

# Risk of pneumonia among patients with splenectomy: a retrospective population-based cohort study

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**BACKGROUND:** People without a spleen are particularly susceptible to various overwhelming infections including pneumonia. Although the association between splenectomy and pneumonia has been previously studied, there has been no study using the national claims data.

**OBJECTIVES:** The aim of the study was to investigate the association between splenectomy and pneumonia.

**DESIGN:** A retrospective population-based cohort analysis.

**SETTINGS:** Database of the Taiwan National Health Insurance Program.

**PATIENTS:** Persons newly diagnosed with splenectomy from 2000 to 2010 were compared with randomly selected subjects without splenectomy. The groups were matched by sex, age, comorbidities, and the year of index date and analyzed by multivariate methods.

**MAIN OUTCOME MEASURE:** The difference in incidence of pneumonia at the end of 2011.

**RESULTS:** In 12757 individuals aged 20-84 years with splenectomy, the overall incidence of pneumonia was 1.86-fold higher than in the 51 019 individuals without splenectomy (25.0 vs. 13.4 per 1000 person-years, 95% CI 1.78, 1.95). After multivariate analysis, the adjusted hazard ratio for pneumonia was 2.2 for subjects with splenectomy (95%CI 2.07, 2.34). In further analysis, in the absence of any comorbidity, the adjusted HR for pneumonia was 3.03 for those with splenectomy alone (95% CI 2.76, 3.33) and 5.28 (95% CI 4.82, 5.78) for splenectomy and any comorbidity.

**CONCLUSIONS:** Although not a novel finding, we confirmed that splenectomy increases the relative risk for developing pneumonia in a large study population. Even in the absence of any comorbidity, the risk remains high. Patients with splenectomy should receive preventive interventions for pneumonia, such as vaccination.

**LIMITATIONS:** ICD-9 codes do not differentiate if pneumonia is caused by a viral, a bacterial or unspecified organisms, and some behavioral factors like smoking could not be ascertained directly.

The spleen is an important organ associated with various immune functions.<sup>1</sup> There is a growing body of evidence that people without a spleen are particularly susceptible to various overwhelming infections including pneumonia, which carries a high mortality rate.<sup>2-6</sup>

Pneumonia is one of the most common infectious diseases in Taiwan. It ranked as the third leading cause of death in Taiwan in 2016.<sup>7</sup> In addition to its high mor-

ality, care for patients with pneumonia is relatively costlier, which has an impact on the global health service budget in Taiwan.<sup>8</sup>

Although the association between splenectomy and pneumonia has been previously studied, there has been no formal study based on national claims data that focuses on Taiwan. Therefore, we conducted a retrospective population-based cohort study using claims data of the Taiwan National Health Insurance Program

to investigate the association between splenectomy and pneumonia.

## PATIENTS AND METHODS

The Taiwan National Health Insurance Program has covered 99% of the Taiwan population since 1995.<sup>9</sup> The claims data provide researchers with anonymous identification numbers associated with relevant claim information, including sex, date of birth, utilization of medical services, and prescriptions. The details of the insurance program have been described in previous reports.<sup>10-14</sup> This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115).

In this retrospective population-based cohort study, all subjects aged 20-84 who underwent splenectomy from 2000 to 2010 were regarded as the splenectomy group (International Classification of Diseases, Ninth Revision, Clinical Modification, ICD-9 procedure code 41.5). The date for undergoing splenectomy was defined as the index date. For each subject with splenectomy, approximately 4 subjects without splenectomy were randomly selected from the same database and assigned to the non-splenectomy group. Both splenectomy and non-splenectomy groups were matched for sex, age (within 5-year interval), comorbidities, and the year of index date. To diminish the possibility of bias,

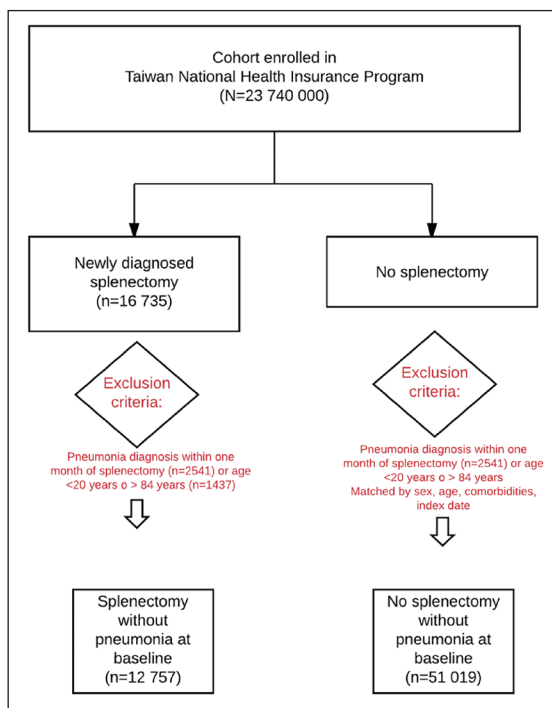
subjects with a pneumonia diagnosis (ICD-9 codes 480-486) within one month after undergoing splenectomy were excluded from the study (**Figure 1**).

The main outcome was a diagnosis of pneumonia based on hospital discharge registries during the follow-up period. Each subject was monitored from the index date until diagnosed with pneumonia, or until the end of 2011. Comorbidities potentially related to pneumonia were included as follows: alcohol-related disease, cancer, chronic kidney disease, chronic liver disease (including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis), chronic obstructive pulmonary disease, and diabetes mellitus. All comorbidities in the study were diagnosed based on ICD-9 codes. The validity of these ICD-9 codes have been well discussed in previous studies.<sup>15-19</sup>

Differences in sex, age, and comorbidities between the splenectomy group and the non-splenectomy group were compared using the chi-square test for categorical variables and the t test for continuous variables. The incidence of pneumonia was measured as the number of pneumonia events identified during the follow-up period, divided by the total follow-up person-years for each group. The incidence rate ratio (IRR) with 95% confidence interval (CI) for the splenectomy to non-splenectomy group was measured using Poisson regression, stratified by sex and age. At first, all variables were included in a univariate model. Those found to be statistically significant in a univariate model were further included in a multivariate model. A multivariate Cox proportional hazards regression model was used to measure the hazard ratio (HR) and 95% CI for pneumonia associated with splenectomy and other comorbidities. All statistical analyses were performed by using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). Two-tailed  $P < .05$  was considered statistically significant.

## RESULTS

There were 12757 subjects with splenectomy and 51019 subjects without splenectomy during the study period, with similar distributions of sex and age (**Table 1**). Males constituted a higher proportion in both groups. The mean ages of the study subjects were not statistically different between the groups. The mean follow-up periods were 4.32 (3.43) years in the splenectomy group and 5.68 (3.33) years in the non-splenectomy group (t test,  $P < .001$ ). The proportions of alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus were equally distributed in the splenectomy group and the non-splenectomy group



**Figure 1.** Subject selection diagram.

(chi-square test,  $P > .05$  for all).

At the end of the cohort study, the overall incidence of pneumonia was 1.86-fold higher in the splenectomy group than in the non-splenectomy group (25.0 vs. 13.4 per 1000 person-years, 95% CI 1.78, 1.95) (Table 2). The incidence of pneumonia, as stratified by sex and age, was higher in the splenectomy group than in the non-splenectomy group. The incidence of pneumonia increased with age in both groups, with the highest in the splenectomy group aged 65-84 years (64.8 per 1,000 person-years). The sub-analysis stratified by follow-up demonstrated that the incidence rate ratio of pneumonia between the splenectomy group and the non-splenectomy group was 2.07 (27.4 vs. 13.2 per 1000 person-years, 95% CI 1.98-2.17) in the first 5 years of follow-up. The incidence rate ratio of pneumonia was 1.35 (18.8 vs. 13.9 per 1000 person-years, 95% CI 1.25-1.46) even after 5 years. The Kaplan-Meier model demonstrates that the splenectomy group had a higher cumulative incidence of pneumonia than the non-splenectomy group (19.3% vs. 12.8% at the end of follow-up;  $P < 0.001$ , Figure 2).

Only variables found to be statistically significant in a univariate model were further examined in a multivariate model. After multivariate analysis, the multivariate Cox proportional hazards regression model demonstrated that the adjusted HR for pneumonia was 2.2 for subjects with splenectomy (95% CI 2.07, 2.34), compared with subjects without splenectomy (Table 3). In addition, male sex, alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus were associated with pneumonia. Every one-year increase in age was associated with a 1.06-fold increased risk of pneumonia (95% CI 1.05, 1.06).

Table 4 shows the interaction effects on the risk of pneumonia between splenectomy and other comorbidities including alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus. As a reference for subjects without splenectomy and without any comorbidity, the adjusted HR of pneumonia was 3.03 for subjects with splenectomy alone and without any comorbidity (95% CI 2.76, 3.33). The adjusted HR markedly increased to 5.28 for those with splenectomy and with any comorbidity (95% CI 4.82, 5.78).

## DISCUSSION

We found that the overall incidence of pneumonia was 1.86-fold higher in the splenectomy group than that in the non-splenectomy group. This finding suggests that approximately 12 additional cases of pneumonia

**Table 1.** Baseline characteristics of the splenectomy and non-splenectomy groups.

Variable	Non-splenectomy (n=51019)	Splenectomy (n=12757)	P value*
	n (%)	n (%)	
<b>Sex</b>			<b>.99</b>
Female	19873 (39.0)	4969 (39.0)	
Male	31146 (61.0)	7788 (61.0)	
<b>Age group (years)</b>			<b>.99</b>
20-39	13328 (26.1)	3331 (26.1)	
40-64	23907 (46.9)	5980 (46.9)	
65-84	13784 (27.0)	3446 (27.0)	
<b>Age (years), mean (standard deviation)†</b>	<b>52.0 (17.1)</b>	<b>52.3 (17.0)</b>	<b>.12</b>
Follow-up period (years), mean (standard deviation)†	5.68 (3.33)	4.32 (3.43)	<.001
<b>Baseline comorbidities</b>			
Alcohol-related disease	1784 (3.50)	448 (3.51)	.93
Cancer	7612 (14.9)	1905 (14.9)	.97
Chronic kidney disease	943 (1.85)	236 (1.85)	.99
Chronic liver disease	7570 (14.8)	1894 (14.9)	.98
Chronic obstructive pulmonary disease	1515 (2.97)	379 (2.97)	.99
Diabetes mellitus	7430 (14.6)	1859 (14.6)	.98

Data are number (percentages) or mean (standard deviation). \*Chi-square test, and †t test comparing subjects with and without splenectomy.

would develop per 1000 patients with splenectomy annually. We also found that the incidence of pneumonia was higher in patients with splenectomy regardless of sex or age. The incidence of pneumonia in patients with splenectomy seemed higher than in patients with schizophrenia in Taiwan (25.0 vs. 11.4 per 1,000 person-years),<sup>12</sup> but lower than in patients with chronic kidney disease in Taiwan (25.0 vs. 65.6 per 1,000 person-years).<sup>13</sup> We noticed that patients aged 65-84 years in the splenectomy group had the highest incidence of pneumonia (64.8 per 1,000 person-years). The sub-analysis stratified by follow-up period demonstrated that the risk of pneumonia in the splenectomy group was significantly higher in the first 5 years of follow-up (incidence rate ratio 2.07, 95% CI 1.98-2.17). However, the risk of pneumonia still existed in the splenectomy group even after 5 years (incidence rate ratio 1.35, 95% CI 1.25-1.46).

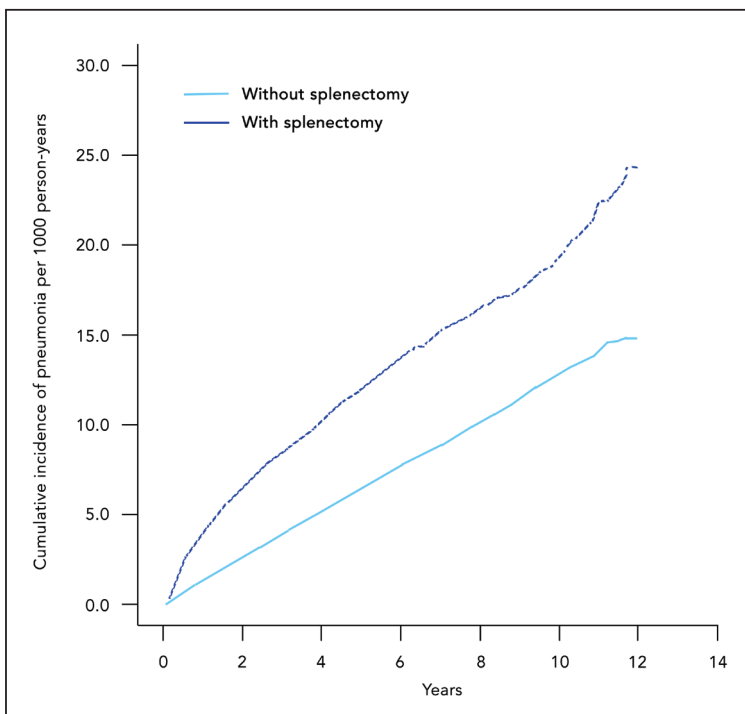
After multivariate analysis, we noticed that splenec-

**Table 2.** Incidence of pneumonia stratified by sex and age between the splenectomy and non-splenectomy groups.

Variable	Non-splenectomy				Splenectomy				IRR#	95% CI
	N	Event	Person-years	Incidence†	N	Event	Person-years	Incidence†		
All	51019	3890	289864	13.4	12757	1380	55168	25.0	1.86	(1.78, 1.95)
<b>Sex</b>										
Female	19873	1078	114942	9.38	4969	391	22075	17.7	1.89	(1.75, 2.04)
Male	31146	2812	174921	16.1	7788	989	33093	29.9	1.86	(1.76, 1.97)
<b>Age group (years)</b>										
20–39	13328	242	83427	2.90	3331	176	19351	9.10	3.14	(2.86, 3.44)
40–64	23907	1234	137984	8.94	5980	543	25616	21.2	2.37	(2.22, 2.53)
65–84	13784	2414	68452	35.3	3446	661	10202	64.8	1.84	(1.70, 1.99)

†Incidence: per 1000 person-years

#Incident rate ratio non-splenectomy vs splenectomy adjusted for sex and age



**Figure 2.** Kaplan-Meier graph for incidence of pneumonia in splenectomy and non-splenectomy groups (19.3% vs. 12.8% at the end of follow-up; log-rank test,  $P < .001$ ).

tomy was associated with a 2.2-fold increased risk of pneumonia. Patients with splenectomy seemed to have a higher hazard ratio for pneumonia compared with patients with schizophrenia in Taiwan (adjusted HR 1.39).<sup>12</sup> This finding suggests that patients with splenectomy are more likely to develop pneumonia than those with schizophrenia. Some patients could develop pneumonia early due to procedural complications of splenectomy. A subject with a pneumonia diagnosis in the first month was excluded since the diagnosis could be an early surgical complication rather than a splenectomy-related immunocompromised status.

In addition, the lack of a difference in the prevalence of comorbidities between the splenectomy group and the non-splenectomy group indicates that the increased HR was not confounded by comorbidities. That is, the increased risk of pneumonia in patients with splenectomy could not be completely attributable to the impact of comorbidities. In further analysis, even in the absence of any comorbidity, patients with splenectomy still had a higher risk of pneumonia (adjusted HR 3.03, **Table 4**). This finding means that splenectomy has a unique role in the risk of developing pneumonia no matter whether comorbidity co-exists or not. The risk markedly increased for those with splenectomy and any comorbidity (adjusted HR 5.28, **Table 4**). This finding suggests that there is an interaction effect on the risk of pneumonia between splenectomy and comorbidities. Although the association between splenectomy

and blood borne infections has been acknowledged for many years,<sup>1</sup> these findings are consistent with previous studies that patients with splenectomy are more susceptible to various overwhelming infections including pneumonia.<sup>2-6,10,12,19</sup>

Some limitations in the present study deserve discussion. First, pneumococcal vaccination significantly reduces the risk of pneumonia in patients with splenectomy, and therefore vaccination is recommended by many countries.<sup>20</sup> However, vaccination for pneumococcal pneumonia and influenza was not universally performed in Taiwan from 2000 to 2010. We were unable to investigate whether pneumococcal and influenza vaccination might decrease the risk of pneumonia among patients with splenectomy because vaccination records were incomplete. Second, some behavioral risk factors for pneumonia, such as alcohol consumption and cigarette smoking, were not recorded in the database. In our analysis, we used alcohol-related disease instead of alcohol consumption and chronic obstructive pulmonary disease in place of cigarette smoking. Third, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are the most common causative pathogens of pneumonia in Taiwan, accounting for 45%-59% of pneumonia patients.<sup>21,22</sup> ICD-9 codes do not differentiate if the pneumonia is caused by a viral, a bacterial or unspecified organisms. We could not investigate which pathogens were more likely to be found among patients with splenectomy. It would be of interest to distinguish the different pathogens causing pneumonia so as to optimize a vaccination program. Fourth, the diagnosis of pneumonia was based on the ICD-9 codes recorded in the hospital discharge registries. Though radiographs were not recorded. Also, we could not assess sensitivity/specificity of a single code for pneumonia, but in view of the high quality of medical practice in Taiwan, chest radiographs should have been performed during hospitalization among patients suspected of having pneumonia. Only after radiological confirmation is the diagnosis of pneumonia made. Thus, pneumonia based on the ICD-9 codes recorded in the hospital discharge registries is accurate. Last, a diagnosis based on the coding system also fails to distinguish between community-acquired and hospital-acquired pneumonia. Most of hospital-acquired pneumonia is caused by multidrug resistant bacteria, which may not be relevant with splenectomy. Whether splenectomy also increases the risk of hospital-acquired pneumonia is a question for future research.

A strength of our study is the use of high-quality claims data with a large sample size, which increases the statistical power. The results were fairly impressive.

**Table 3.** Hazard ratio and 95% confidence interval for pneumonia associated with splenectomy and comorbidities .

Variable	Crude		Adjusted <sup>#</sup>	
	HR	(95% CI)	HR	(95% CI)
Sex (male vs. female)	1.70	1.60, 1.81	1.70	1.59, 1.80
Age (per year)	1.06	1.05, 1.06	1.06	1.05, 1.06)
<b>Baseline comorbidities (yes vs. no)</b>				
Splenectomy	1.85	1.74, 1.97	2.20	2.07, 2.34
Alcohol-related disease	1.70	1.50, 1.92	2.58	2.27, 2.93
Cancer	2.37	2.22, 2.53	1.72	1.61, 1.84
Chronic kidney disease	3.39	2.98, 3.86	2.40	2.10, 2.73
Chronic liver disease	1.46	1.36, 1.57	1.35	1.26, 1.46
Chronic obstructive pulmonary disease	5.77	5.29, 6.29	2.36	2.16, 2.58
Diabetes mellitus	2.74	2.58, 2.91	1.76	1.65, 1.87

<sup>#</sup>Variables found to be statistically significant in a univariable model (all were statistically significant) were further examined in a multivariable model. Adjusted for sex, age, alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus

**Table 4.** Cox proportional hazard regression analysis for risk of pneumonia stratified by splenectomy and comorbidities.

Variable	Any comorbidity <sup>*</sup>	Event (n)	Incidence <sup>†</sup>	Adjusted HR# (95% CI)
No	No	1321	6.77	(Reference)
No	Yes	2569	27.1	2.98 (2.78, 3.18)
Yes	No	654	16.8	3.03 (2.76, 3.33)
Yes	Yes	726	44.5	5.28 (4.82, 5.78)

<sup>†</sup>Incidence: per 1000 person-years

<sup>#</sup>Adjusted for sex and age

<sup>\*</sup>Comorbidities including alcohol-related disease, cancer, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes mellitus

Though the matter of an increase in pneumonia in patients with splenectomy has been reported before, this study provides updated evidence for this country based on national claims data. We conclude that splenectomy increases the relative risk for developing pneumonia 2.2-fold in Taiwan. Five years after splenectomy, the risk persists. Even in the absence of any comorbidity, the risk remains high. Patients with splenectomy should re-

ceive preventive interventions for pneumonia such as vaccination.

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collection and analysis, decision to publish, or preparation of the manuscript.

### Specific author contributions

Shih-Wei Lai planned and conducted this study. He contributed to the conception of the article, initiated the draft of the article, and revised the article. Cheng-Li Lin conducted the data analysis and reviewed the article. Kuan-Fu Liao planned and conducted this study. He participated in the data interpretation and revised the article.

### Conflict of interest

The authors declared no conflicts of interest.

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