Pneumococcal disease: a retrospective cohort study on associated factors and risk factors for mortality among hospitalised adults in Singapore

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Abstract

Background: Streptococcus pneumoniae infections can lead to severe morbidity and mortality, especially in patients with invasive pneumococcal disease (IPD). This study assesses factors associated with pneumococcal disease, and risk factors for mortality among hospitalised adults in Singapore.

Methods: Retrospective study of patients with pneumococcal disease, based on streptococcal urinary antigen testing and/or sterile site cultures positive for S. pneumoniae , admitted to a tertiary hospital from 2015-2017. IPD and non-IPD cases were compared against a control group of patients, admitted over the same period but with negative results for the abovementioned tests.

Results: We identified 496 pneumococcal disease cases, of whom 92 (18.5%) had IPD. The mean age of cases was 69.1±15.4yrs, and 65.5% were male. Compared with controls (N=9,181), IPD patients were younger (mean age 61.5±16.3yrs, vs 72.2±16.1yrs in controls; p<0.001) and with less co-morbidities [median Charlson's score 1 (IQR 0-4), vs 3 (1-5) in controls; p<0.001]. IPD patients also had the highest proportions with intensive care unit (ICU) admission (20.7%), inpatient mortality (26.1%) and longest median length of stay [9 (8-17) days]. On multivariate analysis, IPD was negatively associated with prior pneumococcal vaccination (adjusted odds ratio=0.20, 95%CI 0.06–0.69; p=0.011). Risk factors for mortality among pneumococcal disease patients were ICU admission, diagnosis of IPD, age ≥85yrs and Charlson's score >3.

Conclusion: Patients with pneumococcal disease (especially IPD) were younger and had less co-morbidities than controls, but had higher risk of severe clinical outcomes and mortality. Pneumococcal vaccination was negatively associated with IPD and should be encouraged among high-risk patients.

Background

Pneumococcal disease is caused by *Streptococcus pneumoniae* and can lead to severe clinical outcomes and death. *S. pneumoniae* is the most common cause of community-acquired pneumonia (CAP), estimated to cause 27.3% of CAPs worldwide [1], and accounting for 29.2% of isolated pathogens from CAPs in Asia [2]. Other common sites of infection include otitis media and sinusitis. Invasive pneumococcal disease (IPD), defined as isolation of *S. pneumoniae* from a normally sterile site (such as blood or cerebrospinal fluid), carries an even higher risk of mortality and morbidity [3].

From 1995 to 2004, the overall mean annual hospitalisation rate for pneumococcal disease was 10.9 per 100,000 population and the case-fatality rate was 3.2%. Cases were predominantly male, and patients 65yrs and above had the highest hospitalisation rates (56.4 per 100,000) and case-fatality rates [4,5]. Specifically for IPD, locally reported case-fatality rates have ranged from 13.1% to 21.4% [6].

Pneumococcal disease may be transmitted via respiratory droplets from people with pneumococcal disease or asymptomatic individuals with carriage of the organism in their nasopharynx [7]. Risk factors for pneumococcal disease include presence of chronic diseases involving cardiovascular, pulmonary,

hepatic, neurological or endocrine systems; immunosuppressed states; cigarette smoking history; alcohol abuse; recent influenza infection; institutionalised status; male sex and extremes of age [8]. Successful empiric antibiotic therapy is vital to avoid treatment failure and subsequent costs [9]. However, increasing antibiotic resistance in *S. pneumoniae* in the community has been reported [10]. Hence, while updated treatment recommendations (especially for CAP) have reduced disease-associated complications and mortality, the risks from infection still remain significant [11].

Vaccination is an effective measure for upstream prevention of pneumococcal disease. Both the 13-valent pneumococcal conjugate vaccine (PCV13) (which covers for serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) (which covers for serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F) [12], are effective against IPD [13–15]. PCV13 has also been shown to reduce the risk of subtype-specific non-invasive pneumococcal pneumonia [14]. Adult immunisation with both PCV13 and PPSV23 in elderly and high-risk groups is recommended by the United States Advisory Committee on Immunisation Practices (ACIP) [16], as well as the Singapore Ministry of Health (MOH) [17]. However, pneumococcal vaccination uptake in adults has been low, estimated to be 6.1% among adults ≥65yrs in 2013 [18].

Previous studies in Asia have described the changing epidemiology of pneumococcal disease due to introduction of pneumococcal vaccines [19,20]. This paper evaluates the factors associated with pneumococcal disease and risk factors for mortality among hospitalised adults in Singapore. We also report on the effectiveness of pneumococcal vaccination in reducing the risk of adverse health outcomes.

Methods

Patient population and study design

We conducted a retrospective study on patients with pneumococcal disease admitted to Tan Tock Seng Hospital (TTSH), the second largest adult acute tertiary care hospital in Singapore with 1,600 beds, from January 2015 through December 2017. Cases with pneumococcal disease were defined as either having i) a positive result on testing for streptococcal urinary antigen, or ii) growth of *S. pneumoniae* from sterile site clinical cultures. For patients with multiple admissions for pneumococcal disease, only the first admission was included for this study. We further stratified cases into those with IPD versus those with non-IPD. IPD was defined as either having i) a sterile site culture (e.g. blood, joint fluid, or pleural fluid) positive for *S. pneumoniae,* or ii) a positive streptococcal urinary antigen test and a clinical diagnosis suggesting invasive disease (e.g. meningitis, septic arthritis, or pleural empyema), with cultures from the relevant site negative for any other causative pathogen.

To identify factors associated with IPD and non-IPD, we also recruited a group of control patients of similar risk as the case group but without diagnosis of pneumococcal disease. We defined our controls as patients admitted to TTSH over the same period, with a negative test for streptococcal urinary antigen and all laboratory cultures yielding negative results. Again, for patients with multiple admissions, only the

first admission fulfilling the definition was considered. Patients who did not have both streptococcal urinary antigen tests and at least one sterile site culture (typically at least one blood culture) performed during their admission were excluded from the study.

Data sources and classification

All data for the study was captured using the hospital's electronic medical record system, which comprehensively captures the demographics, clinical characteristics, laboratory results, and vaccination records of patients. Pneumococcal vaccination was defined as ever having had any record for PCV–13 and/or PPSV–23 given prior to the date of hospital admission. Inpatient mortality was defined as death resulting from any cause during the pneumococcal disease-related admission. International Classification of Diseases, 10th Revision (ICD–10) was used to establish patient diagnoses, comorbidities, risk factors, and infectious disease history. The co-morbidity status was assessed according to Charlson's co-morbidity score classification [21].

Statistical analysis

Descriptive statistics were analysed for the overall cohort and patient subgroups, including the number and proportions for categorical characteristics, mean and standard deviation for normally distributed continuous variables, and median and interquartile range (IQR) for non-normally distributed variables. Across our three patient subgroups (IPD, non-IPD and controls), differences in proportions were assessed using Chi-square or Fisher's exact tests for categorical variables, while continuous variables were evaluated using the one-way ANOVA (for means) or Kruskal-Wallis test (for medians) as appropriate. Multinomial regression analysis was used to further evaluate factors significantly associated with IPD and non-IPD on univariate analysis, comparing to non-pneumococcal disease patients as the base group, with calculation of adjusted odds ratios (AORs) for independent variables.

Within the case group, we also evaluated factors associated with inpatient mortality. Univariate analysis of demographic and clinical variables was first performed, and significant variables were included in a multiple logistic regression model with adjustment for demographic confounders. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to determine the strength of association between variables and in-hospital all-cause mortality. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata version 13 (StataCorp 2013, College Station, TX).

Ethics approval

Ethics approval for this study was obtained from the Domain-Specific Review Board of the National Healthcare Group (NHG DSRB No: 2017/00347).

Results

A total of 496 cases with pneumococcal disease were identified over the study period (Table 1). Cases were predominantly elderly (mean age 69.1 ± 15.4yrs), male (N = 325, 65.5%), and of Chinese ethnicity (N = 359, 72.4%). The median Charlson's comorbidity score was 2 (IQR 1–4). The most common co-morbidities were chronic pulmonary disease (30.0%), diabetes mellitus (29.6%), myocardial infarction/congestive cardiac failure (28.8%), and renal disease (18.8%). Majority had pneumonia as their primary diagnosis (70.0%). Eighty (16.1%) had received pneumococcal vaccination (PCV13 and/or PPSV23) at any time prior to admission. Ninety-two (18.5%) cases had IPD. Within this group, 84 (91.3%) had growth of *S. pneumoniae* in blood cultures only, 3 (3.3 %) in pleural fluid cultures only, and 1 (1.1%) each in cerebrospinal fluid and joint fluid cultures only. A further 1 (1.1%) case had both blood and cerebrospinal fluid cultures positive, 1 (1.1%) had both blood and joint fluid cultures positive, and 1 (1.1%) was culture negative, but had a diagnosis of meningitis and a positive streptococcal urinary antigen test, with no other organisms implicated.

When comparing IPD, non-IPD and control group (N = 9,181) patients (Table 2), significant differences across groups were observed for age (mean age in controls: 72.2 ± 16.1yrs, non-IPD patients:70.8 ± 14.7yrs, IPD patients: 61.5 ± 16.3yrs; p<0.001), gender (with higher proportions of males among IPD and non-IPD patients), history of pneumococcal vaccination (IPD patients: 3.3%, non-IPD patients: 19.1%, controls: 18.5%; p = 0.001), influenza vaccination in the past 1yr before admission (IPD patients: 6.5%, non-IPD patients: 17.1%, controls: 15.2%; p = 0.039), and Charlson's co-morbidity score (median score in controls: 3, non-IPD patients: 2, IPD patients: 1; p<0.001). In terms of clinical outcomes, IPD was associated with the highest proportion of ICU admissions (20.7%, versus 8.7% in non-IPD patients and 6.3% in controls; p<0.001) and in-hospital all-cause mortality (26.1% versus 11.4% and 9.1% respectively; p<0.001). Similarly, length of stay was longest for IPD patients (median duration 9 days, versus 8 days in non-IPD and control groups; p = 0.003).

On multivariate analysis (Table 2), IPD patients were much less likely than controls to have a history of any pneumococcal vaccination prior to admission (AOR = 0.20, 95%CI 0.06–0.69; p = 0.011). IPD was also positively associated with male gender (AOR = 1.87, 95%CI 1.18–2.96; p = 0.008), and negatively associated with increasing age groups, with patients ≥85yrs being 0.19 times as likely to have IPD compared to patients <65yrs (p<0.001). Although influenza vaccination was negatively associated with IPD on univariate analysis, this factor was non-significant after multivariate adjustment. Non-IPD patients were also more likely than controls to be of male gender, although the effect size was smaller than in IPD patients (AOR = 1.42, 95%CI 1.15–1.76; p = 0.001). Patients ≥85yrs and those with Charlson's score of >3 were also less likely to have non-IPD, and no significant differences in vaccination status was observed.

Of the 496 patients with pneumococcal disease, 70 (14.1%) died during their admission (Table 3). The case fatality rates for IPD and non-IPD were 26.1% and 11.4% respectively. Patients who died were more likely to be older (mean age 74.4 ± 14.3yrs vs 68.2 ± 15.4yrs; p<0.001), have a Charlson's score >3, a diagnosis of IPD, or ICU admission. Presence of co-morbidities such as myocardial infarction/congestive

heart failure, cerebrovascular disease and dementia were also significantly associated with mortality. After adjustments in our multivariate model, factors significantly and independently associated with mortality from pneumococcal disease were age ≥85yrs (compared to below 65yrs) (AOR = 10.78, 95%CI 4.10–28.37; p<0.001), Charlson's score >3 (AOR = 1.93, 95%CI 1.02–3.64; p = 0.042), diagnosis of IPD (AOR = 3.19, 95%CI 1.55–6.59; p = 0.002) and ICU admission (AOR = 23.22, 95%CI 11.07–48.70; p<0.001).

Discussion

Among our cases comprising hospitalised patients with pneumococcal disease, a high proportion were in older age groups, of male gender, and with chronic disease. The ethnic distribution of the patients was reflective of the national census [22]. However, compared to the control group, IPD patients demonstrated a trend towards being younger, and with lower Charlson's scores. Non-IPD patients were more similar to the control group, but with only slightly lower mean age and Charlson's scores. Within our hospital cohort, patients in older age groups or with more co-morbidities might have had increased prior healthcare exposures, or had specific risk factors (such as swallowing impairment) which resulted in them being more likely to develop infections[23,24] from other aetiologies [25,26]. However, there was a reverse trend in the ICU admission and in-hospital mortality rates, which were highest in IPD patients and lowest in the control group. This reflects the virulence of the disease and highlights the importance of early recognition, treatment, and prevention where possible.

Our findings showed that prior pneumococcal vaccination was associated with a reduced risk of IPD by about 80%, after adjustments for age, gender, Charlson's score and influenza vaccination status. This was consistent with previous studies evaluating the effectiveness of PCV13 and PPSV23 [13–15]. Pneumococcal serotypes covered by these vaccines have been shown to be well matched to those circulating in the Singapore population [6,10,27]. In particular, serotypes 3, 6B, 7F, 8, 19A and 23F are predominant in the 19–64yrs age group, while serotypes 3, 14 and 19A are predominant among those 65yrs and above [27].

In addition, 50 (54.4%) of the IPD cases among our hospital patients were below 65yrs of age, of whom 24 (48.0%) had some form of chronic disease. A Japanese study of 10.4 million individuals demonstrated that younger adults with at least one medical condition were at greater risk of IPD compared to healthy older adults. For example, an adult aged 50–64yrs with an underlying medical condition had a higher risk compared to a healthy adult aged ≥65yrs [28]. Although the overall incidence in younger adults is lower than in older age groups [4,29], the increased susceptibility of adults <65yrs with chronic diseases, as suggested by our study, suggests that targeted efforts to vaccinate this population might be beneficial in reducing IPD incidence.

Overall, our results support current recommendations to vaccinate at-risk individuals to prevent IPD. This may be provided by primary care practitioners as part of chronic disease management, or alongside other preventive services such as health screening. In addition, our hospital has ongoing vaccination

programmes to identify and opportunistically vaccinate high-risk groups according to standardised protocols. In the inpatient setting, high-risk inpatients are counselled on and given vaccination prior to discharge, while in the outpatient setting, selected specialist clinics have a nurse-led programme for counselling and vaccination administration for high-risk patients, in conjunction with the medical consultation.

Our study, however, did not demonstrate any significant effect of PCV13 vaccination on reducing risk of non-IPD, likely due to the low proportion of patients in our study given this vaccine. Apart from adult vaccination, widespread introduction of pneumococcal conjugate vaccine in children has been shown to reduce the incidence of IPD across all ages groups due to herd immunity, despite evidence of serotype replacement [30–33]. Singapore introduced PCV7 into the National Childhood Immunisation Programme (NCIP) in October 2009 [34], and this was switched to PCV13 in December 2011 [17]. The cost-effectiveness of childhood vaccination in the Singapore setting has been demonstrated by Tyo et al [35]. Future studies are warranted to study the effectiveness of increasing PCV13 vaccination uptake, in both adults and children, to reduce incidence of invasive and non-invasive pneumococcal disease.

Finally, our study also demonstrated key factors associated with in-hospital mortality among pneumococcal patients. ICU admission was the strongest predictor, with those having admission being 23 times as likely as those who did not to die during their admission. Other factors included age ≥85yrs, higher Charlson's score and diagnosis of IPD. Medical teams should especially note the increased mortality risk in these patients and ensure prompt management to reduce the risk of death.

The strengths of our study include a systematic selection of cases and controls among hospitalised patients. As such, our study population is likely to represent the population at risk for pneumococcal disease and selection bias (if any) is likely to be minimal. Furthermore, we followed up the patients longitudinally to the point of discharge from the hospital. Our findings are useful to guide the identification of patients at high risk of in-hospital mortality from the disease.

Our study also has some limitations. Our definition of cases included the use of results from streptococcal urinary antigen testing, which has an estimated sensitivity of 74.0% and specificity of 97.2% [36]. Some cases of pneumococcal disease may hence have been misclassified as controls (i.e. false negatives). Such a misclassification could have reduced the magnitude of our findings, but not negated them. As our data was obtained through hospital electronic medical records, clinical data from other sources (such as from other hospitals or the primary care sector) were not available. However, majority of our patients tended to return back to our hospital if future admissions were required. Moreover, it is likely that this issue would result in non-differential misclassification (if any) as data would not be captured differently across the study groups. Although we captured a wide range of variables in our study to allow for statistical adjustments, we were unable to capture data for some known risk factors, such as smoking history and socioeconomic status. Pneumococcal serotype data were also not available for this study, as this is not routinely performed for isolates. Nevertheless, we have reviewed

data from serotyping studies conducted in the local setting, which we believe to be applicable to our cohort. The generalisability of our study is limited to hospitalised adult patients.

Conclusion

In conclusion, while patients with pneumococcal disease tended to be younger and with less co-morbidities compared to those without pneumococcal disease, risk of ICU admission and death were nevertheless higher, especially in IPD patients. Mortality risk was highest in those with ICU admission, age ≥85yrs, higher Charlson's score and diagnosis of IPD. Pneumococcal vaccination was associated with reduced risk of IPD and should be encouraged among high-risk patients, including those from younger age groups.

Declarations

Availability of the data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Tables

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Supplementary Files

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