

Pneumococcal pneumonia infection is associated with end-stage renal disease in adult hospitalized patients

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Pneumococcal disease leads to renal complications ranging from persistent proteinuria to end-stage renal disease (ESRD) in pediatric patients. However, long-term renal effects after pneumococcal pneumonia infection in adult patients remains largely unknown. To evaluate this we conducted a population-based retrospective cohort study consisting of 18,733 adult patients at the time of pneumococcal pneumonia diagnosis, using claims data from Taiwan's National Health Insurance Research Database (NHIRD) with a comparison cohort of 73,409 age- and gender-matched patients without pneumococcal pneumonia. The overall incidence rate ratio of ESRD was 23% higher in those with pneumococcal pneumonia than in those without pneumococcal pneumonia (5.26 vs. 3.10 per 1000 person-years), with an adjusted hazard ratio of 1.14 (95% confidence interval 1.01–1.29). In addition, the risk of developing ESRD was associated with covariates including age, gender, chronic kidney disease, diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, and heart failure. The ESRD cumulative incidence curve showed a considerably higher risk of ESRD in those with pneumococcal pneumonia than in those without pneumococcal pneumonia (significant by log-rank test). Thus, pneumococcal pneumonia may be associated with an increased risk of ESRD in adult patients. A long-term follow-up of renal function is recommended for adult hospitalized patients with pneumococcal pneumonia infection.

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Streptococcus pneumoniae is the most common pathogen in community-acquired pneumonia (CAP) cases. CAP caused by *S. pneumoniae* has a poorer long-term prognosis compared with those of other forms of CAP, with a high all-cause mortality rate and cardiovascular-related mortality rate in elderly patients.^{1,2} Pneumococcal pneumonia (PP) might also contribute to extrapulmonary complications, including bacteremia with metastatic infection, endocarditis, and meningitis.^{3–5} An association between PP and acute cardiac events, such as myocardial infarction, arrhythmia, and congestive heart failure (HF), has also been reported.^{6,7} The proposed pathogenesis of the cardiac events associated with PP includes inflammation, hypoxia, and hypotension⁶; moreover, high circulating levels of interleukin 6 and tumor necrosis factor- α in pneumonia patients suggest that inflammatory cytokines might affect the myocardium.^{8,9}

Pneumococcal disease also leads to renal complications, ranging from persistent proteinuria to end-stage renal disease (ESRD), in pediatric patients. Pneumococcal-associated hemolytic-uremic syndrome (P-HUS) has emerged as the most common form of atypical P-HUS in children.¹⁰ P-HUS often results in acute renal failure that requires dialysis. Recent studies have reported variability in the long-term outcomes of P-HUS.^{10–13} Investigators have reported chronic renal sequelae and have recommended that children receive long-term follow-up to reduce the risk of permanent renal injury.^{12,13} Although studies on P-HUS and invasive pneumococcal disease have characterized the long-term renal effects in pediatric patients, the long-term renal effects in adult patients diagnosed with PP remain unclear. The aim of our current study was to determine the

relationship between PP and the subsequent risk for ESRD. We conducted a retrospective cohort study in Taiwan, and the incidence of ESRD in adult patients at the time that PP diagnosis was recorded. The demographic characteristics, comorbidities, and long-term outcomes of PP patients were examined and compared with those of control group patients.

RESULTS

During the study period, there were 44,621 hospitalized patients diagnosed with PP (Figure 1). Among them, patients with ESRD before the index date, under 20 years of age, and with missing information were excluded.

The remaining 18,733 PP cases without ESRD at baseline were included in the study cohort. The comparison cohort included all people covered within the Taiwan National Health Insurance Program whether or not the people had ever been admitted to the hospital for other causes. For the non-PP comparison cohort, 73,409 subjects were randomly selected in a 1:4 ratio and matched with the PP cases on age, sex, comorbidities, and index year. The proportion of adult PP patients declined from 0.104 per thousand in 1998 to 0.071 per thousand in 2004, and increased to 0.084 per thousand in 2010. The average duration of hospitalization in the PP cohort was 21.9 ± 48.5 days (mean = 9 days, interquartile range = 1,265).

The characteristics of the participants' frequency matched by sex, age, and comorbidities are displayed in Table 1. The PP group comprised more men than women (65.9% vs. 34.1%). The average ages of the non-PP and PP participants were 65.8 and 66.1 years, respectively. Among the baseline comorbidities, hyperlipidemia, chronic kidney disease

(CKD), peripheral vascular disease (PVD), HF, and malignancy were slightly more prevalent in the PP cohort than in the non-PP cohort. No significant difference was observed in

Table 1 | Demographic characteristics and comorbidities in patients with and without a history of pneumococcal pneumonia

Variable	Pneumococcal pneumonia		P-value
	No N = 74,762	Yes N = 18,733	
Sex	n (%)		
Female	25,487 (34.1)	6391 (34.1)	0.99
Male	49,275 (65.9)	12,342 (65.9)	
Age (mean ± s.d., years)	65.5 ± 17.9	66.1 ± 17.8	0.0003 ^a
Stratified age	n (%)		
20-34	6060 (8.11)	1517 (8.10)	0.99
35-49	8859 (11.9)	2219 (11.9)	
50-64	14,109 (18.9)	3532 (18.9)	
65-74	16,742 (22.4)	4191 (22.4)	
75+	28,992 (38.8)	7274 (38.8)	
Comorbidity	n (%)		
Hypertension	24,883 (33.3)	6245 (33.3)	0.89
Diabetes mellitus	15,257 (20.4)	3836 (20.5)	0.83
Hyperlipidemia	5038 (6.74)	1281 (6.84)	0.63
Chronic kidney disease	1653 (2.21)	431 (2.30)	0.46
Chronic obstructive pulmonary disease	18,441 (24.7)	4637 (24.8)	0.81
Peripheral vascular disease	1227 (1.64)	328 (1.75)	0.29
Heart failure	7322 (9.79)	1856 (9.91)	0.64
Malignancy	2447 (3.27)	628 (3.35)	0.59
Death events (death and withdrawal from the Insurance system)	19,143 (26.1)	8782 (46.9)	

χ² test.

^aTwo-sample t-test.

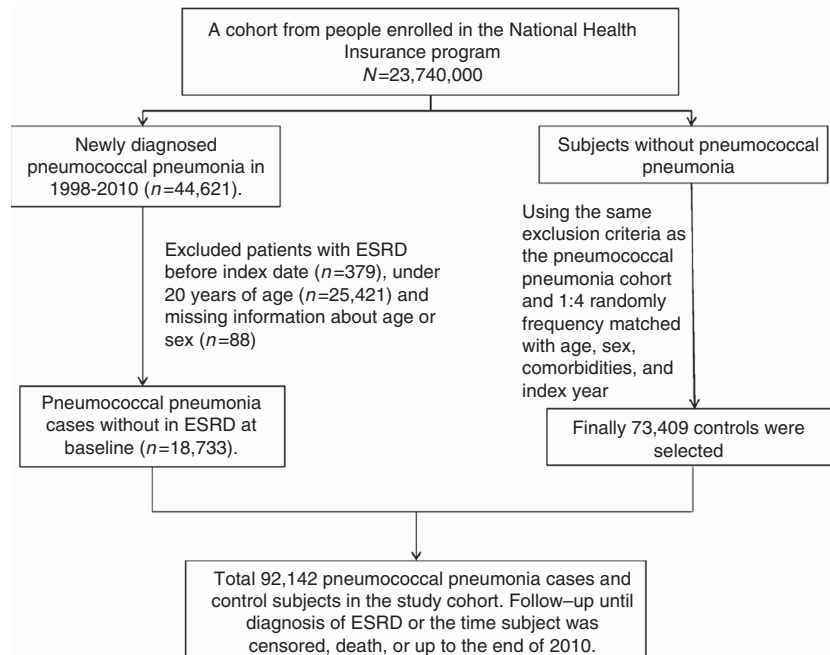


Figure 1 | Patient selection flowchart.

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