

# Relationship between pneumonia and cardiovascular diseases: A retrospective cohort study of the general population

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## ARTICLE INFO

### Keywords:

Cardiovascular diseases (CVDs)  
Pneumonia  
Hyperlipidemia  
Community-acquired pneumonia (CAP)  
Hospital-acquired pneumonia (HAP)

## ABSTRACT

**Aims:** To evaluate the relationship between cardiovascular diseases (CVDs) and pneumonia in the general population.

**Methods:** This retrospective observational study included two cohorts, namely CVD ( $n = 28,363$ ) and non-CVD ( $n = 28,363$ ) cohorts, which were matched by propensity score and examined for cases of pneumonia. Data were obtained from 2000 to 2011. In both cohorts, pneumonia risk was measured using multivariable Cox proportional hazard models.

**Results:** With the non-CVD cohort as reference, the corresponding adjusted hazard ratios (aHRs) [95% confidence intervals (CIs)] of pneumonia were 2.03 [1.77–2.31] for coronary artery disease, 4.11 [3.15–5.36] for heart failure, 3.21 [2.70–3.81] for cerebrovascular disease, 1.46 [1.07–1.98] for peripheral vascular disease, and 2.27 [2.01–2.56] for the CVD cohort. The cohort with comorbidities had a higher risk (all  $p < .05$ ) of pneumonia compared with that without comorbidities, except for patients with the comorbidities of hypertension, hyperlipidemia, obesity, and liver disease. The aHR (95% CI) of pneumonia for antibiotic use was 1.26 (1.09–1.47). The aHRs of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) were 3.25 (95% CI = 1.04–10.1) and 2.95 (95% CI = 2.25–3.88), respectively. The aHRs (95% CI) were 1.78 (1.05–3.03) for intensive care unit (ICU) risk and 0.98 (0.96–0.99) for length of admission.

**Conclusion:** Pneumonia risk was associated with CVDs, especially heart failure, regardless of age, gender, comorbidities, and antibiotic use, particularly in elderly male patients. In addition, Patients with CVDs had a higher risk of CAP and HAP. The CVD cohort had a higher frequency of ICU admissions, but shorter admission lengths.

## 1. Introduction

Cardiovascular diseases (CVDs) consist of disorders of the heart and blood vessels, including coronary artery disease (CAD), heart failure, cerebrovascular disease, aortic disease, and peripheral vascular disease (PVD) [1]. CVDs are the leading cause of death globally; an estimated 17.7 million people died from CVDs in 2015, representing 31% of all deaths worldwide [2].

The mortality rate for pneumonia is high among patients hospitalized in America, Europe, and other regions of the world. Patients with

pneumonia living independently in the community and also those who are hospitalized for reasons other than pneumonia for  $< 48$  h before respiratory symptom development are considered to have community-acquired pneumonia (CAP), pathogens include *Streptococcus pneumoniae*, *Staphylococcus pneumoniae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*, meaning that inoculation likely occurred before admission. By contrast, pneumonia that occurs  $> 48$  h after admission and does not appear to be incubating at the time of admission is considered hospital-acquired pneumonia (HAP, pathogens include *Klebsiella pneumoniae*) [3]. In addition, HAP that develops 48–72 h after endotracheal

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<https://doi.org/10.1016/j.ejim.2018.08.003>

Received 14 May 2018; Received in revised form 3 August 2018; Accepted 3 August 2018

Available online 09 August 2018

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intubation because of respiratory failure in an intensive care unit (ICU) is considered ventilator-associated pneumonia (VAP). Pneumonia that occurs in nonhospitalized patients who reside in nursing homes and have undergone IV therapy (including chemotherapy and cancer treatment), had nonsurgical wound dressings changed or removed < 30 days before pneumonia occurrence, been hospitalized in an acute care hospital for  $\geq 2$  days < 90 days before pneumonia occurrence, or visited a hospital or hemodialysis center < 30 days before pneumonia occurrence is considered health care-associated pneumonia (HCAP). HCAP pathogens include *Pseudomonas aeruginosa* and *Staphylococcus aureus* in addition to the usual community-acquired pathogens. The symptoms and signs of HCAP are similar to those of pneumonia that occurs in other settings, except that fewer prominent changes in vital signs are observed in many elderly patients. The mortality rate is moderately high, but this may be partly caused by coexisting CVDs. However, the definition of HCAP has several limitations and requires further study [4].

*Streptococcus pneumoniae* infects the myocardium and induces necroptosis and apoptosis, which are followed by cardiac scarring and heart failure [4]. *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, and the oxidative stress caused by these infections, are associated with atherosclerosis in patients with CVDs [5]. Studies have seldom investigated whether CVD [5] is a predisposing factor [6] for pneumonia infection [7] in the general population. However, we speculated that patients with CVDs may be at a relatively high pneumonia risk. We tested this hypothesis through a cohort study of the general population. Because the role of statin in pneumonia risk among patients with CVDs and hyperlipidemia is debatable [8–11], we investigated the effect of statins on patients with pneumonia and CVDs and on patients with pneumonia but without CVDs.

## 2. Methods

### 2.1. Data source

We conducted a population-based retrospective cohort study using data from the Longitudinal Health Insurance Research Database (LHID2000) of citizens enrolled in the Taiwan National Health Insurance (NHI) program. The NHI program began in March 1995 and has enrolled > 99% of the 23 million people living in Taiwan in 2014 [1]. The NHI program and LHID2000 were described in previous studies [2]. The Research Ethics Committee of China Medical University and Hospital in Taiwan (Institutional Review Board permit number: CMUH104-REC2-115-CR3) approved this study.

### 2.2. Study participants

We identified patients aged  $\geq 20$  years who had, from 2000 to 2011, received a new diagnosis of a CVD, including CAD (International Classification of Diseases, 9th Revision [ICD-9] codes 410–414), heart failure (ICD-9 code 428), cerebrovascular disease (ICD-9 codes 430–438), and PVDs (ICD-9 codes 440–448). These patients were included in a CVD cohort. The date on which a CVD was diagnosed was defined as the index date. An equal number of comparison patients without CVDs were randomly selected from the LHID2000 for a non-CVD cohort. The non-CVD cohort was matched using a propensity score with the CVD cohort according to the index year of CVD diagnosis, age (every 5-year span), gender, urbanization level of residence, and occupation; comorbidities of diabetes, chronic obstructive pulmonary disease (COPD), hypertension, hyperlipidemia, mental disorders, chronic kidney disease, obesity, cancer, liver diseases, and asthma; and statin and antibiotic use. We excluded patients diagnosed with pneumonia (ICD-9 codes 481, 482, 483.0, and 483.1) before the index date and those with incomplete gender or age information from both cohorts.

### 2.3. Outcome and relevant variables

The primary outcome was newly diagnosed pneumonia (ICD-9 codes 483.0 and 483.1) or (ICD-9 codes 481 and 482), and it was determined from the patients' medical records. All patients were followed until withdrawal from the NHI program, death, or December 31, 2011, whichever came first. Baseline comorbidities considered were diabetes (ICD-9-CM code 250), COPD (ICD-9-CM codes 491, 492, and 496), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), mental disorders (ICD-9-CM codes 290–319), chronic kidney disease (ICD-9-CM code 585), obesity (ICD-9-CM code 278), cancer (ICD-9-CM codes 140–208), liver diseases (ICD-9-CM codes 570–573), and asthma (ICD-9-CM code 493). A medication history of statin and antibiotic use was included in the analysis.

### 2.4. Statistical analysis

The CVD and non-CVD cohorts were matched by propensity score. The standardized mean difference was used to quantify the differences in the mean or proportion of continuous or categorical variables, respectively, between the CVD and non-CVD cohorts. Cumulative incidence of a pneumonia was calculated using the Kaplan–Meier method, and the difference between the cohorts was evaluated using a logrank test. We estimated the incidence density rate of pneumonia for different risk factors by using the follow-up time in person-years, and we further stratified the rate according to gender, age, monthly income, and comorbidity. Univariable and multivariable Cox proportional hazard regression models were used to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) for pneumonia. Age, gender, urbanization level of residence, occupation, and comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma were included in the multivariable model, whereas antibiotic use was included in the univariable Cox model. The odds ratios (ORs) for 30-day mortality, ICU admission, and length of admission after pneumonia diagnosis were also measured using the logistic regression model. We used SAS 9.4 (Statistical Analysis System Institute Inc., Cary, NC, USA) for data analysis. A two-tailed  $p < .05$  was considered statistically significant.

## 3. Results

We established two cohorts, CVD and non-CVD, each consisting of 28,363 patients. In the CVD cohort, > 50% of the patients were 20–49 years old and 51.5% were men (Table 1). The mean age of the patients was  $49.2 \pm 13.1$  years for the CVD cohort and  $49.0 \pm 13.5$  years for the non-CVD cohort. Distributions of age, gender, urbanization level of residence, occupation, comorbidities, and medications were similar in both cohorts. The average follow-up duration was  $6.85 \pm 3.42$  years for the CVD cohort and  $7.01 \pm 3.25$  years for the non-CVD cohort. Fig. 1 illustrates that the cumulative incidence of pneumonia was higher in the CVD cohort than it was in the non-CVD cohort (logrank test  $p < .001$ ) at the end of the follow-up period.

The overall incidence density rates of pneumonia were 1.89, 4.05, 8.94, 5.78, 2.06, and 4.31 per 1000 person-years in the non-CVD, CAD, heart failure, cerebrovascular disease, PVD, and CVD cohorts, respectively (Table 2). The corresponding adjusted HRs (aHRs) of pneumonia were 2.03 (95% CI = 1.77–2.31) for CAD, 4.11 (95% CI = 3.15–5.36) for heart failure, 3.21 (95% CI = 2.70–3.81) for cerebrovascular disease, 1.46 (95% CI = 1.07–1.98) for PVD, and 2.27 (95% CI = 2.01–2.56) for the CVD cohort compared with the non-CVD cohort after adjusting for age, gender, urbanization level of residence, and occupation; comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma; and antibiotic use. In the multivariable model, the risk of pneumonia increased with age from 1.26 to 2.81 and was 1.40-fold higher for men than for women

**Table 1**  
Comparison of patient characteristics between the CVD and non-CVD cohorts.

	Cardiovascular diseases				Standardized mean differences <sup>a</sup>
	Yes		No		
	(N = 28,363)		(N = 28,363)		
	n	%	n	%	
<b>Age, year</b>					
20–49	15,835	55.7	15,302	53.8	0.04
50–64	9781	34.4	9041	31.8	0.06
≥ 65	3351	11.8	3558	12.5	0.02
Mean (SD) <sup>a</sup>	49.0	13.5	49.2	13.1	0.14
<b>Gender</b>					
Female	13,638	48.0	13,784	48.5	0.01
Male	14,796	52.0	14,650	51.5	0.01
<b>Urbanization level<sup>b</sup></b>					
1 (Highest urbanization)	8526	30.0	8479	29.8	0.004
2	873	29.8	8356	29.4	0.009
3	4951	17.4	5179	18.2	0.021
4 (Lowest urbanization)	6484	22.8	6420	22.6	0.005
<b>Occupation</b>					
Housekeeping	5788	20.4	5571	19.6	0.02
White collar	11,110	39.1	11,428	40.2	0.02
Blue collar	8961	31.5	8744	30.8	0.02
Others <sup>c</sup>	2575	9.06	2691	9.46	0.01
<b>Comorbidity</b>					
Diabetes	1523	5.36	1383	4.86	0.02
COPD	1477	5.19	1465	5.15	0.02
Hypertension	5892	20.7	5347	18.8	0.05
Hyperlipidemia	4017	14.1	3783	13.3	0.02
Mental disorders	7545	26.5	7789	27.4	0.004
Chronic kidney disease	164	0.58	133	0.47	0.02
Obesity	277	0.97	288	1.01	0.004
Cancer	524	1.84	607	2.13	0.004
Liver diseases	3928	13.8	4090	14.4	0.004
Asthma	1049	3.69	1101	3.87	0.004
<b>Medication</b>					
Statin	1314	4.62	1176	4.14	0.02
Antibiotic treatment	22,757	80.0	22,819	80.3	0.02

<sup>a</sup> A value of the standard mean difference equals  $\leq 0.1$ , which indicates a negligible difference in means between the CVD cohort and the matched non-CVD cohort.

<sup>b</sup> Urbanization level was categorized into four levels according to residential area population density, with Level 1 the most urbanized and Level 4 the least urbanized.

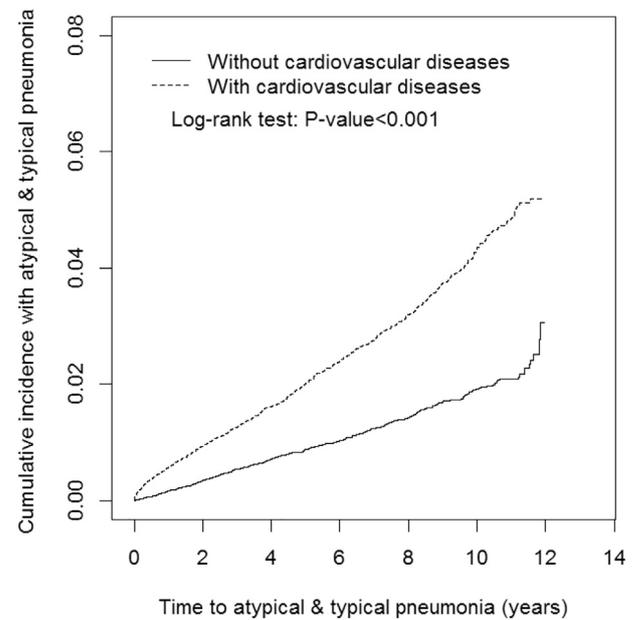
<sup>c</sup> Other occupations included primarily retired, unemployed, or low-income populations.

(95% CI = 1.24–1.58). The risk of pneumonia was significantly higher for patients living in regions with lower urbanization levels compared with patients living in highly urbanized areas. Patients employed in housekeeping and blue-collar jobs had a higher risk of pneumonia than those employed in white-collar jobs.

The risk of developing pneumonia was higher in patients with diabetes (aHR = 1.75, 95% CI = 1.43–2.14), COPD (aHR = 2.18, 95% CI = 1.82–2.60), mental disorder (aHR = 1.20, 95% CI = 1.06–1.36), chronic kidney disease (aHR = 1.87, 95% CI = 1.10–3.18), cancer (aHR = 2.18, 95% CI = 1.60–2.98), and asthma (aHR = 1.72, 95% CI = 1.38–2.13) than in those without these comorbidities.

Regarding antibiotic use, we considered the CVD-cohort patients who did not use antibiotics as reference 1; the aHR (95% CI) for antibiotic use was 1.26 (1.09–1.47).

After stratification for gender, age, urbanization level of residence, occupation comorbidities, and antibiotic use, the risk of pneumonia in the CVD cohort was determined to be higher than that in the non-CVD cohort (Table 3). Furthermore, the patients in the CVD cohort were



**Fig. 1.** Cumulative incidence of pneumonia between the CVD and non-CVD cohorts.

3.25-fold more likely to develop CAP (95% CI = 1.04–10.1) and 2.95-fold more likely to develop HAP (95% CI = 2.25–3.88) than the patients in the non-CVD cohort were (Table 4).

Table 5 shows no statistically significant difference in 30-day mortality after pneumonia between the CVD and non-CVD cohorts (7.27% vs. 8.24%) with an adjusted OR = 1.51 (95% CI = 0.93–2.46). The ICU admission risk was higher in the CVD cohort than it was in the non-CVD cohort (adjusted OR [aOR] = 1.78, 95% CI = 1.05–3.03). The risk of longer length of admission was lower for patients with CVDs than it was for those without CVDs (aOR = 0.98, 95% CI = 0.96–0.99).

#### 4. Discussion

The primary finding of this study was that pneumonia (caused by *Streptococcus pneumoniae*, *Staphylococcus*, *Klebsillae pneumoniae*, *Pseudomonas aeruginosa*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*) is associated with CVDs, regardless of age, gender, comorbidity, and antibiotic use. However, the pneumonia incidence rate in the CVD cohort was particularly high in the elderly male population and in patients with comorbidities. We also found that the heart failure group had the highest aHR of the non-CVD patients. In another study, pneumonia risk was closely related to the degree of ventricular function impairment, and heart failure was found to be an independent risk factor for pneumonia [12]. The high risk of pneumonia associated with heart failure [13] observed in our study was in accordance with this finding [14]. Moreover, the CVD cohort had a higher risk of ICU admission than the non-CVD cohort did. CVDs, such as CAD, are associated with a high frequency of admission to the coronary care unit, which may explain this finding [15]. In Taiwan, a large proportion of patients with CAD receive antihypertension drugs, antihyperlipidemia drugs, beta blockers, and aspirin [16]. These drugs may aid recovery from CAD or cerebrovascular disease [17], resulting in the CVD cohort having a lower frequency of lengthy admissions than the non-CVD cohort had [16]. A study revealed that CVDs are associated with longer admission stays [18]. These different findings warrant further studies for clarification.

In this study, we determined that patients aged > 65 years, men, and patients with comorbidities such as diabetes, COPD, mental disorder, chronic kidney disease, cancer, and asthma [19] have a high risk of pneumonia. Additionally, patients with these CVDs have a high

**Table 2**  
Incidence of and risk factors for pneumonia.

Variable	Event	PY	Rate <sup>b</sup>	Crude HR (95% CI)	Adjusted HR <sup>a</sup> (95% CI)
<b>Cardiovascular diseases</b>					
No	376	199,285	1.89	1.00	1.00
Coronary artery disease (CAD)	526	129,797	4.05	2.14 (1.87, 2.44) <sup>***</sup>	2.03 (1.77, 2.31) <sup>***</sup>
Heart failure	65	7274	8.94	4.75 (3.65, 6.19) <sup>***</sup>	4.11 (3.15, 5.36) <sup>***</sup>
Cerebrovascular disease	201	34,771	5.78	3.08 (2.60, 3.66) <sup>***</sup>	3.21 (2.70, 3.81) <sup>***</sup>
Peripheral vascular diseases (PVD)	47	22,835	2.06	1.10 (0.81, 1.49)	1.46 (1.07, 1.98) <sup>*</sup>
All	839	194,678	4.31	2.28 (2.02, 2.57) <sup>***</sup>	2.27 (2.01, 2.56) <sup>***</sup>
<b>Age, year</b>					
20–49	505	222,502	2.27	1.00	1.00
50–64	373	129,672	2.88	1.27 (1.11, 1.45) <sup>***</sup>	1.26 (1.10, 1.45) <sup>***</sup>
≥ 65	337	41,788	8.06	3.58 (3.12, 4.11) <sup>***</sup>	2.81 (2.40, 3.29) <sup>***</sup>
<b>Gender</b>					
Female	513	196,118	2.62	1.00	1.00
Male	702	197,845	3.55	1.36 (1.22, 1.53) <sup>***</sup>	1.40 (1.24, 1.58) <sup>***</sup>
<b>Urbanization level<sup>b</sup></b>					
1 (Highest urbanization)	266	116,519	2.28	1.00	1.00
2	375	116,809	3.21	1.40 (1.20, 1.64) <sup>***</sup>	1.34 (1.14, 1.57) <sup>***</sup>
3	221	69,556	3.18	1.39 (1.16, 1.66) <sup>***</sup>	1.33 (1.11, 1.59) <sup>***</sup>
4 (Lowest urbanization)	353	91,078	3.88	1.69 (1.44, 1.98) <sup>***</sup>	1.44 (1.22, 1.70) <sup>***</sup>
<b>Occupation</b>					
Housekeeping	274	76,781	3.57	1.61 (1.37, 1.88) <sup>***</sup>	1.26 (1.06, 1.49) <sup>**</sup>
White collar	341	154,144	2.21	1.00	1.00
Blue collar	454	127,736	3.55	1.60 (1.39, 1.84) <sup>***</sup>	1.23 (1.05, 1.43) <sup>**</sup>
Others <sup>c</sup>	146	35,302	4.14	1.87 (1.54, 2.27) <sup>***</sup>	1.30 (1.06, 1.59) <sup>*</sup>
<b>Comorbidity</b>					
<b>Diabetes</b>					
No	1108	376,238	2.94	1.00	1.00
Yes	107	17,724	6.04	2.08 (1.70, 2.53) <sup>***</sup>	1.75 (1.43, 2.14) <sup>***</sup>
<b>COPD</b>					
No	1033	375,140	2.75	1.00	1.00
Yes	182	18,823	9.67	3.55 (3.03, 4.15) <sup>***</sup>	2.18 (1.82, 2.60) <sup>***</sup>
<b>Hypertension</b>					
No	931	317,489	2.93	1.00	1.00
Yes	284	76,474	3.71	1.27 (1.11, 1.45) <sup>***</sup>	0.89 (0.78, 1.03)
<b>Hyperlipidemia</b>					
No	1061	340,584	3.12	1.00	1.00
Yes	154	53,379	2.89	0.93 (0.79, 1.10)	
<b>Mental disorders</b>					
No	851	286,262	2.97	1.00	1.00
Yes	364	107,701	3.38	1.14 (1.01, 1.29) <sup>*</sup>	1.20 (1.06, 1.36) <sup>**</sup>
<b>Chronic kidney disease</b>					
No	1201	392,197	3.06	1.00	1.00
Yes	14	1766	7.93	2.60 (1.53, 4.40) <sup>***</sup>	1.87 (1.10, 3.18) <sup>*</sup>
<b>Obesity</b>					
No	1205	390,553	3.09	1.00	1.00
Yes	10	3410	2.93	0.97 (0.52, 1.80)	–
<b>Cancer</b>					
No	1173	388,498	3.02	1.00	1.00
Yes	42	5464	7.69	2.56 (1.88, 3.48) <sup>***</sup>	2.18 (1.60, 2.98) <sup>***</sup>
<b>Liver diseases</b>					
No	1038	341,209	3.04	1.00	1.00
Yes	177	52,754	3.36	1.11 (0.95, 1.31)	
<b>Asthma</b>					
No	1109	380,215	2.92	1.00	1.00
Yes	106	13,748	7.71	2.67 (2.19, 3.26) <sup>***</sup>	1.72 (1.38, 2.13) <sup>***</sup>
<b>Medication</b>					
<b>Statin</b>					
No	1163	380,427	3.06	1.00	1.00
Yes	52	13,536	3.84	1.28 (0.97, 1.69)	
<b>Antibiotic treatment</b>					
No	229	85,743	2.67	1.00	1.00
Yes	986	308,220	3.20	1.22 (1.05, 1.40) <sup>**</sup>	1.26 (1.09, 1.47) <sup>**</sup>

CI, confidence interval; HR, hazard ratio; PY, person-years.

Rate, incidence rate per 1000 person-years.

<sup>a</sup> Multivariable analysis including age, gender, urbanization level of residence, and occupation; comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma; and antibiotic use.

<sup>b</sup> Urbanization level was categorized into four levels according to residential area population density, with Level 1 the most urbanized and Level 4 the least urbanized.

<sup>c</sup> Other occupations included primarily retired, unemployed, or low-income populations.

\*  $p < .05$ .

\*\*  $p < .01$ .

\*\*\*  $p < .001$ .

**Table 3**

Incidence and HRs of pneumonia between the CVD and non-CVD cohorts according to gender, age group, urbanization level of residence, occupation, comorbidity, and medication.

Variables	Cardiovascular diseases						Crude HR (95% CI)	Adjusted HR <sup>a</sup> (95% CI)
	Yes			No				
	Event	PY	Rate <sup>c</sup>	Event	PY	Rate <sup>c</sup>		
<b>Gender</b>								
Female	169	98,522	1.72	344	97,596	3.52	2.05 (1.71, 2.47) <sup>***</sup>	2.03 (1.69, 2.45) <sup>***</sup>
Male	207	100,763	2.05	495	97,082	5.10	2.48 (2.11, 2.91) <sup>***</sup>	2.47 (2.10, 2.90) <sup>***</sup>
<b>Age, year</b>								
20–49	334	111,262	3.00	171	111,240	1.54	1.95 (1.62, 2.35) <sup>***</sup>	1.94 (1.61, 2.33) <sup>***</sup>
50–64	238	62,066	3.83	135	67,607	2.00	1.92 (1.55, 2.37) <sup>***</sup>	1.93 (1.56, 2.38) <sup>***</sup>
≥65	267	21,350	12.5	70	20,439	3.42	3.63 (2.79, 4.72) <sup>***</sup>	3.59 (2.75, 4.68) <sup>***</sup>
<b>Urbanization level<sup>a</sup></b>								
1 (Highest urbanization)	196	57,656	3.40	70	58,863	1.19	2.86 (2.17, 3.75) <sup>***</sup>	2.91 (2.21, 3.82) <sup>***</sup>
2	249	58,411	4.26	126	58,398	2.16	1.97 (1.59, 2.44) <sup>***</sup>	1.95 (1.57, 2.41) <sup>***</sup>
3	149	33,379	4.46	72	36,177	1.99	2.24 (1.69, 2.97) <sup>***</sup>	2.15 (1.62, 2.85) <sup>***</sup>
4 (Lowest urbanization)	245	45,232	5.42	108	45,847	2.36	2.29 (1.83, 2.87) <sup>***</sup>	2.29 (1.82, 2.87) <sup>***</sup>
<b>Occupation</b>								
Housekeeping	191	38,745	4.93	83	38,036	2.18	2.25 (1.74, 2.91) <sup>***</sup>	2.25 (1.74, 2.92) <sup>***</sup>
White collar	218	75,037	2.91	123	79,107	1.55	1.87 (1.50, 2.33) <sup>***</sup>	1.89 (1.52, 2.36) <sup>***</sup>
Blue collar	319	64,090	4.98	135	63,646	2.12	2.34 (1.92, 2.87) <sup>***</sup>	2.32 (1.90, 2.84) <sup>***</sup>
Others <sup>d</sup>	111	16,805	6.60	35	18,497	1.89	3.48 (2.38, 5.09) <sup>***</sup>	3.37 (2.30, 4.94) <sup>***</sup>
<b>Comorbidity<sup>b</sup></b>								
No	297	78,929	3.76	116	90,605	1.28	2.93 (2.37, 3.63) <sup>***</sup>	2.96 (2.39, 3.67) <sup>***</sup>
Yes	542	115,748	4.68	260	108,681	2.39	1.95 (1.69, 2.26) <sup>***</sup>	1.95 (1.68, 2.26) <sup>***</sup>
<b>Medication</b>								
<b>Antibiotic treatment</b>								
No	171	42,115	4.06	58	43,628	1.33	3.04 (2.26, 4.09) <sup>***</sup>	3.14 (2.33, 4.23) <sup>***</sup>
Yes	668	152,563	4.38	318	155,657	2.04	2.14 (1.87, 2.45) <sup>***</sup>	2.11 (1.85, 2.42) <sup>***</sup>

CI, confidence interval; HR, hazard ratio; PY, person-years.

Rate, incidence rate per 1000 person-years.

<sup>a</sup> Multivariable analysis including age, gender, urbanization level of residence, and occupation; comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma; and antibiotic use.

<sup>b</sup> Patients with any comorbidity of diabetes, COPD, hypertension, hyperlipidemia, mental disorder, chronic kidney disease, obesity, cancer, liver diseases, and asthma were classified into the comorbidity group.

<sup>c</sup> Urbanization level was categorized into four levels according to residential area population density, with Level 1 the most urbanized and Level 4 the least urbanized.

<sup>d</sup> Other occupations included primarily retired, unemployed, or low-income populations.

\*\*\*  $p < .001$ .

**Table 4**

Incidence and HRs of different severities of pneumonia between patients with and without cardiovascular diseases.

Outcome	Event	Rate <sup>#</sup>	Crude HR(95% CI)	Adjusted HR <sup>&amp;</sup> (95% CI)
<b>Cardiovascular diseases</b>				
<b>CAP</b>				
No	4	0.02	1 (Reference)	1 (Reference)
Yes	12	0.06	3.05 (0.98, 9.46)	3.25 (1.04, 10.1) <sup>*</sup>
<b>Cardiovascular diseases</b>				
<b>HAP</b>				
No	70	0.35	1 (Reference)	1 (Reference)
Yes	205	1.05	2.99 (2.28, 3.92)	2.95 (2.25, 3.88) <sup>***</sup>
<b>Cardiovascular diseases</b>				
<b>HCAP</b>				
No	1	0.01	1 (Reference)	1 (Reference)
Yes	2	0.01	2.05 (0.19, 22.6)	1.30 (0.10, 16.1)

CI, confidence interval; HR, hazard ratio.

<sup>#</sup> Rate, incidence rate per 1000 person-years.

<sup>&</sup> Multivariable analysis including age, gender, urbanization level of residence, and occupation; comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma; and antibiotic use.

\*  $p < .05$ .

\*\*\*  $p < .001$ .

**Table 5**

The 30-day mortality, ICU admission, and length of admission after pneumonia and estimated odds ratio through logistic regression analysis.

	Cardiovascular diseases	
	No (n = 28,363)	Yes (n = 28,363)
Death/Pneumonia	31/376	61/839
Mortality rate (%)	8.24	7.27
cOR (95% CI)	1 (Reference)	1.15 (0.73, 1.80)
aORs (95% CI) <sup>a</sup>	1 (Reference)	1.51 (0.93, 2.46)
ICU/Pneumonia	33/376	136/839
ICU rate (%)	8.78	16.2
cOR (95% CI)	1 (Reference)	2.54 (1.55, 4.15) <sup>***</sup>
aORs (95% CI) <sup>a</sup>	1 (Reference)	1.78 (1.05, 3.03) <sup>*</sup>
Length of admission stay		
Mean (SD)	4.63 (11.7)	9.27 (19.5)
cOR (95% CI)	1 (Reference)	1.00 (0.98, 1.01)
aORs (95% CI) <sup>a</sup>	1 (Reference)	0.98 (0.96, 0.99) <sup>*</sup>

Abbreviations: cOR, crude odds ratio; aOR, adjusted odds ratio.

<sup>a</sup> Adjusted for age, gender, urbanization level of residence, and occupation; comorbidities of diabetes, COPD, hypertension, mental disorders, chronic kidney disease, cancer, and asthma; and antibiotic use.

\*  $p < .05$ .

\*\*\*  $p < .001$ .

frequency of ICU admission (VAP) with respiratory failure. We also discovered that environmental factors [20] such as living in areas with low urbanization levels and working in housekeeping or blue-collar jobs had a significant effect on pneumonia risk. Living conditions in urban areas are overall better than those in rural settings; specifically, better housing, sanitation, ventilation, and social services all play a role in this improvement [21]. This explains the association between low levels of urbanization and higher risk of pneumonia. Living with cats, dogs, or birds and the number of pets at home was also noted to increase CAP risk; this may explain the higher pneumonia risk for those working in housekeeping [22]. Furthermore, exposure to inorganic dust, metal fumes, and chemicals can lead to airway inflammation among those working in blue-collar occupations, which may explain the high incidence of pneumonia in these patients [23].

One possible means of explaining the relationship between cerebrovascular disease and pneumonia is through combining aspiration theory with stroke-induced immunosuppression [24]. Evidence indicates that stroke impairs systemic immune responses and increases susceptibility to pneumonia [24]. Another explanation is that myocardial enzyme release and echocardiographic wall motion abnormalities are associated with impaired left ventricular performance after subarachnoid hemorrhage [25], and impaired left ventricular performance with heart failure may contribute to the risk of pneumonia.

Pneumonia in elderly patients is often underdiagnosed due to atypical symptoms and signs [26]. Swallowing difficulty and dysphagia [27] in CAD and cerebrovascular disease are critical risk factors for pneumonia [28], especially among elderly patients. In our study, patients with CAP or HAP aged > 65 years had a higher risk of pneumonia than those aged < 65, which supports cerebrovascular disease as a risk factor for pneumonia. Moreover, previous antibiotic use among elderly patients may affect development of CAP [22] and HAP [4, 29], indicating that antibiotic use is associated with higher pneumonia risk.

The relationship of pneumonia with PVD has rarely been addressed in the literature, but we observed that pneumonia is associated with PVD. *Klebsiella pneumoniae* was associated with PVD [30] in one observational study. Similar to the systemic septic embolism effect in stroke, systemic septicemia in pneumonia is a critical factor for PVD. The higher incidence of PVD with CAP risk in another study agrees with our finding [31].

Obesity is a critical risk factor for hyperlipidemia, diabetes, and hypertension. In Taiwan, obese patients with hyperlipidemia are typically treated with statins [32]. In our study, the CVD cohort comprised patients with hyperlipidemia, hypertension, and obesity. We found that the CVD cohort was not associated with pneumonia risk, regardless of statin use [33]. Similarly, in a study by Teepe et al., obesity was not associated with CAP risk [34]. Furthermore, Kornum et al. reported that obesity is not associated with a higher risk of hospitalization with pneumonia among women [35]. Moreover, another study reported that obesity has little impact on the clinical outcome of pneumonia (mortality of HAP), which supports the aforementioned findings [36].

Up to 30% of patients with CAP develop CVDs, such as new and worsening heart failure, arrhythmias, myocardial infarctions, or strokes, immediately and up to 10 years after CAP contraction. Therefore, pneumonia has in fact been considered a CVD [7] in another study. This implies that a pneumonia–CVD interaction [37, 38] may play a role in the relationship between pneumonia and CVDs [9, 10]. The interplay between CVDs and lungs using cytokines may support these findings [39–42]. This speculation requires detailed biochemistry data for confirmation.

#### 4.1. Strengths and limitations of this study

The definition of pneumonia in Taiwan is strict owing to policies restricting antibiotic use [43]. Stroke is diagnosed through clinical manifestation, computed tomography, magnetic resonance imaging, and angiography [44, 45]. The validity and consistency of CVD and

stroke diagnosis based on Taiwan's National Health Insurance Research Database (NHIRD) was well [45]. The statin use factor was based on Taiwanese guidelines [32]. These policies mean that the coding of CVDs and pneumonia in the present study was strict [43]. However, some limitations were as follows: (1) Patients with hyperlipidemia may not have used statins, fibrates, or diet-control treatments. (2) The NHI claims database lacks information concerning several key factors, including serum cholesterol, sugar concentration, blood pressure, obesity (body mass index), and smoking status. Therefore, we replaced obesity with hypertension, hyperlipidemia, and diabetes [46] and smoking status with COPD [47] for the multiple regression analysis. (3) Adverse drug reactions or treatment nonadherence, despite being infrequent, may precipitate CVD onset. (4) The cutoff values of colony count were unavailable in the NHIRD; thus, we could not analyze the frequency of airway colonization. (5) Defining HCAP, which includes both HAP and VAP, is problematic and controversial, and pneumonia risk in this cohort requires further research [48].

## 5. Conclusion

Pneumonia risk was associated with CVDs, especially heart failure, regardless of age, gender, comorbidities, and antibiotic use, particularly among elderly male patients. The patients with CVDs had a higher risk of CAP and HAP and a higher frequency of ICU admission, although with shorter admission lengths.

## Author contributions

All authors contributed significantly to the study and agree with the manuscript content. **Conception/Design:** Jun-Jun Yeh, Chia-Hung Kao; **provision of study materials:** Chia-Hung Kao; **collection and/or assembly of data:** all authors; **data analysis and interpretation:** all authors; **manuscript writing:** all authors; **final approval of manuscript:** all authors.

## Acknowledgments

This work was supported by grants from the Ministry of Health and Welfare, Taiwan (MOHW107-TDU-B-212-123004); China Medical University Hospital (CMU107-ASIA-19, DMR-107-192); the Academia Sinica Stroke Biosignature Project (BM10701010021); the MOST Clinical Trial Consortium for Stroke (MOST 106-2321-B-039-005-); the Tseng-Lien Lin Foundation, Taichung, Taiwan; and the Katsuzo and Kiyo Aoshima Memorial Funds, Japan. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding was received for this study.

## Conflict of interest statement

The authors have no competing interests to declare.

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