20.3	1.29 (1.03-1.60)*	-
Hypertension								
No	721	418368	17.2	143	55203	25.9	1.50 (1.26-1.80)**	reference
Yes	323	46904	68.9	189	21853	86.5	1.26 (1.05-1.50)*	2.07 (1.77-2.41)**
Diabetes mellitus								
No	863	442984	19.5	217	62796	34.6	1.77 (1.53-2.06)**	reference
Yes	181	22288	81.2	115	14261	80.6	0.99 (0.79-1.25)	1.77 (1.48-2.11)**
Hyperlipidemia								
No	959	456264	21.0	275	72730	37.8	1.80 (1.57-2.06)**	reference
Yes	85	9008	94.4	57	4326	131.8	1.40 (1.00-1.95)	2.14 (1.70-2.68)**
COPD								
No	988	456012	21.7	259	67144	38.6	1.78 (1.55-2.04)**	reference
Yes	56	9260	60.5	73	9913	73.6	1.22 (0.86-1.72)	1.09 (0.87-1.38)

Rate[†]per 10000 person-year; [§]Adjusted for age and gender. IRR[a] represented incidence rate ratio; aHR[b]represented adjusted hazard ratio: mutually adjusted for age, gender, and comorbidities in Cox proportional hazardregression; CI, confidence interval; *P<0.05, **P<0.01

Table 4. Joint effects of associated comorbidities on pneumococcal pneumonia and non- pneumococcal pneumonia for acute coronary syndrome

	Pneumococcal pneumonia		Non-pneumococcal pneumonia	
Variables	Event	aHR (95% CI)	Event	aHR (95% CI)
None	92	1.00 (reference)	632	1.00 (reference)
withhypertension	189	2.67 (2.05-3.48)***	323	2.99 (2.59-3.44)***
withdiabetes mellitus	115	2.81 (2.12-3.73)***	181	3.78 (3.18-4.48)***
withdyslipidaemia	57	4.80 (3.42-6.75)***	85	4.76 (3.79-5.99)***
with COPD	73	1.91 (1.33-2.73)**	56	2.24 (1.69-2.97)***

aHRrepresented adjusted hazard ratio: mutually adjusted for age, gender CI, confidence interval; *P<0.05,**P<0.01, ***P<0.001

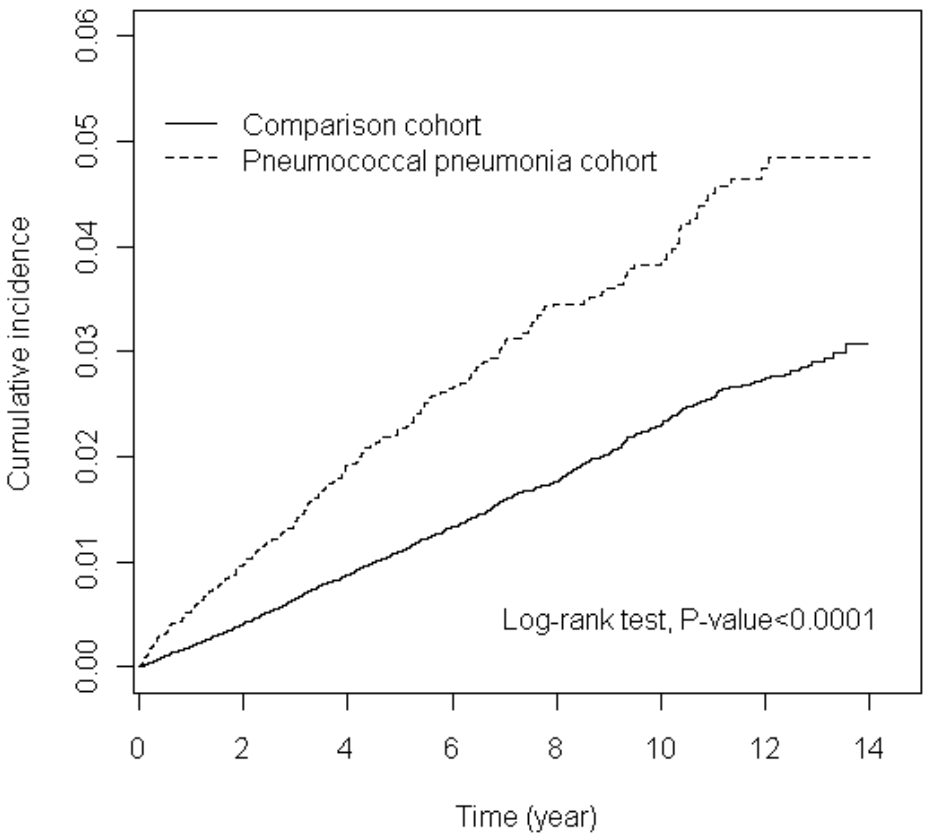

Figure 1. Cumulative incidence of acutecoronary syndrome for pneumococcal pneumonia and comparison cohorts in Taiwan.


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