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# Risk of invasive pneumococcal disease in patients with asplenia/hyposplenism: A nationwide population-based study in Korea, 2009–2018

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ABSTRACT

*Objectives:* We aimed to determine the incidence and relative risk (RR) of invasive pneumococcal disease (IPD) in patients with asplenia/hyposplenism, using a nationwide population-based database.
*Methods:* From 2009 to 2018, all claimed cases of newly diagnosed asplenia/hyposplenism in the National Health Insurance Service in South Korea were included. The incidence and RR of IPD in asplenia/hyposplenism patients were investigated using the Korean Center for Disease Control criteria.
*Results:* Fifty-seven IPD cases were identified among 21,376 patients with 82,748 person-years of exposure. The cumulative 8-year IPD incidence was 0.5%; 45.6% of the infections occurred within two years after an asplenia/hyposplenism diagnosis. The age-standardised incidence rate was 104.5 per 100,000 person-years (95% confidence interval [CI], 103.6–105.4). Patients aged <5 years had a 15.1-times higher risk of IPD than those aged ≥60 years (95% CI: 5.8–39.5, $p < 0.0001$). The RR of IPD was 32.0 times higher in patients with asplenia/hyposplenism than in the general population (95% CI, 21.7–47.0); the standardized incidence ratio was 17.9(95% CI, 11.8–26.0).
*Conclusions:* This large population-based study highlights the high IPD incidence rate and RR in Korean patients with asplenia/hyposplenism. Increased awareness and effective prevention strategies are needed for these high-risk populations, especially children aged <5 years.


## Background

Asplenia, the absence of the spleen, is typically a result of splenectomy and is rarely congenital. Hyposplenism is a disorder in which the spleen's function and size are reduced due to several underlying diseases (Di Sabatino et al., 2011). As various immune cells and elements in the spleen, including heterogeneous splenic macrophages, opsonins, IgM, and memory B cells, contribute to the filtering of blood pathogens and induction of an appropriate immune response, asplenia/hyposplenism can cause serious bloodstream infections, especially infections caused by encapsulated pathogens, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* (Borges da Silva et al., 2015; Rubin and Schaffner, 2014).

Numerous studies of such infections, especially invasive pneumococcal disease (IPD) after splenectomy, have been published (Krauth et al., 2008; King and Shumacker, 1952; Theilacker et al., 2016). A systematic review reported an IPD incidence of 2.9% in patients with severe post-splenectomy infections, while another review reported 890 IPD cases per 100,000 person-years of severe post-splenectomy infection among 21,404 person-years of exposure (Cullingford et al., 1991; Holdsworth et al., 1991). However, those studies were conducted before the 1990s and may not reflect the current situation after the introduction of the pneumococcal

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conjugate vaccine (PCV). Also, the effect of rare conditions, such as congenital asplenia or hyposplenism, on the development of IPD, compared with splenectomy, is unclear (William et al., 2007).

This study aimed to investigate the incidence of IPD among patients with asplenia/hyposplenism and to determine the relative risk (RR) of IPD in the PCV era, using a nationwide population-based database. We also evaluated the risk factors for IPD and the occurrence of invasive *N. meningitidis* and *H. influenzae* infections in these high-risk populations.

## Methods

### *Health Insurance Review and Assessment (HIRA) service database*

South Korea has a universal health coverage system, the National Health Insurance Service (K-NHIS), which covers approximately 98% of the overall Korean population (51,420,000 citizens in the 2017 census) (Kim et al., 2014). The HIRA assesses the claims from almost 80,000 medical institutions included in the K-NHIS and has an extensive database that contains detailed information about the diagnoses, treatment, surgical history, and prescription drugs of patients from the entire population.

### *The National Infectious Disease Surveillance System in Korea*

The Korean Center for Disease Control (KCDC) operates the National Infectious Disease Surveillance System and provides real-time information on the occurrence of mandatory notifiable infectious diseases through an Infectious Disease Portal (http://www.cdc.go.kr/npt/biz/npp/nppMain.do). The KCDC publishes the Infectious Disease Surveillance Yearbook annually with various statistics on infectious diseases, and data on the age distribution of the general population (KCDC, 2017). *S. pneumoniae* (since September 2014), *H. influenzae* type B (since September 2013), and *N. meningitidis* (since 2001) infections are mandatorily notifiable diseases; clinicians or medical institutions that diagnose or detect these infections are obligated by law to report all such cases. Also, the National Immunisation Program (NIP) provides free of charge vaccination against those pathogens for the pediatric population. From 2015 to 2018, the complete vaccination rate included in the NIP (except *N. meningitidis*) is 94–97% for 1-year olds and 92–95% for 2-year olds in Korea.

### *Study population*

All claimed cases of asplenia/hyposplenism in South Korea from 1 January 2008 to 31 December 2018 were included. Patients with asplenia/hyposplenism were identified using the Korean Classification of Disease (KCD) codes adapted from the International Classification of Diseases 10th revision (ICD-10). Patients with asplenia/hyposplenism were defined as those diagnosed with congenital asplenia (Q89.00)/hyposplenism (D73.0) or those who underwent a splenectomy (procedure codes: P2091–P2093). As previous cases may confound the actual incidence, the claims data for 2008 were excluded, to account for a wash-out period.

### *Definitions*

To analyze the incidence and risk factors of IPD in asplenia/hyposplenism patients, all codes defining IPD among the KCD codes were included [Method 1]. IPD was defined using the KCD codes, namely, A40.3 (pneumococcal sepsis), G00.1 (pneumococcal meningitis), K67.8 (pneumococcal peritonitis), J13 (pneumococcal pneumonia), A49.1 (pneumococcal infection), I30.1 (pneumococcal endocarditis), M00.1 (pneumococcal arthritis), and B95.3 (pneumococcal infections in other sites), with at least one of the following diagnostic codes: K65.0 (acute peritonitis), M00.8 (arthritis and polyarthritis due to other specified bacterial agents), O85 (puerperal sepsis), P23.6 (congenital pneumonia due to other bacterial agents), and/or I33.0 (acute and subacute infective endocarditis). To compare the incidence rate of IPD between the patients with asplenia/hyposplenism and the general population, we used the IPD criteria of the KCDC to unify the case definition [Method 2]. The KCDC criteria use only the K65 and B95.3 codes for pneumococcal peritonitis (except the K67.8 code) and exclude the A49.1 code for non-specific pneumococcal infection. In case of other invasive infections due to encapsulated bacteria, invasive *N. meningitidis* infection was defined using the A39.0–39.9 codes, and invasive *H. influenzae* infection was defined using the A41.3, A49.2, G00.0, J14, J20.1, G00.0, and B96.3 codes.

Comorbidity was defined as a disease whose code was registered or persisted between one year prior to the index date (date when the first asplenia-related code was inserted) and 30 days after the index date. We used the Charlson Comorbidity Index with modifications to categorize the comorbidities (Quan et al., 2005). We selected Hodgkin's disease, portal hypertension, idiopathic thrombocytopenic purpura, thalassemia, hereditary spherocytosis, autoimmune lymphoproliferative syndrome, post-transplant lymphoproliferative disease, and primary immunodeficiency diseases, including hemophagocytic lymphohistiocytosis, as the known risk factors for severe post-splenectomy infection (Bisharat et al., 2001; Sinwar, 2014). Antimicrobial prophylaxis was defined as administering oral antimicrobials for at least nine months within one year of the index date. IPD-related deaths were

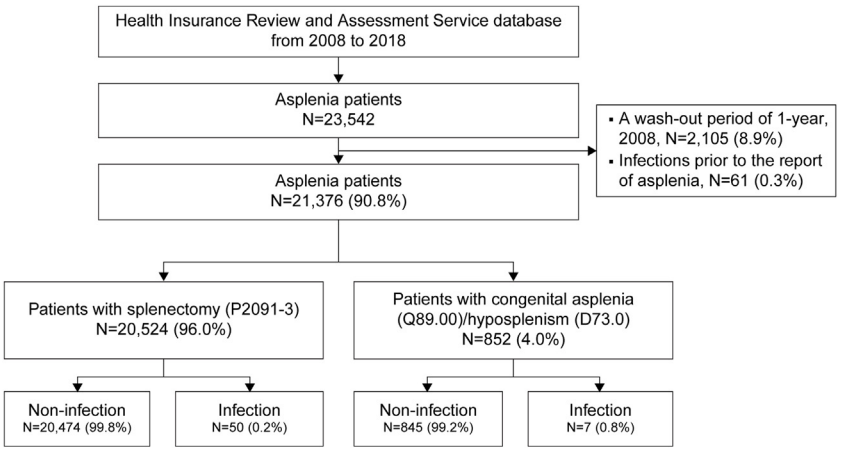


**Figure 1.** Flowchart for inclusion of the study population.

defined as cases in which the discharge code for death was used during intravenous antimicrobial treatment due to IPD.

*Statistical analysis*

Continuous variables were expressed as the mean ± standard deviation and were compared using the independent *t*-test. Categorical variables were expressed as number (%) and were compared using the chi-square test or Fisher's exact test. Cox proportional hazards regression analysis was performed to identify the factors associated with infection risk after asplenia/hyposplenism (sex, age at diagnosis/surgery, comorbidities, and cause of asplenia/hyposplenism). The Kaplan-Meier method and log-rank test were used to compare the cumulative incidence rates of infection according to the cause of asplenia/hyposplenism. Age-specific rates, age-standardized rates (ASRs), and standardized incidence ratios (SIR) with 95% confidence intervals (CIs) were calculated. Rates were expressed per 100,000 person-years. The ASRs were calculated for different age groups (0–4, 5–19, 20–39, 40–59, and ≥60 years), and the SIR was used to compare the incidence of infection between asplenia patients and the general population. For comparison, we used the number of reported cases of infectious diseases in the general population, as recorded in the 2017 Infectious Disease Surveillance Yearbook (KCDC, 2017). The 95% confidence intervals of SIR were calculated using a Poisson distribution. All statistical tests were two-sided, and P values (p) <0.05 were considered statistically significant. SAS Enterprise 9.4 software (SAS Institute, Cary, NC) was used for statistical analysis. R software (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) was used to draw the cumulative incidence curves.

*Ethical statement*

Since we extracted the patients' information after de-identification, the patient's informed consent was waived, and institutional review board approval was not required.

## Results

The details of patient selection in this study are shown in Figure 1. From January 2008 to December 2018, 23,542 patients with asplenia/hyposplenism were identified from the HIRA database. After excluding 2105 patients based on the exclusion criteria, 21,376 (20,524 [96.0%] who underwent splenectomy and 852 [4.0%] diagnosed with congenital asplenia/hyposplenism) were included. Among patients with congenital asplenia, 87 (10.2%, 87/852) had the diagnostic codes for congenital heart diseases, and 13 of them (14.9%, 13/87) had a diagnostic code for right isomerism. The male-to-female ratio was 52.5:47.5, and the average age at the time of asplenia/hyposplenism (at the time of splenectomy or diagnosis of congenital asplenia/hyposplenism) was 56.0 years (±16.9 years). The annual number of claimed cases for asplenia/hyposplenism tended to increase slightly over the years, with a non-significant trend (average annual percentage change = 0.4%; p = 0.08). The mean follow-up duration was 3.9 years (± 3.0 years).

**Table 1**
Characteristics of the study population.

| Number of patients | Total N, N = 21,376 | (%) | Non-infection, N = 21,319 | (%) | Infection, N = 57 | (%) | P-value |
|---|---|---|---|---|---|---|---|
| Age at diagnosis of congenital asplenia/splenectomy, mean years, SD | 56.02 ± 16.90 | | 56.04 ± 16.88 | | 50.56 ± 22.40 | | 0.07 |
| 0 to 4 years | 123 | 0.58 | 118 | 0.55 | 5 | 8.77 | <.0001 |
| 5 to 19 years | 712 | 3.33 | 712 | 3.34 | 0 | 0.00 | |
| 20 to 39 years | 2481 | 11.61 | 2471 | 11.59 | 10 | 17.54 | |
| 40 to 59 years | 7922 | 37.06 | 7905 | 37.08 | 17 | 29.82 | |
| Over 60 years | 10,138 | 47.43 | 10,113 | 47.44 | 25 | 43.86 | |
| Sex | | | | | | | |
| Male | 11,214 | 52.46 | 11,179 | 52.44 | 35 | 61.40 | 0.17 |
| Female | 10,162 | 47.54 | 10,140 | 47.56 | 22 | 38.60 | |
| Mean duration of follow-up, years, SD | 3.87 ± 2.97 | | 3.87 ± 2.97 | | 2.20 ± 2.12 | | <.0001 |
| Causes of asplenia | | | | | | | |
| Splenectomy | 20,524 | 96.01 | 20,474 | 96.04 | 50 | 87.72 | 0.0073 |
| Congenital asplenia/hyposplenism | 852 | 3.99 | 845 | 3.96 | 7 | 12.28 | |
| Comorbidities[a] | | | | | | | |
| Any comorbidities | 20,544 | 96.11 | 20,491 | 96.12 | 53 | 92.98 | 0.28 |
| Cardiovascular disease | 10,889 | 50.94 | 10,857 | 50.93 | 32 | 56.14 | 0.43 |
| Neurological disease | 1225 | 5.73 | 1219 | 5.72 | 6 | 10.53 | 0.14 |
| Endocrine disease | 9787 | 45.78 | 9757 | 45.77 | 30 | 52.63 | 0.30 |
| Liver disease | 9111 | 42.62 | 9090 | 42.64 | 21 | 36.84 | 0.38 |
| Respiratory disease | 8773 | 41.04 | 8750 | 41.04 | 23 | 40.35 | 0.92 |
| Renal disease | 656 | 3.07 | 655 | 3.07 | 1 | 1.75 | 1.00 |
| Malignancy or immunosuppression | 14,381 | 67.28 | 14,346 | 67.29 | 35 | 61.4 | 0.34 |
| Gastrointestinal disease | 8925 | 41.75 | 8902 | 41.76 | 23 | 40.35 | 0.83 |
| Rheumatic disease | 1022 | 4.78 | 1017 | 4.77 | 5 | 8.77 | 0.20 |
| Others | 9263 | 43.33 | 9235 | 43.32 | 28 | 49.12 | 0.38 |
| Risk factors for severe post-splenectomy infection | 1964 | 9.19 | 1959 | 9.19 | 5 | 8.77 | 0.91 |
| Hodgkin disease | 12 | 0.06 | 12 | 0.06 | 0 | 0.00 | >0.999 |
| Portal hypertension | 27 | 0.13 | 27 | 0.13 | 0 | 0.00 | >0.999 |
| Idiopathic thrombocytopenic purpura | 1581 | 7.40 | 1577 | 7.40 | 4 | 7.02 | >0.999 |
| Thalassemia | 3 | 0.01 | 3 | 0.01 | 0 | 0.00 | >0.999 |
| Hereditary spherocytosis | 330 | 1.54 | 329 | 1.54 | 1 | 1.75 | 0.5885 |
| Autoimmune lymphoproliferative syndrome | 13 | 0.06 | 13 | 0.06 | 0 | 0.00 | >0.999 |
| Post-transplant lymphoproliferative disease | 4 | 0.02 | 4 | 0.02 | 0 | 0.00 | >0.999 |
| Primary immunodeficiency | 18 | 0.08 | 18 | 0.08 | 0 | 0.00 | >0.999 |
| Antimicrobial prophylaxis[a] | 191 | 0.89 | 189 | 0.89 | 2 | 3.51 | 0.09 |

SD, standard deviation.
[a] Antimicrobial prophylaxis was defined as oral antimicrobials prescribed for at least nine months during one year after the index date (date when the first asplenia-related code was inserted).

Of 21,376 patients, the majority (96.1%, n = 20,544) had more than one comorbidity, and the proportion of patients with any risk factor for severe post-splenectomy infection was 9.2% (n = 1964); only 0.9% (n = 191) received oral antimicrobial prophylaxis (Table 1). The most commonly used oral antimicrobial agents were cephalosporins (mostly cephalexin, cephradine, cefadroxil, and cefuroxime), accounting for 44.5%, followed by quinolones, 25.2%; penicillin, 25.1%; and macrolides, 9.1%.

*Incidence of IPD in asplenia/hyposplenism patients*

Of 21,376 patients with asplenia/hyposplenism, 57 experienced IPD in 82,748 person-years of exposure. Only one elderly patient with IPD had a concurrent *H. influenzae* infection. The 1-, 5-, and 8-year cumulative IPD incidence was 0.1%, 0.3%, and 0.5%, respectively, after asplenia/hyposplenism (Figure 2A). Almost half of the infections (45.6%, 26/57) developed within two years after asplenia/hyposplenism, while 14.0% of the infections (8/57) developed after more than five years (Figure 2B). By age group, the 8-year cumulative IPD incidence in patients aged <5 years of 12.0% was significantly higher than that in the other age groups (0.5%; $p < 0.0001$ by log-rank test; Figure 2C).

The crude incidence rate of IPD was 68.9 per 100,000 person-years in all age groups (95% CI: 52.2–89.3), and the ASR was 104.5 per 100,000 person-years (95% CI: 103.6–105.4). After sex standardization, the patients with asplenia aged 0–4 years had the highest incidence rate of 748.8 per 100,000 person-years (95% CI: 737.3–760.4; Figure 2D).

*Characteristics of IPD in patients with asplenia/hyposplenism*

Among the 57 IPD cases, IPD developed in the 50 (87.7%) patients with splenectomy and in seven (12.3%) patients with congenital asplenia/hyposplenism. There were six (10.5%, 6/57) IPD-related mortalities. Non-specific pneumococcal infection (A49.1) was the most common diagnosis (31.6%, 18 patients), followed by pneumococcal pneumonia (J13), peritonitis (K67.8), sepsis (A40.3), arthritis (M00.1), and infectious endocarditis (I30.1), accounting for 31.6% (n = 18), 29.8% (n = 17), 21.1% (n = 12), 8.8% (n = 5), 5.3% (n = 3), and 3.5% (n = 2) of the cases, respectively. Among the 18 patients with ''non-specific pneumococcal infections', we additionally searched the other inserted diagnostic codes to specify the infection site or organ. There were seven cases of pneumonia (38.9%, 7/18), four cases of peritonitis

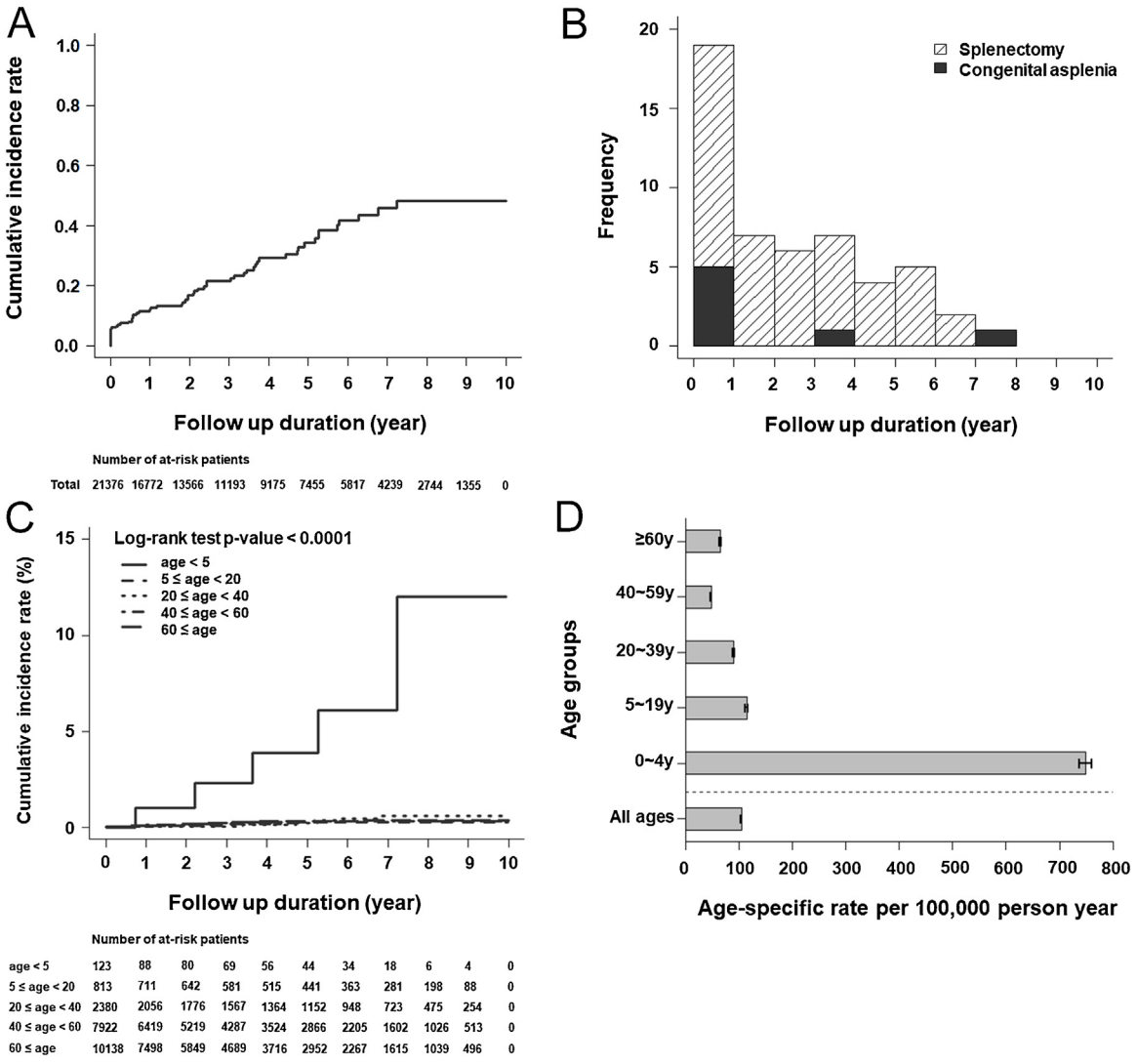


**Figure 2.** Cumulative incidence of invasive pneumococcal disease (IPD) in patients with asplenia/hyposplenism (A). Distribution of IPD after asplenia/hyposplenism (B). Cumulative incidence of IPD in patients with asplenia/hyposplenism according to age groups (C). Sex standardized, age-specific rate of IPD according to the two different IPD criteria (D).

(22.2%, 4/18), two cases of skin soft tissue infection (11.1%, 2/18), two cases of neutropenic fever (11.1%, 2/18), one case of bacteremia (5.6%, 1/18), and one of osteomyelitis (5.6%, 1/18). For the remaining one patient, it was difficult to estimate the site of infection through additional diagnostic code searching.

Two patients with IPD were observed in the 0–4 years group. One was diagnosed with congenital asplenia before his first birthday and had IPD at the age of one. The other patient had a splenectomy at the age of two years and had IPD at four years. Both of these patients survived.

*Risk factors for IPD*

In the univariate analysis, young age (<5 years) and congenital asplenia/hyposplenism diagnosis were significant risk factors for IPD (Table 2). After adjusting for sex, comorbidities, risk factors for severe post-splenectomy infections, and antimicrobial prophylaxis, the IPD rate was still 13.8 times higher in patients aged <5 years than in those aged ≥60 years (95% CI, 3.7–51.6; $p < 0.0001$); however, no significant difference occurred for congenital asplenia/hyposplenism (adjusted hazard ratio = 1.7; 95% CI, 0.6–4.5; $p = 0.33$; Table 2).

*RR of IPD compared with that in the general population*

Based on the Korean CDC case definition [Method 2], 18 non-specific pneumococcal infections, and twelve pneumococcal peritonitis cases were excluded from the analysis. Detailed age-specific rates, according to the KCDC criteria, are shown in Supplementary Table S1. According to the age group and KCDC criteria, the crude IPD RR was 32.0 (32.6 vs. 1.02 per 100,000 person-years in the asplenia group and general population, respectively; Table 3). After age standardization, the RR of IPD was 17.9 times higher in the asplenia/hyposplenism group than in the general population (SIR = 17.9; 95% CI, 11.8–26.0; Figure 3). In particular, the SIR in the age groups of 5–19, 20–39, and <5 years were 100-fold higher than the IPD incidence in the general population (Figure 3).

## Discussion

This population-based study shows the incidence of IPD in patients with asplenia/hyposplenism in the PCV era. The incidence rate of IPD in this study was 68.9 per 100,000 person-years in the crude analysis and 104.5 per 100,000 person-years after age adjustment, which is comparable to that reported in previous studies (36 to 3000 per 100,000 person-years, Table 3) (Aavitsland et al., 1994; Arnott et al., 2018; Backhaus et al., 2016; Bisharat et al., 2001; Choe et al., 2017; Cullingford et al., 1991; Eber et al., 1999; Ejstrud et al., 2000; Foss Abrahamsen et al., 1997; Holdsworth et al., 1991; Kyaw et al., 2006; Madenci et al., 2019; Marrie et al., 2016). Our data also showed that the risk of IPD was 17.9 (age-adjusted) to 32.0 (crude) times higher in the study population than in the general population. Previous studies, since the 1990s, have shown that the RR in asplenia patients ranges from 14.1 to 36.6 without age adjustment (Table 3) (Aavitsland et al., 1994; Arnott et al., 2018; Backhaus et al., 2016; Bisharat et al., 2001; Choe et al., 2017; Cullingford et al., 1991; Eber et al., 1999; Ejstrud et al., 2000; Foss Abrahamsen et al., 1997; Holdsworth et al., 1991; Kyaw et al., 2006; Madenci et al., 2019; Marrie et al., 2016). Our high RR implies that improved awareness among patients and the development of effective prevention strategies are still warranted, even in the PCV era.

This epidemiological study has several strengths. First, our study investigated the IPD incidence in more than 21,000 patients with 82,000 person-years of exposure, minimizing the likelihood of overestimation. In previous studies, the incidence of IPD varied in each study, from 36 to 3000 per 100,000 persons-years. Several possible reasons may be suggested for this difference, such as different case definitions, ethnicity, regional diversity, and various national vaccination programs. Also, the study population's size is one of the most important factors in estimating the incidence of IPD. The number of studies reporting a high incidence of IPD (>1000 per 100,000) has not been large; most study populations have been relatively small, with less than 1000 study participants (Ejstrud et al., 2000; Madenci et al., 2019; Marrie et al., 2016). Second, our data reflect the status of high pneumococcal vaccination coverage in the general population. In Korea, the PCV13/PCV10 vaccination for all young children has been included in the National Immunisation Program (NIP) since 2014, and the pneumococcal polysaccharide vaccine (PPSV23) for older adults aged ≥65 years was introduced in 2013 (Heo et al., 2018). After implementing the NIP, the coverage rate of PCV increased from 65% in 2012 to 97% in 2017, and that of PPSV23 among older adults increased from 5% in 2013 to 57% in 2014 (Heo et al., 2018). Thus, it is likely that pneumococcal vaccinations were given as scheduled,

**Table 2**
Risk factors for invasive pneumococcal infection in patients with splenectomy/asplenia.

| Variable | | Crude HR[a] | | Adjusted HR[a] | |
|---|---|---|---|---|---|
| | | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age at diagnosis/surgery | 0 to 4 years | 15.10 (5.78–39.46) | <.0001 | 13.79 (3.68–51.63) | <.0001 |
| | 5 to 19 years | 0.73 (0.17–3.07) | 0.66 | 0.71 (0.16–3.22) | 0.66 |
| | 20 to 39 years | 1.06 (0.48–2.35) | 0.89 | 1.06 (0.47–2.44) | 0.88 |
| | 40 to 59 years | 0.78 (0.42–1.45) | 0.43 | 0.79 (0.42–1.46) | 0.44 |
| | Over 60 years | 1 (reference) | | 1 (reference) | |
| Sex | Male | 1 (reference) | | 1 (reference) | |
| | Female | 0.70 (0.41–1.19) | 0.19 | 0.73 (0.42–1.24) | 0.24 |
| Comorbidities | No | 1 (reference) | | 1 (reference) | |
| | Yes | 0.67 (0.24–1.86) | 0.45 | 0.92 (0.30–2.75) | 0.87 |
| Risk factors for severe post-splenectomy infection | No | 1 (reference) | | 1 (reference) | |
| | Yes | 0.80 (0.32–2.01) | 0.64 | 0.90 (0.35–2.32) | 0.82 |
| Antimicrobial prophylaxis[b] | No | 1 (reference) | | 1 (reference) | |
| | Yes | 3.45 (0.84–14.13) | 0.09 | 0.51 (0.09–2.85) | 0.44 |
| Causes of asplenia | Splenectomy | 1 (reference) | | 1 (reference) | |
| | Congenital asplenia/hyposplenism | 3.13 (1.42–6.90) | 0.005 | 1.66 (0.61–4.54) | 0.33 |

CI, confidence interval; HR, hazard ratio.
[a] Univariate and multivariate Cox regression analyses were performed.
[b] Antimicrobial prophylaxis was defined as oral antimicrobials prescribed for at least nine months during one year after the index date (date when the first asplenia-related code was inserted).

**Table 3**
Summary of major studies on the incidence of severe infection in patients with asplenia/hyposplenism published since 1990.

| Country, year published | Study method | | | | | Outcome | | | General population | Estimated RR | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Design | Population at risk | No of population | Age | Study period | No of cases | Definition of cases | Case incidence per 100,000 PY (A) | IPD incidence per 100,000 PY (B) | (A)/(B) | |
| UK, 1991 | Literature review | Post-splenectomy | 5902 | Any | 1952–1987 | 173 | All severe infections (B, M, PP) | N/A[b] | | | Holdsworth et al. (1991) |
| Australia, 1991 | Literature review | Post-splenectomy | 21,404 PYs | Any | 1981–1991 | N/A | All severe infections (B, M, PP) | 890 | | | Cullingford et al. (1991) |
| Israel, 2001 | Literature review | Post-splenectomy | 19,680 | Any | 1966–1996 | 236[c] | IPDs (B, M) | N/A | | | Bisharat et al. (2001) |
| Korea, 2019 | Population-based cohort | Asplenia[a]/Hyposplenism | 2137/ 82,748 PY | Any | 2009–2018 | 27 | IPDs | 32.63 | 1.02 | 32.0 | Our data |
| Korea, 2017 | Single-center, retrospective | Post-splenectomy | 213 | ≤ 18 y | 1997–2016 | 6 | All severe infections | 280[d] | | | Choe et al. (2017) |
| Australia, 2018 | Population-based cohort | Asplenia[a]/Hyposplenism | 3221 | Any | 2003–2014 | 28 | Encapsulated bacterial infections | 150 (pre-registry) 36 (registry)[e] | | | Arnott et al. (2018) |
| Australia, 1991 | Population-based cohort | Post-splenectomy | 1490 | Any | 1971–1983 | 22 | All bacteremia | 280[f] | | | Cullingford et al. (1991) |
| US, 2019 | Population-based cohort | Post-splenectomy | 195 | ≤ 18 y | 2005–2014 | 13 | Sepsis requiring hospitalization | 1800 | | | Madenci et al. (2019) |
| Canada, 2016 | Case-control | Post-splenectomy | 825 PYs | Any | 2000–2014 | 37 | IPDs | 3000 | 82 | 36.6 | Marrie et al. (2016) |
| Sweden, 2016 | Population-based cohort | Post-splenectomy | 1500 | Any | 1996–2008 | 41 | IPDs | 210 | 15.1 | 14.1 | Backhaus et al. (2016) |
| Scotland, 2006 | Population-based cohort | Post-splenectomy | 1648 | Any | 1988–1999 | 30 | All severe infections (B, M) | 890 | | | Kyaw et al. (2006) |
| Denmark, 2000 | Population-based cohort | Post-splenectomy | 538 | Any | 1984–1993 | 38 | All bacteremia | 2300[g] | | | Ejstrud et al. (2000) |
| Switzerland, 1999 | Case-series | Post-splenectomy (hereditary spherocytosis) | 330 | Children | 1989–1995 | 4 | All severe infections (B, M) | 690 | | | Eber et al. (1999) |
| Norway, 1997 | Single-center, retrospective | Post-splenectomy (Hodgkin's disease) | 325 | 15–68 | 1969–1980 | 10 | IPDs (B, M) | 226 | 11 | 20.5 | Foss Abrahamsen et al. (1997) |
| Norway, 1994 | Case-control | Post-splenectomy | 3000 PYs | N/A | 1992–1993 | 8 | IPDs (culture-confirmed) | 267 | 11 | 25.0 | Aavitsland et al. (1994) |

B, bacteremia; IPD, invasive pneumococcal disease; M, meningitis; N/A not applicable; PP, pneumococcal pneumonia; PY, patient-years; RR, relative risk.
[a] Asplenia includes post-splenectomy.
[b] *S. pneumoniae* accounts for 56.7%, and *H. influenzae* accounts for 6.3% of cases.
[c] *S. pneumoniae* accounts for 66% of cases among 358 etiology-proven, invasive infections.
[d] 3 Pneumococcal bacteremia infections.
[e] 27 Invasive pneumococcal infections and one *Neisseria meningitidis* infection.
[f] *S. pneumoniae* infection accounts for 31.6% of cases (six cases).
[g] Enterobacteria infections were the most prevalent (45%), and only one *S. pneumoniae* infection was report.

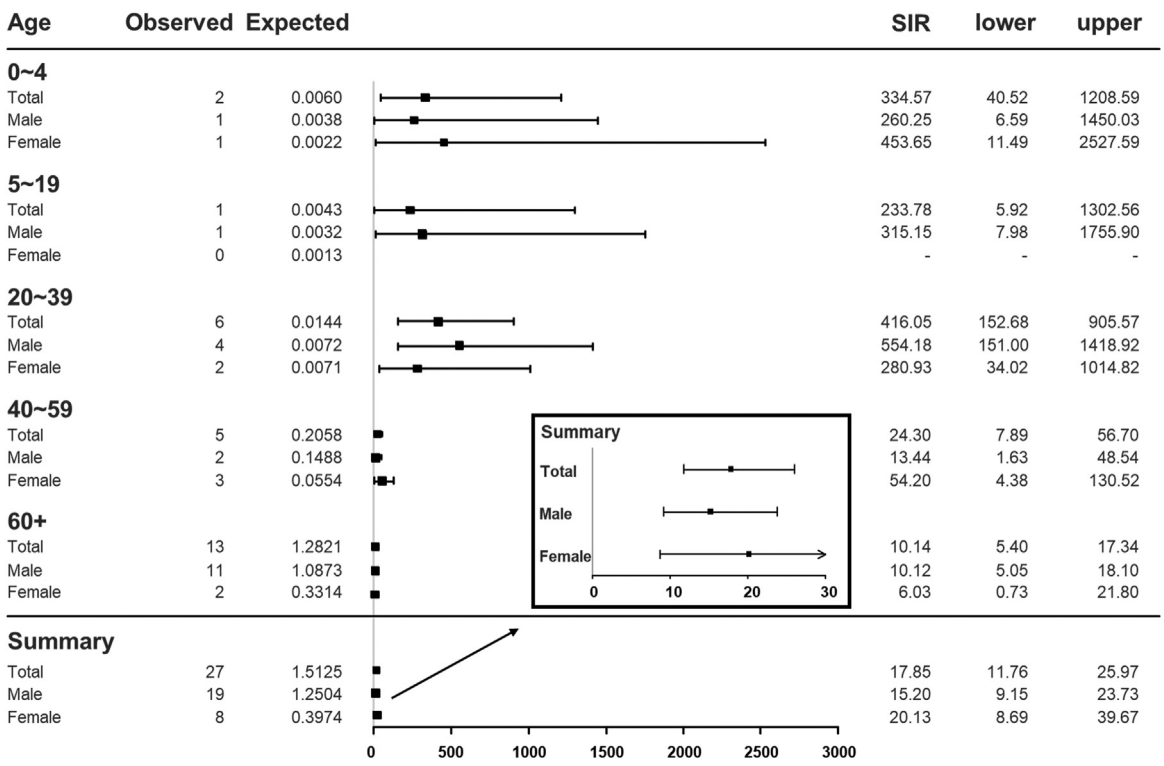


**Figure 3.** Standardized incidence ratios (SIR) of IPD in patients with asplenia/hyposplenism compared with that in the general population.

regardless of the asplenia status in young children or older adult patients. PCV vaccination in young children can also change the carriage strain of older populations from PCV serotypes to less virulent, non-PCV serotypes, which may indirectly affect the unvaccinated adult patients with asplenia/hyposplenism (Kim et al., 2016; Rubin and Schaffner, 2014). However, we could not find significant differences in the incidence of IPD among patients with asplenia/hyposplenism before and after 2014, when PCV/PPSV23 was introduced in the NIP (89.5 and 77.0 per 100,000 person-years before and after 2014, respectively, p = 0.59). A possible explanation may be the presence of reporting bias. In Korea, since PCV was included in the NIP in 2014, reporting of IPD became mandatory. Therefore, there was a possibility of underreporting before 2014. To clarify PCV's effects on this population, a long-term study, including pneumococcal serotype analysis, is warranted.

The extremely low coverage rate (0.9%) of antimicrobial prophylaxis in South Korea is one of our most unexpected findings. We defined antimicrobial prophylaxis as the use of oral antimicrobials for at least nine months within one year of the index date; only 0.9% of the study population fit this criterion. For reference, only 2.3% of patients are prescribed for 3–6 months, and only 1.2% are prescribed for 6–9 months; therefore, it seems that the oral antimicrobial prescription for prophylaxis itself has been not well practiced in South Korea, regardless of the prescription period after splenectomy or diagnosis of asplenia/hyposplenism. We do not know the exact cause of this finding, but the lack of awareness of the importance of antimicrobial prophylaxis and the traditional medical habits of prescribing non-antimicrobial prophylaxis among clinicians, including surgeons in South Korea might be the possible causes. This finding reminds us that actual clinical practice may be inconsistent with the guidelines. In this case, establishing and managing a patient registry can have practical advantages. Arnott et al. recently reported a decrease in IPD incidence from 150 to 36 per 100,000 person-years among 3221 patients with asplenia/hyposplenism after enrolment in the Spleen Registry in Australia. They emphasized the importance of a long-term, multi-disciplinary approach including education, clinical guidance, including advice on antimicrobial prophylaxis and emergency medicine, and a personalized vaccine report for registrants and clinicians (Arnott et al., 2018). However, concerning cost-effectiveness, the emergence of antimicrobial-resistant pathogens and poor compliance, high-level evidence for these recommendations are still lacking; therefore, further studies are needed on the exact effect of each prevention strategy, such as vaccination schedule or antimicrobial prophylaxis (Khasawneh et al., 2019; Spijkerman et al., 2018).

Holdsworth et al. reported that the rate of post-splenectomy infection in children aged <5 years was 10.4%, which was higher than 0.9% of adults (Holdsworth et al., 1991). We confirmed that a patient age <5 years is a significant risk factor for IPD in patients with asplenia/hyposplenism. There was no difference in the incidence rate between splenectomy-related and congenital asplenia/hyposplenism after age adjustment in the multivariate analysis. This finding, regardless of the cause of asplenia/hyposplenism, emphasizes that the spleen's immunological role is particularly important in younger children who still lack immunological experience - both in terms of immunological maturity and exposure to pathogens. Aranburu et al. reported that memory B cells in infants were less mutated, resulting in reduced affinity maturation, but became highly mutated at 6–7 years of age in the presence of a germinal center and spleen (Aranburu et al., 2017). They also reported that children with congenital asplenia could not produce highly mutated IgM memory B cells, even later in life. These findings imply that vaccination may be sub-optimally effective for infants and young children with splenectomy or congenital asplenia/hyposplenism compared to that for splenectomized adult patients. When clinically determining the timing of splenectomy, it is critical to consider delaying the surgery after five years of age, and it is also necessary to induce a sufficient memory immune response by completing PCV vaccination before surgery.

This study had some limitations. First, it was a retrospective study; underreporting was possible. However, despite the possibility

of underestimation, the underreporting bias could be offset because the same KCDC criteria [Method 2] were used when determining the RR of IPD in the patient population compared with that in the general population. Secondly, since the data on vaccination records and pneumococcal serotypes were not available in the HIRA database, the direct effects of IPD following pneumococcal vaccination and serotype differences could not be assessed. Thirdly, the rate of antimicrobial prophylaxis in patients with asplenia/hyposplenism was extremely low in Korea (0.9%); thus, the sample size was insufficient for assessing its effectiveness. Finally, the prevalence of some high-risk factors, such as thalassemia and hereditary spherocytosis, is very low among Korean people, making it difficult to assess the additional IPD risk associated with these diseases.

Nevertheless, this is the largest population-based study to provide information on the high IPD incidence in patients with asplenia/hyposplenism in the PCV era. It is also the first study to present the age-specific RR for IPD in high-risk patients compared with that in the general population. Our data supported the notion that young children had a higher incidence of IPD than other age groups. Moreover, congenital asplenia/hyposplenism did not have an additional risk of IPD compared to splenectomy, in the multivariate analysis.

In conclusion, the incidence of IPD was high at 104.5 per 100,000 person-years in Korean patients with asplenia/hyposplenism. This risk was more than 18 times higher than that in the general population. Increased awareness regarding these high-risk populations, especially children aged <5 years, is required, and further studies are needed to assess the effectiveness of preventive methods, including pneumococcal vaccination.

## Contributions

Ji-Man Kang, Kyong Ihn, and Jong Gyun Ahn designed the study, analyzed and interpreted the data, and wrote the manuscript. Eun Hwa Kim and Minkyung Han collected, assembled, and analyzed the data. Inkyung Jung analyzed and interpreted the data. All authors critically reviewed and approved the manuscript.

## Conflict of interest

None.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.07.013.

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