Epidemiology of pulmonary alveolar proteinosis: a descriptive study using a Japanese national administrative claims database

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To the Editor:

Pulmonary alveolar proteinosis (PAP) is a rare respiratory disease characterised by the progressive accumulation of surfactants in the alveoli, resulting in hypoxaemic respiratory failure [1, 2]. PAP is classified into the different types on the basis of the pathogenetic mechanism: primary PAP, which includes autoimmune and hereditary PAP (APAP and HPAP, respectively), secondary PAP (SPAP) and congenital PAP (CPAP) [3]. Several epidemiological studies have been conducted on PAP (predominantly APAP) [4–7]; however, the reported incidence and prevalence vary depending on the study setting and case definitions. Therefore, further epidemiological data are needed not only for APAP but also for SPAP, CPAP and HPAP. In this study, using a national administrative claims database, we estimated the national incidence and prevalence of APAP, SPAP, HPAP and CPAP. Additionally, we have clarified their demographics and survivals.

We conducted a population-based, cross-sectional study using data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB). The NDB covers 99% of hospitals in Japan, and includes patient-specific identifiers, age and sex, diagnoses, prescriptions and procedures based on original Japanese codes. Further details of the NDB have been described previously [8]. We defined a "prevalent case of PAP according to its subtypes in each year (2014, 2016, 2018 and 2020)" as a case in which at least two claims were issued with the corresponding diagnostic code in different months during the study period (from January 2013 to December 2020) and at least one claim was issued with the corresponding diagnostic code in the year. We defined a "incident case of PAP according to its subtype in each year" as a prevalent case in that year in which no claim with the corresponding diagnostic code was issued before that year. The diagnostic codes associated with PAP included "autoimmune pulmonary alveolar proteinosis", "congenital pulmonary alveolar proteinosis", "hereditary pulmonary alveolar proteinosis", "idiopathic pulmonary alveolar proteinosis" and "pulmonary alveolar proteinosis". The first three codes were assigned according to their corresponding subtypes. "Idiopathic pulmonary alveolar proteinosis" was assigned to APAP because the nomenclature for this condition was changed to "autoimmune pulmonary alveolar proteinosis" [9, 10]. Since "pulmonary alveolar proteinosis" alone was insufficient for subtype classification, we defined cases with diagnostic codes corresponding to underlying diseases (haematological disorders, infectious diseases, autoimmune diseases, post-organ transplantation and non-haematological malignancy) in at least five different claims as SPAP, and other cases as APAP [11]. This definition was based on the following two findings: first, CPAP or HPAP accounted for a small proportion (<5%) of all PAP cases [4]; second, a study describing 223 APAP cases and 40 SPAP cases did not find the previously mentioned underlying diseases in APAP cases [10]. We calculated the annual incidence (prevalence) as the total number of incident (prevalent) cases divided by the estimated population of Japan [12]. We also clarified demographics of the incident and prevalent cases in 2020 and elucidated the usage rate of whole lung lavage and home oxygen therapy in prevalent cases in 2020. Additionally, we estimated survival in incident PAP patients after 2014 using Kaplan–Meier analysis. Owing to the small sample sizes of the CPAP and HPAP data, we exclusively compared survival between APAP and SPAP using log-rank tests. As the NDB contains data on all types of insurance, it tracks individuals throughout the study period. Hence, the survival analysis focused on the period from the beginning of the month of diagnosis until either the end of the study period or date of death. A multivariate Cox proportional hazards model adjusted for age and sex was used to calculate the hazard ratio associated with the type of PAP (APAP and SPAP).

Shareable abstract (@ERSpublications)
The national prevalence of autoimmune and secondary PAP rose during the past decade. The prognoses of secondary and congenital PAP were particularly poor, highlighting the need for further research of the mechanisms underlying these diseases. https://bit.ly/3Z7uBkg

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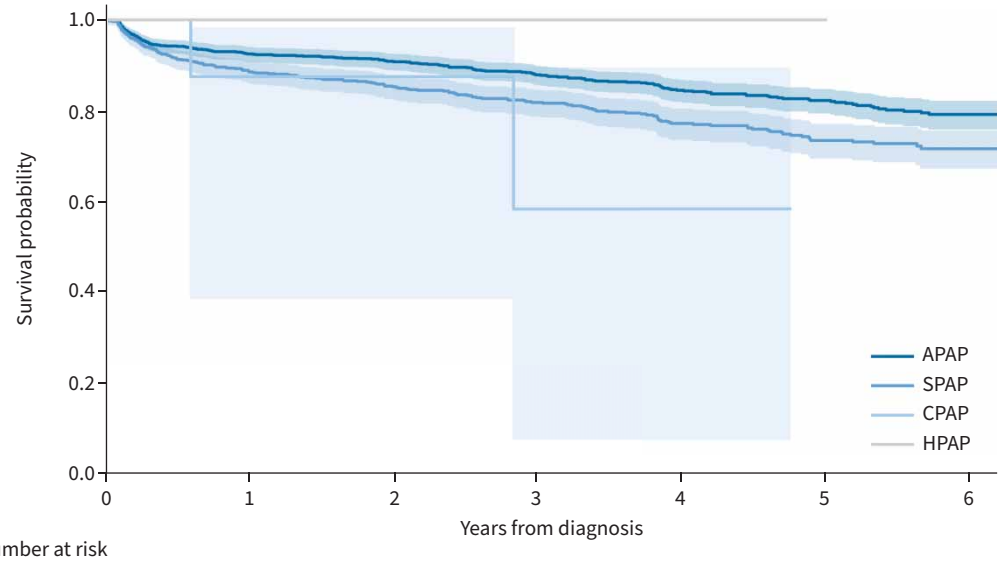
In 2014, 2016, 2018 and 2020, we identified 178, 223, 217 and 177 incident APAP patients and 83, 71, 87 and 80 incident SPAP patients, respectively. Consequently, the incidence (per million person-years) of APAP in each year was 1.4, 1.8, 1.7 and 1.4, respectively, and the incidence of SPAP in each year was 0.7, 0.6, 0.7 and 0.6, respectively. Additionally, we identified 893, 1034, 1112 and 1219 prevalent APAP patients and 280, 333, 368 and 382 prevalent SPAP patients in 2014, 2016, 2018 and 2020, respectively. Consequently, the prevalence (per million persons) of APAP in each year was 7.1, 8.2, 8.8 and 9.7, respectively, and the prevalence of SPAP in each year was 2.2, 2.6, 2.9 and 3.0, respectively. We could not present the incidence and prevalence of CPAP and HPAP, as the number of patients with CPAP or HPAP was less than 10 in many of the examined years, and disclosing a number less than 10 was prohibited by governmental policy on privacy protection.

The median (interquartile ranges) ages of incident cases of APAP, SPAP and CPAP in 2020 were 61 (50–72), 70 (58–76) and 1.5 (0.75–21.5), respectively. There were no cases of HPAP in 2020. The median ages of the prevalent cases of APAP, SPAP, CPAP and HPAP in 2020 were 64 (52–73), 71 (63–78), 1.5 (0.75–5.5) and 4 (3–73) years, respectively.

The usage rate of whole lung lavage and home oxygen therapy in prevalent APAP cases in 2020 was 3.6% (44 out of 1219) and 9.6% (117 out of 1219), respectively; in prevalent SPAP cases, it was 5.2% (20 out of 382) and 15.2% (58 out of 382), respectively.

The survival time in APAP cases was significantly longer than that in SPAP cases (log-rank test: $p<0.001$; adjusted hazard ratio 1.39, 95% CI 1.14–1.70), with estimated 5-year survival rates of 82.4% and 73.5% for APAP and SPAP, respectively (figure 1). Although the sample sizes of the CPAP and HPAP cases included in the survival analysis were small (12 for CPAP and <10 for HPAP), the estimated 5-year survival rates were 58.3% and 100.0% for CPAP and HPAP, respectively.

Using a national administrative database, we clarified that the most recent incidence and prevalence were 1.4 and 9.7 per million for APAP and 0.6 and 3.0 per million for SPAP, respectively. Furthermore, we found that the prevalence of both APAP and SPAP increased during the study period. The increasing prevalence of APAP and SPAP may be a result of heightened awareness of PAP among patients and physicians or improvements in patient management. The designation of PAP as an intractable disease in



Number at risk

APAP	1363	1127	930	737	549	410	203
SPAP	889	722	555	465	311	255	79
CPAP	12	<10	<10	<10	<10	<10	<10
HPAP	<10	<10	<10	<10	<10	<10	<10

FIGURE 1 Survival curves from the diagnosis of pulmonary alveolar proteinosis. APAP: autoimmune pulmonary alveolar proteinosis; SPAP: secondary pulmonary alveolar proteinosis; CPAP: congenital pulmonary alveolar proteinosis; HPAP: hereditary pulmonary alveolar proteinosis.

Japan in 2015 and the widespread use of the granulocyte–macrophage colony-stimulating factor (GM-CSF) antibody measurement for diagnosing APAP in the 2010s may have contributed to the heightened awareness of PAP.

The usage rates of whole lung lavage in APAP and SPAP cases were lower than the 12.0% reported in a previous study using a database of designated incurable diseases in Japan [13]. This discrepancy could be because the database includes only cases with a certain severity, whereas the NDB includes all cases, resulting in a higher proportion of mild cases in this study. We could not determine if some patients needed whole lung lavage but could not access it. However, this is likely minimal, as there is a monthly medical expenditure limit per patient, and PAP patients with a certain severity can receive financial assistance in Japan.

We presented survival data for patients with PAP according to the subtype. The results showed that patients with SPAP had a significantly poorer prognosis than those with APAP (5-year survival rate: APAP, 82.4%; SPAP, 73.5%). The poorer prognosis of SPAP compared to that of APAP has also been suggested in previous studies [3]; however, a direct comparison within a single study has not been conducted. Although novel treatments such as recombinant GM-CSF have emerged for APAP along with an understanding of its mechanism, there are still many unknown aspects regarding the mechanism of SPAP, and further elucidation of its underlying mechanisms is needed to improve outcomes in patients with SPAP. Although we presented mortality data for CPAP and HPAP cases, caution is needed when interpreting these data due to the small number of patients.

This study had several limitations. First, the diagnostic code for PAP has not been validated. In Japan, diagnostic codes are assigned based on the attending physician's diagnosis, with no central validation process to ensure accuracy. However, the diagnostic codes for PAP would have high sensitivity and specificity because of the peculiarity and rarity of the disease. Second, the NDB does not contain data on pathological diagnoses and biological markers, such as GM-CSF antibodies. Hence, we could not definitively confirm the APAP cases that were positive for GM-CSF antibodies. We assigned patients with the diagnostic code "pulmonary alveolar proteinosis" to either the APAP or SPAP group based on underlying diseases. Previous studies report APAP comprises approximately 90% of PAP cases [3], whereas our study found 75–80% prevalent APAP cases. This discrepancy suggests some patients with underlying diseases may have been included in the SPAP group. Third, almost all the patients in this study were of Japanese ethnicity. Further research is necessary to generalise these results to other ethnic groups.

In conclusion, our results revealed an increasing prevalence of APAP and SPAP over the past decade. The prognoses for SPAP and CPAP were particularly poor, highlighting the need for further analyses of the mechanisms underlying these diseases.

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