



Adult invasive pneumococcal disease in the Republic of Korea: Risk medical conditions and mortality stratified by age group



Jong Hun Kim^a, Seung Hee Baik^b, Byung Chul Chun^c, Joon Young Song^d, In-Gyu Bae^e,
Hyo Youl Kim^f, Dong-Min Kim^g, Young Hwa Choi^h, Won Suk Choiⁱ, Yu Mi Jo^{j,1},
Hyun Hee Kwon^k, Hye Won Jeong^l, Yeon-Sook Kim^m, Jeong Yeon Kimⁿ, Jacob Lee^o,
Sae Yoon Kee^p, Jian Hur^q, Jin Won Chung^r, Ki-Eun Hwang^s, Min Ja Kim^{a,t,*}

^a Division of Infectious Diseases, Department of Internal Medicine, Korea University Anam Hospital, Seoul, Republic of Korea

^b Department of Internal Medicine, Cheju Halla General Hospital, Jeju-si, Republic of Korea

^c Department of Preventive Medicine, Korea University College of Medicine, Seoul, Republic of Korea

^d Division of Infectious Diseases, Department of Internal Medicine, Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea

^e Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Republic of Korea

^f Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

^g Department of Internal Medicine, College of Medicine, Chosun University, Gwangju, Republic of Korea

^h Department of Internal Medicine, Ajou University Hospital, Suwon, Republic of Korea

ⁱ Division of Infectious Diseases, Department of Internal Medicine, Ansan Hospital, College of Medicine, Korea University, Ansan, Gyeonggi-do, Republic of Korea

^j Department of Internal Medicine, Konyang University College of Medicine, Daejeon, Republic of Korea

^k Department of Internal Medicine, Daegu Catholic University, Daegu, Republic of Korea

^l Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, Chungbuk National University, Cheongju, Chungcheongbuk-do, Republic of Korea

^m Division of Infectious Diseases, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Republic of Korea

ⁿ Division of Infectious Diseases, Department of Internal Medicine, Sahmyook Medical Center, Seoul, Republic of Korea

^o Division of Infectious Diseases, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea

^p Division of Infectious Diseases, Department of Internal Medicine, Konkuk University Chungju Hospital, Chungju, Republic of Korea

^q Department of Internal Medicine, Yeungnam University Medical Center, Daegu, Republic of Korea

^r Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea

^s Department of Internal Medicine, School of Medicine, Wonkwang University, Iksan, Republic of Korea

^t The Research Institute of Emerging Infectious Diseases, Korea University, Seoul, Republic of Korea

ARTICLE INFO

Article history:

Received 21 May 2018

Received in revised form 18 July 2018

Accepted 19 July 2018

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Invasive pneumococcal disease

Adult

Risk factors

Mortality

ABSTRACT

Objectives: This study aimed to characterize the risk factors for mortality in adult patients with invasive pneumococcal disease (IPD) stratified by age groups, after implementation of the national immunization program of 23-valent polysaccharide vaccine (PPSV23) for those aged ≥ 65 years in the Republic of Korea (ROK).

Methods: Clinical data and pneumococcal isolates from adult patients with IPD (≥ 18 years of age) were collected prospectively from 20 hospitals through the nationwide surveillance program from March 2013 to October 2015.

Results: A total of 319 patients with IPD were enrolled. Median age was 69 years. Overall in-hospital mortality was 34.2%: 17.1% in those aged 18–49 years, 23.7% in those aged 50–64 years, 33.0% in those aged 65–74 years, and 51.0% in those aged ≥ 75 years ($p < 0.001$). In particular, early death within 7 days of hospitalization accounted for 60.6% (66/109). While old age (≥ 65 years), higher Pitt bacteremia score (≥ 4), and bacteremic pneumonia were independently associated with IPD mortality in all age groups, an additional mortality risk factor of immunocompromised status was identified for

* Corresponding author at: Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Incheon-ro 73, Seongbuk-gu, Seoul, 02841, Republic of Korea.

E-mail address: macropha@korea.ac.kr (M.J. Kim).

¹ Present address: Department of Internal Medicine, Gil Hospital, Gacheon University, Incheon, Republic of Korea.

patients aged 50–64 years. PPSV23 serotypes accounted for 64.4% (122/189) of the pneumococcal isolates serotyped.

Conclusions: This study suggests that vaccine-type IPD continues to place a substantial burden on older adults in the ROK, necessitating an effective vaccination strategy for those at higher risk.

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Introduction

Invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae* includes primary bacteremia, meningitis, bacteremic pneumonia, and other deep-seated infections. Underlying medical conditions are known to increase the risk of IPD developing, with substantial mortality (Laurichesse et al., 2001; Robinson et al., 2001). Furthermore, old age itself has been identified as one of the risk factors related to IPD in adults, as an increased burden of IPD with higher mortality has been noted in older patients aged ≥ 65 years (Melegaro et al., 2006). Furthermore, the severity of IPD may be related to the pneumococcal serotype (Jansen et al., 2009a). The emergence of multidrug-resistant (MDR) IPD and the increasing aging population with medical comorbidities continue to pose critical clinical and public health challenges (Song et al., 2004; Global Burden of Disease Study, 2015). Pneumococcal diseases are vaccine-preventable diseases. Currently, the 23-valent polysaccharide vaccine (PPSV23) and the 13-valent conjugate vaccine (PCV13) are used to reduce IPD in adults (Moberley et al., 2013; Whitney et al., 2003).

In the Republic of Korea (ROK), the 7-valent conjugate vaccine (PCV7) was introduced in 2003 for use in infants and young children. This was replaced by PCV13 and PCV10 in 2010. Based on the substantial burden of IPD and low vaccination rate in older adults, a national immunization program (NIP) providing PPSV23 to older adults aged ≥ 65 years was implemented in May 2013 (Yang et al., 2016). IPD has been a nationally notifiable disease since 2014 (Infectious Diseases Surveillance Year Book, 2016). This study aimed to investigate the burden of vaccine-type IPD and to characterize risk factors for mortality in adult IPD patients stratified by age group.

Materials and methods

Study population, data collection, and study design

A multicenter hospital-based pneumococcal disease surveillance program was established and maintained in the ROK from March 2013 to October 2015. This included 20 participating hospitals across the country (18 university-affiliated tertiary care hospitals and 2 community-based general hospitals) from five of the seven major metropolitan cities and six of the nine provinces of the ROK, with a total of approximately 16 700 hospital beds. Subjects included adult IPD patients aged ≥ 18 years. Clinical variables including patient demographic data, comorbid chronic illnesses, microbiological data, clinical management, and outcome were collected on a standardized case report form at each hospital. Characteristics of IPD risk conditions in relation to underlying medical conditions and mortality were compared among age groups. Risk condition categories associated with IPD mortality were analyzed by age group, including age, sex, underlying medical conditions, prior pneumococcal vaccination, clinical severity, risk of the serotypes, antimicrobial susceptibility, and appropriateness of initial antibiotic therapy. This study was approved by the institutional review boards of the participating hospitals.

Definitions

Cases of IPD were defined as the isolation of *S. pneumoniae* from a normally sterile site, such as cerebrospinal fluid (CSF), blood, bone, pleural or joint fluid, and ascites.

Underlying medical conditions were defined as follows: immunocompromised status (IC) was defined as the presence of one or more of HIV, malignancy, multiple myeloma, congenital immunodeficiency, solid or hematopoietic stem cell transplantation, functional or anatomical asplenia, use of systemic steroids (≥ 20 mg/day of prednisone equivalent) or immunosuppressive agents such as alkylating agents, antimetabolites, or the use of immunomodulatory agents such as tumor necrosis factor alpha inhibitors or rituximab; chronic medical conditions (CC) were defined as chronic central nervous system disease (the presence of one or more of epilepsy, Parkinson disease, Alzheimer disease, stroke, and other neurological diseases), chronic heart disease (including heart failure), chronic pulmonary disease (including asthma and chronic obstructive lung disease), chronic liver disease (including liver cirrhosis), chronic kidney disease (including nephrotic syndrome), CSF leakage, the presence of a cochlear implant, and diabetes mellitus.

The serotypes were categorized according to risk as high risk (3, 6A, 6B, 9N, and 19F), low risk (1, 7F, and 8), and intermediate risk (other serotypes not included in the high and low risk groups) (Weinberger et al., 2010). Prior immunization with the pneumococcal vaccine was categorized as 'vaccinated' if a patient had received a PPSV23 (4 weeks to 5 years) or a PCV13 (4 weeks or more) before the onset of IPD.

MDR was defined as antibiotic resistance to three or more classes of antibiotics. Initial antimicrobial therapy was defined as concordant if at least one susceptible antibiotic was administered during the first 24 h of hospital admission due to IPD.

The primary outcome measure was in-hospital mortality. Early in-hospital mortality was defined as death within 7 days after the date of admission for IPD.

Microbiology

Serotyping of pneumococcal isolates was performed using the automated, multiplexed immunoassay for capsular polysaccharides (Yu et al., 2011). Antimicrobial susceptibility testing was performed using the MICroSTREP plus panel with the MicroScan WalkAway System (Siemens Healthcare Diagnostics, USA) and was determined in accordance with the Clinical and Laboratory Standards Institute guidelines (CLSI, Performance Standards for Antimicrobial Disk Susceptibility Tests, 2015).

Statistical analysis

Comparison analyses of risk conditions and clinical variables between the age groups were performed. The Pearson Chi-square test or Fisher's exact test was used for dichotomous variables. The Mann-Whitney *U*-test was used for continuous variables. Variables with a *p*-value < 0.1 on comparison analysis were included in a multiple logistic regression analysis to determine risk factors associated with IPD mortality. Odds ratios (OR) and 95%

confidence intervals (CI) were calculated. A p -value of <0.05 was considered to be statistically significant. SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

Results

Comparison of stacked risks of comorbidities and clinical characteristics of IPD among the age groups

A total of 319 adult patients with IPD were enrolled from the 20 participating hospitals during the study period (3.4 cases per 100 000 hospitalized patients per year). The majority of the participating hospitals (18/20, 90.0%) consisted of tertiary care hospitals. The median age of the patients was 69 years (interquartile range 58–78 years), and 221 (69.3%) patients were male. The patients were stratified into four age groups: 18–49 years (group 1, $n=35$, 1.2 cases per 100 000 hospitalized patients per year), 50–64 years (group 2, $n=93$, 3.1 cases per 100 000 hospitalized patients per year), 65–74 years (group 3, $n=91$, 4.8 cases per 100 000 hospitalized patients per year), and ≥ 75 years (group 4, $n=100$, 6.6 cases per 100 000 hospitalized patients per year). Risk conditions and clinical variables were compared among the four age groups (Table 1).

Bacteremic pneumonia was the most common type of IPD in all age groups (overall, 64.3%; range 54.3–72.0%); meningitis was the second most common type of IPD in group 1 and primary bacteremia was the second most common type in both groups 2

and 4. There was no significant difference in the prevalence of deep-seated infection including empyema, deep-seated abscess, peritonitis, septic arthritis, and osteomyelitis among the age groups.

The majority of patients (71.5%) had one or more CC. Risk levels of comorbidities were stacked in relation to the number of underlying non-IC chronic and IC conditions. Older age groups had one or more CC (45.7% in group 1, 66.7% in group 2, 81.3% in group 3, and 76.0% in group 4; $p<0.001$). The proportion of IC was significantly different among the groups (8.6% in group 1, 34.4% in group 2, 39.6% in group 3, and 23.0% in group 4; $p=0.002$). Prior pneumococcal vaccination was recorded in 67 (21.0%) patients: 65 patients received the PPSV23 at age ≥ 65 years.

The clinical outcome and relevant clinical factors of IPD were compared among the age groups (Table 2). Overall in-hospital mortality was 34.2%. In-hospital mortality increased significantly with older age, from 17.1% in group 1 to 51.0% in group 4. Of note, early mortality within 7 days of admission accounted for overall 60.6% (66/109) of death. In addition, there was substantial mortality for bacteremic pneumonia, with an increasing trend of mortality with age (26.3% in group 1 to 58.3% in group 4). There was a non-significant trend of decreased in-hospital mortality in older patients ≥ 65 years who had received PPSV23 vaccination compared to those who had not (28.4% vs. 34.5%, $p=0.562$).

Antibiotic susceptibility results for the pneumococcal isolates were available for the majority of IPD cases. The MDR rate was high in all four groups (overall, 58.7%; range 41.2–64.1%). However, rates of individual antibiotic susceptibility were not significantly

Table 1
Comparison of stacked risks for invasive pneumococcal disease among age groups, based on chronic medical conditions, immunocompromised conditions, and vaccination status.

Characteristics	Total ($n=319$)	18–49 years ($n=35$)	50–64 years ($n=93$)	65–74 years ($n=91$)	≥ 75 years ($n=100$)	p -Value
Infection type						
Bacteremic pneumonia	205 (64.3)	19 (54.3)	56 (60.2)	58 (63.7)	72 (72.0)	0.187
Meningitis	30 (9.4)	6 (17.1)	11 (11.8)	8 (8.8)	5 (5.0)	0.131
Primary bacteremia	43 (13.5)	5 (14.3)	14 (15.1)	11 (12.1)	13 (13.0)	0.933
Deep-seated infection	41 (12.9)	5 (14.3)	12 (12.9)	14 (15.4)	10 (10.0)	0.702
Empyema	15 (4.7)	0 (0.0)	4 (4.3)	6 (6.6)	5 (5.0)	0.548
Deep-seated abscess	11 (3.4)	2 (5.7)	3 (3.2)	3 (3.3)	3 (3.0)	0.872
Peritonitis	10 (3.1)	2 (5.7)	3 (3.2)	4 (4.4)	1 (1.0)	0.320
Septic arthritis	3 (0.9)	1 (2.9)	1 (1.1)	1 (1.1)	0 (0.0)	0.252
Osteomyelitis	2 (0.6)	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.0)	1.000
Underlying chronic condition						
Any disease ^a	228 (71.5)	16 (45.7)	62 (66.7)	74 (81.3)	76 (76.0)	
No disease	91 (28.5)	19 (54.3)	31 (33.3)	17 (18.7)	24 (24.0)	<0.001
Chronic heart disease	31 (9.7)	2 (5.7)	3 (3.2)	13 (14.3)	13 (13.0)	0.027
Chronic pulmonary disease	43 (13.5)	1 (2.9)	3 (3.2)	14 (15.4)	25 (25.0)	<0.001
Chronic liver disease	30 (9.4)	6 (17.1)	13 (14.0)	8 (8.8)	3 (3.0)	0.013
Chronic kidney disease	14 (4.4)	2 (5.7)	5 (5.4)	5 (5.5)	2 (2.0)	0.483
Chronic CNS disease	37 (11.6)	3 (8.6)	6 (6.5)	12 (13.2)	16 (16.0)	0.181
CSF leakage	1 (0.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.110
Cochlear implant	1 (0.3)	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.110
Diabetes mellitus	67 (21.0)	2 (5.7)	20 (21.5)	26 (28.6)	19 (19.0)	0.040
IC with or without chronic condition	94 (29.5)	3 (8.6)	32 (34.4)	36 (39.6)	23 (23.0)	0.002
IC plus any chronic condition	43 (13.5)	1 (2.9)	12 (12.9)	22 (24.2)	8 (8.0)	0.002
IC without any chronic condition	51 (16.0)	2 (5.7)	20 (21.5)	14 (15.4)	15 (15.0)	0.175
Non-IC and 1 chronic condition	96 (30.1)	9 (25.7)	23 (24.7)	25 (27.5)	39 (39.0)	0.129
Non-IC and 2 chronic conditions	36 (11.3)	4 (11.4)	7 (7.5)	12 (13.2)	13 (13.0)	0.550
Non-IC and ≥ 3 chronic conditions	2 (0.6)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.0)	0.817
Prior pneumococcal vaccination						<0.001
No	248 (77.7)	34 (97.1)	87 (93.5)	71 (78.0)	56 (56.0)	
Yes ^b	67 (21.0)	1 (2.9)	4 (4.3)	20 (22.0)	42 (42.0)	
NA	4 (1.3)	0 (0.0)	2 (2.2)	0 (0.0)	2 (2.0)	

Data are expressed as the number of persons (percentage of the working population) unless stated otherwise. Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; IC, immunocompromised status; NA, not available.

^a Presence of one or more underlying medical condition(s).

^b Receipt of the 23-valent polysaccharide vaccine in 65 patients (97.0%).

Table 2

Comparison of clinical outcomes and risk factors for invasive pneumococcal disease among the age groups.

Characteristics	Total (n = 319)	18–49 years (n = 35)	50–64 years (n = 93)	65–74 years (n = 91)	≥75 years (n = 100)	p-Value
In-hospital mortality	109 (34.2)	6 (17.1)	22 (23.7)	30 (33.0)	51 (51.0)	<0.001
0–7 days ^a	66 (60.6)	6 (100.0)	13 (59.1)	13 (42.3)	34 (66.7)	
8–14 days	14 (12.8)	0 (0.0)	2 (9.1)	6 (20.0)	6 (11.8)	
15–21 days	11 (10.1)	0 (0.0)	1 (4.5)	5 (16.7)	5 (9.8)	
22–28 days	4 (3.7)	0 (0.0)	1 (4.5)	1 (3.3)	2 (3.9)	
≥29 days	14 (12.8)	0 (0.0)	5 (22.7)	5 (16.7)	4 (7.8)	
Serotype risk						0.473
Low risk (1, 7F, and 8)	6 (1.9)	0 (0.0)	2 (2.2)	0 (0.0)	4 (4.0)	
Intermediate risk ^b	147 (46.1)	15 (42.9)	46 (49.5)	45 (49.5)	41 (41.0)	
High risk (3, 6A, 6B, 9N, and 19F)	36 (11.3)	2 (5.7)	10 (10.8)	11 (12.1)	13 (13.0)	
NA	130 (40.8)	18 (51.4)	35 (37.6)	35 (38.5)	42 (42.0)	
Serotypes ^c (n = 189)						
PCV13 serotypes	70 (37.0)	1 (5.9)	25 (43.1)	20 (35.7)	24 (41.4)	0.029
PPSV23 serotypes	124 (65.6)	7 (41.2)	39 (67.2)	42 (75.0)	36 (62.1)	0.046
Non-vaccine serotypes ^d	64 (33.9)	10 (58.8)	18 (31.0)	14 (25.0)	22 (37.9)	0.062
Antibiotic susceptibility ^e						
Penicillin susceptible	228 (72.6)	24 (72.7)	63 (69.2)	71 (78.9)	70 (70.0)	0.449
Penicillin non-susceptible	86 (27.4)	9 (27.3)	28 (30.8)	19 (21.1)	30 (30.0)	
Ceftriaxone susceptible	235 (81.3)	27 (79.4)	63 (76.8)	76 (90.5)	69 (69.0)	0.084
Ceftriaxone non-susceptible	54 (18.7)	7 (20.6)	19 (23.2)	8 (9.5)	20 (20.0)	
Levofloxacin susceptible	300 (94.3)	33 (97.1)	91 (97.8)	85 (93.4)	91 (91.0)	0.181
Levofloxacin non-susceptible	18 (5.7)	1 (2.9)	2 (2.2)	6 (6.6)	9 (9.0)	
MDR ^e	185 (58.7)	14 (41.2)	59 (64.1)	54 (60.0)	58 (58.6)	0.139
Non-MDR	130 (41.3)	20 (58.8)	33 (35.9)	36 (40.0)	41 (41.4)	
Initial concordant antibiotic therapy ^e						0.081
No	38 (14.6)	1 (4.0)	17 (21.5)	7 (9.5)	13 (15.7)	
Yes	223 (85.4)	24 (96.0)	62 (78.5)	67 (90.5)	70 (84.3)	

Data are expressed as the number of persons (percentage of the working population) unless stated otherwise. Abbreviations: NA, not available; MDR, multidrug resistance.

^a Hospital days after admission.^b Neither low nor high risk serotypes.^c Calculation based on available data.^d Serotypes not covered by PCV13 and PPSV23 vaccines.^e Antibiotic resistance to three or more classes of antibiotics.

different among groups. Initial concordant antibiotic therapy was administered to 272 (85.4%) patients, which was not significantly different among the four age groups.

Risk factors for in-hospital mortality of invasive pneumococcal disease by stratified age groups

Comparison and multiple logistic regression analyses were performed to determine risk factors associated with in-hospital mortality in overall IPD patients. In a comparison analysis, non-survivors had significantly more bacteremic pneumonia, were older (age ≥65 years), and had higher Pitt bacteremia scores (≥4) than survivors. However, there was no significant difference regarding underlying medical conditions, prior pneumococcal vaccination, the risk of the serotype, whether it was a vaccine-covered serotype, antibiotic susceptibility rates, or initial concordant antibiotic therapy between survivors and non-survivors. In a multiple logistic regression analysis, old age (≥65 years) (OR 2.88, 95% CI 1.55–3.32, $p = 0.001$), bacteremic pneumonia (OR 2.71, 95% CI 1.36–5.40, $p = 0.005$), and higher Pitt bacteremia score (≥4) (OR 8.62, 95% CI 4.78–15.54, $p < 0.001$) were independent risk factors for overall in-hospital mortality in IPD patients (Table 3).

Risk factors for in-hospital mortality were determined separately for each age group and the results are summarized in Table 4. In group 1, no significant risk factor for in-hospital mortality was identified despite that there were more patients with higher Pitt bacteremia score (≥4) in non-survivors than survivors (83.3% vs. 20.7%, $p = 0.003$). In group 2, IC without any CC (36.4% vs. 16.9%, $p = 0.074$), bacteremic pneumonia (86.4% vs. 52.1%, $p = 0.004$), and

higher Pitt bacteremia score (≥4) (63.6% vs. 8.5%, $p < 0.001$) were more prevalent among non-survivors compared to survivors. In a multiple logistic regression analysis, IC without any CC (OR 7.26, 95% CI 1.57–33.46, $p = 0.011$) and higher Pitt bacteremia score (≥4) (OR 32.66, 95% CI 7.44–143.29, $p < 0.001$) were independent risk factors for in-hospital mortality. In group 3, bacteremic pneumonia (83.3% vs. 54.1%, $p = 0.006$) and higher Pitt bacteremia score (≥4) (56.7% vs. 19.7%, $p = 0.002$) were more common among non-survivors compared to survivors. In a multiple logistic regression analysis, higher Pitt bacteremia score (≥4) (OR 4.47, 95% CI 1.70–11.75, $p = 0.002$) was an independent risk factor for in-hospital mortality. In group 4, bacteremic pneumonia (82.4% vs. 61.2%, $p = 0.019$) and higher Pitt bacteremia score (≥4) (62.7% vs. 10.2%, $p < 0.001$) were more common in non-survivors compared to survivors. Likewise, only higher Pitt bacteremia score (≥4) (OR 14.93, 95% CI 5.01–44.52, $p < 0.001$) was an independent risk factor in group 4.

Predictors of early in-hospital mortality in IPD patients

There were 109 in-hospital deaths in total. The 66 (60.6%) patients with an early death (within 7 days of admission) were compared to the 29 (26.6%) patients with a late death (>15 days of admission) to identify potential risk factors. While there were more cases of bacteremic pneumonia and higher Pitt bacteremia scores (≥4) in the early death group, IC without any CC was more prevalent in the late death group. In a multiple logistic regression analysis, higher Pitt bacteremia score (≥4) (OR 21.263, 95% CI 5.134–88.062, $p < 0.001$) and bacteremic pneumonia (OR 5.164,

Table 3Multiple logistic regression analysis of risk factors for in-hospital mortality in adult patients (≥ 18 years) with invasive pneumococcal disease.

Risk variables	Survived (n = 210)	Died (n = 109)	p-Value	Adjusted OR (95% CI) ^a
Age			<0.001	
<65 years	100 (47.6)	27 (24.8)		Reference
≥ 65 years	110 (52.4)	82 (75.2)		2.88 (1.55–3.32)
Sex			0.895	
Male	146 (69.5)	75 (68.8)		
Female	64 (30.5)	34 (31.2)		
Bacteremic pneumonia			<0.001	
No	96 (45.7)	18 (16.5)		Reference
Yes	114 (54.3)	91 (83.5)		2.71 (1.36–5.40)
Underlying chronic condition				
Any disease ^b	149 (71.0)	79 (72.5)	0.775	
No disease	61 (29.0)	30 (27.5)		
IC with or without chronic condition	64 (30.5)	30 (27.5)	0.583	
IC plus any chronic condition	33 (15.7)	10 (9.2)	0.105	
IC without any chronic condition	31 (14.8)	20 (18.3)	0.407	
Non-IC and 1 chronic condition	63 (30.0)	33 (30.3)	0.959	
Non-IC and 2 chronic conditions	20 (9.5)	16 (14.7)	0.168	
Non-IC and ≥ 3 chronic conditions	2 (1.0)	0 (0.0)	0.549	
Prior pneumococcal vaccination			1.000	
Yes ^c	44 (21.0)	23 (21.1)		
No	163 (77.6)	85 (78.0)		
NA	3 (1.4)	1 (0.9)		
Pitt bacteremia score ^d			<0.001	
<4	162 (84.8)	38 (35.8)		Reference
≥ 4	29 (15.2)	68 (64.2)		8.62 (4.78–15.54)
Serotype risk			0.189	
Low (1, 7F, and 8)	2 (1.0)	4 (3.7)		
Intermediate ^e	101 (48.1)	46 (42.2)		
High (3, 6A, 6B, 9N, and 19F)	23 (11.0)	13 (11.9)		
NA	84 (40.0)	46 (42.2)		
Serotypes ^d				
PCV13 vaccine type	46 (36.5)	24 (38.1)	0.981	
PPSV23 vaccine type	80 (63.5)	44 (69.8)	0.693	
Non-vaccine type ^f	45 (35.7)	19 (30.2)	0.447	
Antibiotic susceptibility ^d				
Penicillin susceptible	152 (73.4)	76 (71.0)	0.651	
Penicillin non-susceptible	55 (26.6)	31 (29.0)		
Ceftriaxone susceptible	154 (81.9)	81 (80.2)	0.721	
Ceftriaxone non-susceptible	34 (18.1)	20 (19.8)		
Levofloxacin susceptible	200 (95.7)	100 (91.7)	0.148	
Levofloxacin non-susceptible	9 (4.3)	9 (8.3)		
MDR ^g	119 (57.5)	66 (61.1)	0.535	
Non-MDR	88 (42.5)	42 (38.9)		
Initial concordant antibiotic therapy ^d			0.927	
Yes	145 (85.3)	78 (85.7)		
No	25 (14.7)	13 (14.3)		

Data are expressed as the number of persons (percentage of the working population) unless stated otherwise. Abbreviations: OR, odds ratio; CI, confidence interval; IC, immunocompromised status; NA, not available; MDR, multidrug resistance.

^a Estimation by multiple logistic regression analysis.

^b Presence of one or more underlying medical condition(s).

^c Receipt of 23-valent polysaccharide vaccine in 66 (97.1%) patients.

^d Calculation based on available data.

^e Neither low nor high risk serotypes.

^f Serotypes not covered by PCV13 and PPSV23 vaccines.

^g Antibiotic resistance to three or more classes of antibiotics.

95% CI 1.003–26.576, $p=0.05$) were independent predictors for early in-hospital death (Table 5).

Serotype distribution of the pneumococcal isolates

Pneumococcal isolates were collected from 189 (61.0%) patients with IPD and were serotyped. The most prevalent serotype was 3

($n=26$, 13.6%), followed by 19A ($n=17$, 9.0%), 34 ($n=15$, 7.9%), and 11A/D/F ($n=12$, 6.3%). Of the isolates that were serotyped, 46.1% were intermediate risk serotypes and 11.3% were high risk serotypes (3, 6A, 6B, 9N, and 19F). The distribution of low to high risk serotypes did not differ significantly among the age groups or between survivors and non-survivors (Table 2). PCV7, PCV13, PPSV23, and non-vaccine serotypes accounted for 11.1%, 37.0%,

Table 4

Summary of the multiple logistic regression analysis of risk factors for in-hospital mortality in invasive pneumococcal disease among the age groups.

Risk factors	18–49 years (n = 35) OR (95% CI)	50–64 years (n = 93) OR (95% CI)	65–74 years (n = 91) OR (95% CI)	≥75 years (n = 100) OR (95% CI)
IC without any chronic condition	NI	7.26 (1.57–33.46)	NI	NI
Pitt bacteremia score (≥4)	NS	32.7 (7.44–143.29)	4.47 (1.70–11.76)	14.93 (5.01–44.52)

Abbreviations: OR, (adjusted) odds ratio; CI, confidence interval; IC, immunocompromised status; NI, not included in the multivariate logistic analysis; NS, not statistically significant.

Table 5

Multiple logistic regression analysis of predictors of early in-hospital mortality for invasive pneumococcal disease.

Risk variables	Early death (≤7 days) (n = 66)	Late death (≥15 days) (n = 29)	p-Value	Adjusted OR (95% CI) ^a
Bacteremic pneumonia			<0.001	
No	5 (7.6)	12 (41.4)		Reference
Yes	61 (92.4)	17 (58.6)		5.164 (1.003–26.576)
Underlying chronic condition				
Chronic heart disease	9 (13.6)	2 (6.9)	0.494	
Chronic pulmonary disease	8 (12.1)	2 (6.9)	0.718	
Chronic liver disease	6 (9.1)	1 (3.4)	0.672	
Chronic kidney disease	1 (1.5)	1 (3.4)	0.520	
Diabetes mellitus	11 (16.7)	7 (24.1)	0.392	
IC plus any chronic condition ^b	4 (6.1)	4 (13.8)	0.242	
IC without any chronic condition	8 (12.1)	9 (31.0)	0.027	0.253 (0.060–1.065) ^f
Pitt bacteremia score ^c				
<2	4 (6.2)	16 (59.3)	<0.001	Reference
2 and 3	5 (7.7)	4 (14.8)	0.441	3.978 (0.615–25.745)
≥4	56 (86.2)	7 (25.9)	<0.001	21.263 (5.134–88.06)
Serotype risk				
Low (1, 7F, and 8)	3 (7.9)	1 (5.6)	1.000	
Intermediate ^d	27 (71.1)	12 (66.7)	0.739	
High (3, 6A, 6B, 9N, and 19F)	8 (21.1)	5 (27.8)	0.736	
MDR ^e	39 (60.0)	17 (58.6)	0.900	
Initial concordant antibiotic therapy ^c	49 (86.0)	18 (81.8)	0.729	

Data are expressed as the number of persons (percentage of the working population) unless stated otherwise. Abbreviations: OR, odds ratio; CI, confidence interval; IC, immunocompromised status; MDR, multidrug resistance.

^a Estimation by multiple logistic regression analysis.^b Presence of one or more of underlying medical condition(s).^c Calculation based on available data.^d Neither low nor high risk serotypes.^e Antibiotic resistance to three or more classes of antibiotic.^f Reference for no IC without any chronic condition.

65.6%, and 33.9%, respectively. Compared to the older age groups, group 1 showed a significantly lower proportion of PCV13 and PPSV23 serotypes, but group 1 had an inversely higher proportion of non-vaccine serotypes.

Discussion

This prospective, multicenter, observational study investigated the burden of IPD in the adult population and potential risk factors for fatal outcome in stratified age groups during the 30-month period following the implementation of vaccination with PPSV23 targeted at the elderly (age ≥65 years) as part of the NIP in the ROK.

A higher incidence of IPD among older hospitalized patients was observed as evidenced by increased cases per 100,000 hospitalized patients in the older age groups. Overall in-hospital mortality was 34.2%, but this increased significantly among the older age groups. The factors associated with in-hospital mortality in the total patient population with IPD included older age (≥65 years), higher Pitt bacteremia score (≥4), and bacteremic pneumonia. Furthermore, IC status was an additional risk factor

for mortality in patients aged 50–64 years. Also, a higher Pitt bacteremia score (≥4) and bacteremic pneumonia were the predictors of early in-hospital mortality, which contributed to 60.6% of the fatal outcome. These results indicate that age group-related risk factors for a fatal outcome should be considered when developing effective strategies for the NIP to reduce the mortality of adult IPD.

The Korean Centers for Disease Control and Prevention have reported previously that the cumulative uptake rate achieved for the single-dose PPSV23 in the target population (≥65 years) as part of the NIP was approximately 60% by October 2015, which matched with the end of the enrollment period of the present study. However, the prior PPSV23 vaccination rate was lower (33.3%) in the older patients with IPD (≥65 years) included in the present study. On the other hand, the majority of patients in both the younger age group 1 (18–49 years) and age group 2 (50–64 years) had received no prior pneumococcal vaccination. Also, there was a high prevalence rate of CC or IC in the older IPD patients aged ≥65 years. Therefore, the present study results indicate that IPD in older patients ≥65 years of age may occur primarily in elderly patients with CCs who have not received the PPSV23 vaccine. Furthermore,

unlike the pneumococcal conjugate vaccine, which is known for having an indirect herd effect (Kim et al., 2016b), PPSV23 has not been shown to demonstrate indirect herd effects. Taken together, achieving maximal levels of PPSV23 coverage would be necessary to offer substantial protection against IPD among the elderly population ≥ 65 years of age.

In this study, the in-hospital mortality of adult IPD patients was highest (51.0%) in group 4 (≥ 75 years), accounting for 46.8% of all deaths. The risk factors for a fatal outcome identified among all adult IPD patients included old age (≥ 65 years), bacteremic pneumonia, and higher Pitt bacteremia score (≥ 4).

Higher Pitt bacteremia score (≥ 4) was a universal predictor of mortality in the three age groups 2–4. Based on the clinical parameters of the Pitt bacteremia score (fever, hypotension, mechanical ventilation, and mental status), patients presenting with higher Pitt bacteremia scores (≥ 4) are more likely to have septic shock or severe sepsis. These findings support that disease severity may play essential roles in the fatal outcome of IPD (Yu et al., 2003; Feldman et al., 2009). Also, the study findings that bacteremic pneumonia was the most common IPD with a high mortality rate of 44.4% are similar to the findings of previous studies (Jansen et al., 2009b; Ardanuy et al., 2012; Capelastegui et al., 2014). Furthermore, both a higher Pitt bacteremia score (≥ 4) and bacteremic pneumonia were found to be independent risk factors predicting early in-hospital death within 7 days of admission, reaffirming the significance of bacteremic pneumonia-associated severe sepsis or septic shock with regard to in-hospital mortality. Notably, more than two-thirds of age group 4 (≥ 75 years) died within 1 week of hospitalization, indicating the challenges in the care of elderly patients with IPD and the need for optimal management around the time of hospital admission for a better outcome.

Consistent with a previous study (Marrie et al., 2011), old age (≥ 65 years) was one of the significant independent risk factors for overall mortality in the analysis. There are several potential explanations for these observations. The effects of old aging on increasing IPD mortality might be likely due to decreased neutrophil (Christy et al., 2010) and immune function (Janssens and Krause, 2004), and the increase in medical comorbidities with advancing age (Yu et al., 2003; Piccirillo et al., 2008; Kyaw et al., 2005). Therefore, higher proportion of older age (median 69 years vs. median 51 years) and underlying medical comorbidities (71.5% vs. 48.2%) noted in our study patients compared to a previous study (Yu et al., 2003) might explain the trend of higher case fatality rate of IPD in our older age groups. Furthermore, when compared to a previous IPD study reported in the ROK (Song et al., 2013), our study patients were older (mean age 67 years vs. 61 years) with a higher mortality rate (34.2% vs. 30.9%), reaffirming the importance of the age factor in IPD mortality.

Based on the analyses of risk factors for mortality by each age group, comorbidities of the immunocompromised status without chronic condition was a significant mortality risk factor in the age group 2 (50–64 years). A recent study reported that the relative risk of IPD incidence in group 2 (50–64 years) was twice that in group 1 (18–49 years), as one or more IPD-disposing medical comorbidities occur more frequently after the age of 50 years (Baxter et al., 2016). An additional study has determined that multiple risk factors (stacked risks) for pneumococcal disease increase the 30-day mortality among adults aged ≥ 50 years with severe pneumococcal disease (Morton et al., 2017). However, in the present study, no other underlying CCs of pneumococcal vaccination indications, single or stacked, were found to be significant risk factors for mortality in the overall patients or analyses according to age groups, probably due to a similar distribution of these underlying comorbidities between survivors and non-survivors.

In this study, the overall rate of non-susceptibility to penicillin of IPD was higher (72.6%) compared with a recent study (Song et al., 2013), reflecting the continuing trend of increasing penicillin non-susceptibility of IPD in the ROK. The MDR rate was high (58.7%), which is similar to the results of previous studies in the ROK (Kim et al., 1996; Lee et al., 2010). Initial discordant antibiotic therapy did not result in a negative contributory impact on mortality in the study patients. The lack of significance between initial discordant antibiotic therapy and mortality from IPD has been demonstrated in other studies (Ho et al., 2006; Fica et al., 2014), suggesting that host factors or disease severity may have a more significant impact on mortality.

Contrary to the results of a previous meta-analysis on mortality-related serotype risks (Weinberger et al., 2010), there was no significant association between the risk serotype groups and mortality in the overall patients or in the age-stratified groups in the present study. These results may be due in part to the different geographical distribution of serotype risks or possible underestimation as a result of the unavailability of serotype information for 40.8% of the IPD cases. However, two other studies conducted separately in the ROK have shown a changing epidemiology of vaccine formulation serotypes among adults with IPD. In one study, the prevalence of PCV7 serotypes decreased from 40.9% in 1996–1999 to 33.3% in 2007–2008 among patients aged ≥ 65 years (Lee et al., 2013). In the other study, it was shown that the prevalence of PCV13 serotypes decreased from 63.3% in 1997–2003 to 48.6% in 2011–2012 among patients aged ≥ 16 years (Kim et al., 2016a). In line with these findings, our study showed that the proportions of PCV7, PCV13, and non-vaccine serotypes were 11.1%, 37.0%, and 33.9%, respectively, of the isolates from adults with IPD, reflecting continuing serotype replacement and herd immunity with indirect effects on adult IPD following childhood immunization with conjugate pneumococcal vaccines.

A meta-analysis on the efficacy of pneumococcal polysaccharide vaccine updated in 2013 demonstrated substantial evidence of pneumococcal polysaccharide vaccine efficacy against IPD in adults with no statistical heterogeneity, but no association with substantial reductions in all-cause mortality (Moberley et al., 2013). Although the present study did not demonstrate a statistically significant difference, the results showed a trend towards decreased in-hospital mortality in older patients aged ≥ 65 years who had received the PPSV23 vaccination compared to those who had not. Considering the higher mortality of IPD in the elderly with age-related factors (Yoshikawa, 2000) and the reduced functional antibody activity following PPSV23 vaccination (Romero-Steiner et al., 1999), there is a substantial need to improve the strategy of the NIP of pneumococcal vaccination to overcome this problem in the elderly population. Also, the effectiveness of PPSV23 among the older adults in the ROK after the implementation of the NIP needs to be analyzed after adjusting for underlying medical comorbidities; this analysis is being conducted separately.

This study has limitations. First, this was a multicenter, observational study, and clinical variables were recorded at each participating hospital. Thus, sampling bias from the small number of patients and confounding factors from unmeasured variables such as alcohol intake and smoking might be present. Also, selection bias as a result of IPD cases being entered into the study mainly from tertiary care hospitals might have contributed to the high in-hospital mortality and possible under-reporting of IPD cases in younger age group patients (18–49 years). However, a standardized case report form was used and the potential bias was minimized by using multiple logistic regression analyses. Second, the sample size of the risk serotypes was insufficient to determine an association between some variables and mortality in the stratified age groups. Third, the epidemiology of IPD may differ

regionally, with possible racial difference. Our result of the proportion of male patients (69.3%) is higher than that of IPD study conducted in Europe (52.0%) (Wagenvoort et al., 2017). However, our rate is similar to the rate reported in a previous IPD study conducted in East Asia (66.3% from China) (Zhao et al., 2013). Therefore, the present study result is in agreement with that of a previous study conducted in East Asia.

In conclusion, this study reports the epidemiology and reliable baseline data for IPD in adults at the time of 60% cumulative uptake of PPSV23 achieved as part of the NIP in the target population in the ROK. Vaccine-type IPD continues to place a substantial burden on older adults in the ROK, with significant mortality, particularly when presented in patients with severe sepsis or septic shock and bacteremic pneumonia. Therefore, there is the need for an effective vaccination strategy for those at higher risk in order to prevent IPD in the older population. Also, the age group 50–64 years carrying an increased IC status should be considered an emerging population to be targeted to reduce the burden of IPD. Further studies involving a larger number of patients with continuing surveillance are needed to define the changing epidemiology of IPD in the ROK.

Author contributions

JHK, BCC, and MJK were involved in the conception or the design of the study project. All authors contributed to the collection of study data. JHK, BCC, and MJK were involved in the analyses of study data. JHK drafted the manuscript. MJK revised the manuscript.

Acknowledgements

The authors thank Professor Moon Nahm at the University of Alabama (Birmingham, AL, USA) for providing reagents for the serotyping of pneumococcal isolates and for consultations.

Funding source

This study was supported by a fund (#20133200301) by a research grant of Korea Center for Disease Control and Prevention.

Ethical approval

The Institutional Review Board of Korea University College of Medicine, Seoul, Republic of Korea approved the study (2013AN153).

Conflict of interest

All authors have no conflicts of interest.

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