Original article

Risk of contracting pneumonia among patients with predialysis chronic kidney disease: a population-based cohort study in Taiwan

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1. Introduction

Pneumonia continues to be a major public health problem due to the substantial number of deaths it causes as well as the high economic cost to treat it globally. Pneumonia has been ranked as the third leading cause of death in the world.\(^{[1]}\) In addition, pneumonia was the fourth most common cause of death in Taiwan in 2015.\(^{[2]}\) Lin et al.’s study showed that patients with pneumonia needed longer lengths of hospital stays than average to recover and higher health care expenditures, both of which have placed a significant economic burden on Taiwan. \(^{[3]}\)

Meanwhile, chronic kidney disease was the ninth most common cause of death in Taiwan in 2015.\(^{[2]}\) Much evidence has already shown that pneumonia is a common comorbidity among patients with chronic kidney disease.\(^{[4, 5]}\) Thus, we made a rational hypothesis that there could be a potential link between predialysis chronic kidney disease and pneumonia in Taiwan. If the link can be made, from a view of preventive medicine, vaccination for pneumonia might be something to take into account among patients with predialysis chronic kidney disease. With the above in mind, our study employed a population-based cohort design using the database of the Taiwan National Health Insurance (NHI) Program to investigate the association between predialysis chronic kidney disease and pneumonia.
Subjects who had a history of pneumonia (ICD-9 codes 480-486) before the index date were excluded from the study. Subjects who were currently receiving dialysis therapy or had received renal transplantation before the major endpoint were excluded from the study (Fig. 1).

2.3. Major endpoint

The major endpoint was a new diagnosis of pneumonia during the follow-up period. Each subject was followed-up with until they were diagnosed with pneumonia, or until the end of 2013.

2.4. Comorbid conditions

The comorbid conditions potentially related to contracting pneumonia that were included were as follows: alcohol-related disease, cancer, cardiovascular disease (including coronary artery disease, heart failure, cerebrovascular disease, and peripheral atherosclerosis), chronic liver disease (including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis), chronic obstructive pulmonary disease, hyperlipidemia, hypertension, and diabetes mellitus. All comorbidities in the study were diagnosed with ICD-9 codes, which have been well examined in previous studies.[12-21]

2.5. Statistical analysis

The differences in the sex, age, and comorbidities between the predialysis chronic kidney disease group and the non-chronic kidney disease group were compared via a Chi-square test for categorical variables and a t-test for continuous variables. The incidence of contracting pneumonia was calculated as the number of
pneumonia cases identified during the follow-up period, divided by the total number of follow-up person-years for each group. In the beginning, all variables were included in a univariable model. Then, variables found to be statistically significant in the univariable model were further included in the multivariable model. The multivariable Cox proportional hazards regression model was used to calculate the hazard ratio (HR) with 95% confidence interval (CI) of contracting pneumonia associated with predialysis chronic kidney disease along with other comorbidities. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, North Carolina, USA). Two-tailed \( P < 0.05 \) was considered statistically significant.

### 3. Results

#### 3.1. Demographic information and comorbidities of the study population

Table 1 shows the distributions of sex, age, and comorbidities between the predialysis chronic kidney disease and non-chronic kidney disease groups. There were 18807 subjects in the predialysis chronic kidney disease group and likewise 18807 subjects in the non-chronic kidney disease group, with similar distributions of sex and age. The mean ages (standard deviation) of the study’s subjects were 58.5 (15.0) years in the predialysis chronic kidney disease group and 58.2 (15.0) years in the non-chronic kidney disease group (\( t \)-test, \( P = 0.05 \)). The comorbidities were equally distributed in the predialysis chronic kidney disease group and the non-chronic kidney disease group (\( \chi^2 \)-square test, \( P > 0.05 \) for all).

#### 3.2. Incidence of contracting pneumonia in the study population stratified by sex and age

Table 2 shows that the overall incidence of contracting pneumonia was 1.47-fold higher in the predialysis chronic kidney disease group than that in the non-chronic kidney disease group (24.6 vs. 16.7 per 1,000 person-years, 95% CI 1.40, 1.55). As stratified by sex and age, the incidences of contracting pneumonia were all higher in the predialysis chronic kidney disease group than those in the non-chronic kidney disease group. The incidences of contracting pneumonia increased with age in both groups, with the highest incidence rate being in the predialysis chronic kidney disease group aged 65-84 years (45.2 per 1,000 person-years).

Using the Kaplan-Meier model, we have shown that the cumulative incidence of contracting pneumonia was higher in the predialysis chronic kidney disease group than that in the non-chronic kidney disease group (23.0% vs. 16.8% at the end of follow-up; \( P < 0.001 \), Fig. 2).

#### 3.3. Hazard ratio of contracting pneumonia associated with predialysis chronic kidney disease and comorbidities

Table 3 shows the hazard ratio (HR) of contracting pneumonia


Table 2 – Incidence of pneumonia stratified by sex and age between predialysis chronic kidney disease group and non-chronic kidney disease group.

| Variable          | N  | Event | Person-years | Incidence\(^1\) | N  | Event | Person-years | Incidence\(^1\) | IRR\(^2\) (95% CI) |
|-------------------|----|-------|--------------|----------------|----|-------|--------------|----------------|------------------|
| **Non-chronic kidney disease** |    |       |              |                |    |       |              |                |                  |
| **Sex**           |    |       |              |                |    |       |              |                |                  |
| Female            | 7655 | 748   | 54399        | 13.8           | 7655 | 1035  | 48472        | 21.4           | 1.55 (1.43, 1.68) |
| Male              | 11152 | 1365  | 72223        | 18.9           | 11152 | 1786  | 66241        | 27.0           | 1.43 (1.34, 1.52) |
| **Age group (years)** |    |       |              |                |    |       |              |                |                  |
| 20–39             | 5367 | 292   | 43624        | 6.69           | 5367 | 473   | 41350        | 11.4           | 1.71 (1.53, 1.90) |
| 40–64             | 6243 | 569   | 42385        | 13.4           | 6243 | 794   | 38994        | 20.4           | 1.52 (1.38, 1.66) |
| 65-84             | 7197 | 1252  | 40613        | 30.8           | 7197 | 1554  | 34369        | 45.2           | 1.47 (1.36, 1.58) |
| **Predialysis chronic kidney disease** |    |       |              |                |    |       |              |                |                  |
| All               | 18807 | 2113  | 126622       | 16.7           | 18807 | 2821  | 114713       | 24.6           | 1.47 (1.40, 1.55) |

\(^1\)Incidence: per 1,000 person-years.

\(^2\)IRR (incidence rate ratio): predialysis chronic kidney disease vs. non-chronic kidney disease (95% confidence interval)

Fig. 2 - Kaplan–Meier curves showing a significant difference in cumulative incidences of pneumonia among patients with predialysis chronic kidney disease and without chronic kidney disease. (23.0% vs. 16.8% at the end of follow-up; \(P < 0.001\))



3.4. Association of contracting pneumonia stratified by predialysis chronic kidney disease and comorbidities

As a reference of subjects in the study without predialysis chronic kidney disease and without any comorbidity, the adjusted HR of contracting pneumonia was 1.53 for subjects with predialysis chronic kidney disease alone and without any comorbidity (95% CI 1.32, 1.76). The adjusted HR markedly increased to 2.16 for those with predialysis chronic kidney disease and with any comorbidity (95% CI 1.91, 2.43) (Table 4).

4. Discussion

In the study, we noted that the overall incidence of contracting pneumonia was 1.47-fold higher in the predialysis chronic kidney disease group than in the non-chronic kidney disease group, particularly among the predialysis chronic kidney disease group aged 65-84, who had the highest incidence of contracting pneumonia (45.2 per 1,000 person-years). Of note, the incidence of contracting pneumonia in patients with predialysis chronic kidney disease appears to be much higher than that in patients with sleep apnea (24.6 vs. 20.9 per 1,000 person-years), [22] but much lower than that in patients with pulmonary tuberculosis in Taiwan (24.6 vs. 51.6 per 1,000 person-years).[23] From a preventive medicine view, therefore, it is suggested that vaccination for pneumonia might be worth taking into account as an option among patients with predialysis chronic kidney disease, particularly for those with predialysis chronic kidney disease who are aged 65-84 due to their having the highest observed incidence of contracting pneumonia.

After adjusting for co-variables, we noted that patients with predialysis chronic kidney disease demonstrated a 1.52-fold increased hazard of contracting pneumonia, compared with subjects without chronic kidney disease (Table 3). Upon further analysis, patients with predialysis chronic kidney disease alone still had an increased risk of contracting pneumonia (adjusted HR 1.53, Table 4). This finding indicates that patients with predialysis chronic kidney disease alone are at a substantially increased risk for contracting pneumonia even in the absence of any comorbidity. In addition, we noted that if patients were comorbid with predialysis chronic kidney disease and any of the comorbidities studied, the adjusted HR of contracting pneumonia markedly increased to 2.16. This finding indicates that there might be a synergistic effect on the risk of contracting pneumonia between predialysis chronic kidney disease and any of the comorbidities studied.

We can conclude that patients with predialysis chronic kidney disease...
Table 3 – Hazard ratio (HR) and 95% confidence interval of contracting pneumonia associated with predialysis chronic kidney disease and certain comorbidities.

| Variable                                      | Crude HR (95% CI)       | Adjusted HR (95% CI)          |
|-----------------------------------------------|-------------------------|--------------------------------|
| Sex (male vs. female)                         | 1.29 (1.22, 1.37)       | 1.33 (1.25, 1.41)             |
| Age (per one year)                            | 1.04 (1.04, 1.05)       | 1.04 (1.03, 1.04)             |
| Predialysis chronic kidney disease            | 1.46 (1.38, 1.55)       | 1.52 (1.43, 1.60)             |
| Baseline comorbidities (yes vs. no)           |                         |                                |
| Alcohol-related disease                       | 1.27 (1.11, 1.45)       | 1.35 (1.18, 1.55)             |
| Cancer                                        | 1.57 (1.36, 1.80)       | 1.30 (1.12, 1.49)             |
| Cardiovascular disease                        | 2.15 (2.03, 2.28)       | 1.24 (1.17, 1.33)             |
| Chronic liver disease                         | 0.93 (0.87, 1.00)       | -                             |
| Chronic obstructive pulmonary disease         | 2.12 (1.98, 2.26)       | 1.40 (1.31, 1.51)             |
| Hyperlipidemia                                | 0.96 (0.91, 1.02)       | -                             |
| Hypertension                                  | 2.01 (1.89, 2.14)       | 1.03 (0.96, 1.11)             |
| Diabetes mellitus                             | 1.99 (1.87, 2.11)       | 1.59 (1.49, 1.69)             |

†Variables found to be statistically significant in a univariable model were further examined in a multivariable model. Adjustments for sex, age, alcohol-related disease, cancer, cardiovascular disease, chronic obstructive pulmonary disease, hypertension, and diabetes mellitus.

Table 4 – Association of contracting pneumonia stratified by predialysis chronic kidney disease and comorbidities.

| Predialysis chronic kidney disease | Any comorbidity* | Event | Incidence † | Adjusted HR ‡ (95% CI) |
|----------------------------------|------------------|-------|-------------|------------------------|
| No                               | No               | 321   | 7.82        | (Reference)           |
| No                               | Yes              | 1792  | 20.9        | 1.45 (1.28, 1.64)     |
| Yes                              | No               | 468   | 11.9        | 1.53 (1.32, 1.76)     |
| Yes                              | Yes              | 2353  | 31.2        | 2.16 (1.91, 2.43)     |

†Incidence: per 1,000 person-years  
‡Adjusted for sex and age  
*Comorbidities include alcohol-related disease, cancer, cardiovascular disease, chronic obstructive pulmonary disease, hypertension, and diabetes mellitus

disease have a 1.52-fold increased risk of contracting pneumonia as compared to those with non-chronic kidney disease. Thus, even in the absence of any comorbidity, the risk of contracting pneumonia can be said to be high among patients with predialysis chronic kidney disease.

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Specific author contributions

Shih-Wei Lai planned and conducted this study. He substantially contributed to the conception of the article, initiated the first draft of the article, and critically revised the article.

Cheng-Li Lin conducted the data analysis and critically reviewed the article.

Kuan-Fu Liao planned and conducted this study. He participated in the data interpretation and also critically revised the article.

Conflicts of Interest Statement

The authors wish to disclose they have no conflicts of interest.
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