Epidemiology, vaccine effectiveness, and risk factors for mortality for pneumococcal disease among hospitalised adults in Singapore: a case-control study

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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 evaluated factors associated with pneumococcal disease, pneumococcal vaccine effectiveness, and risk factors for all-cause mortality in hospitalised adults with pneumococcal disease in Singapore.

Methods: Retrospective case-control study of patients tested for pneumococcal disease with streptococcal urinary antigen testing and at least one sterile site culture, during their admission to a tertiary hospital in Singapore from 2015-2017. Patients were defined as cases of IPD or non-IPD, or as controls, based on laboratory results and clinical diagnoses. Multivariable models were constructed to determine factors associated with IPD/non-IPD, and risk factors for mortality from pneumococcal disease. Vaccine effectiveness against IPD/non-IPD was estimated using a variation of the test-negative design.

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 (IQR 8-17) days]. On multivariable analysis, IPD was negatively associated with prior pneumococcal vaccination (adjusted relative risk 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 effectiveness against IPD was estimated to be about 80%, 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\textsuperscript{1}, and accounting for 29.2% of isolated pathogens from CAPs in Asia\textsuperscript{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\textsuperscript{3}. Cases of pneumococcal disease were predominantly male, and patients 65yrs and above had the highest hospitalisation rates and case-fatality rates\textsuperscript{4,5}. From 1995 to 2004, the overall mean annual hospitalisation rate for pneumococcal disease in Singapore was 10.9 per 100,000 population and the case-fatality rate was 3.2%\textsuperscript{4}. Specifically for IPD, locally reported case-fatality rates have ranged from 13.1% to 21.4%\textsuperscript{6}.

Transmission of the pneumococcus occurs via respiratory droplets from people with pneumococcal disease or asymptomatic individuals with carriage of the organism in their nasopharynx\textsuperscript{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\textsuperscript{8}. Successful empiric antibiotic therapy is vital to avoid treatment failure and subsequent costs\textsuperscript{9}.

However, increasing antibiotic resistance in *S. pneumoniae* in the community has been reported\textsuperscript{10}. Hence, while updated treatment recommendations (especially for CAP) have reduced disease-associated complications and mortality, the risks from infection still remain significant\textsuperscript{11}.

Adult 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)\textsuperscript{12}, are effective against IPD\textsuperscript{13-15}. PCV13 has also been shown to reduce the risk of subtype-specific non-invasive pneumococcal pneumonia\textsuperscript{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) \(^\text{16}\). The Singapore Ministry of Health (MOH) also recommended PPSV23 vaccination in adults in 2009 and subsequently both PCV13 and PPSV23 in 2017 \(^\text{17}\). However, pneumococcal vaccination uptake in adults has been low, estimated to be 6.1% among adults ≥65yrs in 2013 \(^\text{18}\).

Previous studies in Asia have described the changing epidemiology of pneumococcal disease due to introduction of pneumococcal vaccines \(^\text{19,20}\). However, there have been few reports on the epidemiology of hospitalised adult patients with pneumococcal disease. Furthermore, evaluating the vaccine effectiveness in this group of patients may help strengthen the case for hospital-based and nationwide adult vaccination programmes.

The aims of this study were to evaluate the factors associated with pneumococcal disease, vaccine effectiveness in preventing severe outcomes of pneumococcal disease, and the risk factors for all-cause mortality in hospitalised adults with pneumococcal disease in Singapore.

**Methods**

*Patient population and study design*

We conducted a case-control study on patients suspected to have 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. Our participants comprised all patients (aged 16 years and above) admitted over the study period who were evaluated for pneumococcal disease using streptococcal urinary antigen testing and at least one sterile site clinical culture during their admission. Cases of 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 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. A non-IPD case was defined as a patient with a positive streptococcal urinary antigen test, but without positive cultures or any clinical diagnosis suggesting invasive disease.

To identify factors associated with IPD and non-IPD, the cases were compared to a control group comprising the remainder of the participants. For clarity, controls were defined as patients admitted to TTSH over the same study period, with a negative test for streptococcal urinary antigen, and all laboratory cultures yielding negative results for *S. pneumoniae*. 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 this 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 any record for PCV13 and/or PPSV23 given at least 14 days 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 \(^2\).  

**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.
We subsequently analysed differences in patient characteristics 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 patient factors associated with IPD and non-IPD, as IPD, non-IPD and non-pneumococcal disease patients were considered as three unranked categories of patients, based on their laboratory results and clinical diagnosis. This also enabled us to analyse our entire study cohort using a single model. Factors to include in the model were determined based on a p value threshold of 0.05 on univariate analysis, using non-pneumococcal disease patients as the base comparison group, with calculation of adjusted relative risk ratios (RRRs) for independent variables. Within our multivariable model, we included pneumococcal vaccination status (receipt of PCV13 and/or PPSV23 vaccination at least 14 days prior to admission date) as a variable to determine its effectiveness in reducing risk of IPD / non-IPD. This was a variation of the test-negative design used for vaccine effectiveness studies, using multinomial logistic regression to construct the statistical model.

Among the cases, we also evaluated factors associated with inpatient all-cause mortality. Univariate analysis of demographic and clinical variables was first performed, and variables were included in a multiple logistic regression model again based on a p value threshold of 0.05 on univariate analysis, 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.

For all analyses, a p value of <0.05 was considered statistically significant. Furthermore, inclusion of variables into multivariable logistic regression models also took into account confidence intervals and clinical significance of variables. All statistical analyses were performed using Stata version 13 (StataCorp 2013, College Station, TX).

Results
A total of 496 cases with pneumococcal disease were identified over the study period (Table 1). Cases
were predominantly elderly (mean age $69.1 \pm 15.4$ yrs), 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 patients (N=92), non-IPD patients (N=404) and non-pneumococcal disease patients (N=9,181)(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).

In our multivariable models (Table 2), IPD patients were much less likely than controls to have a history of any pneumococcal vaccination prior to admission (RRR=0.20, 95%CI 0.06–0.69; p=0.011). IPD was also positively associated with male gender (RRR=1.87, 95%CI 1.18-2.96; p=0.008), and negatively associated with increasing age groups, with very elderly patients (≥85yrs) being less
likely to have IPD compared to younger counterparts (<65yrs) (p<0.001). Although influenza vaccination was negatively associated with IPD on univariate analysis, this factor was non-significant after multivariable 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 (RRR=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 multivariable models, 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, majority were aged ≥65 years and of male gender, and about a quarter had a Charlson’s score of >3. The ethnic distribution of the patients was reflective of the national census. 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. In our study, 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 from other aetiologies other than S. pneumoniae. However, in contrast to the age and co-morbidity trends, the ICU admission and in-hospital mortality rates 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% in our study population, after adjustments for age, gender, Charlson’s score and influenza vaccination status. This was consistent with studies in other settings evaluating the effectiveness of PCV13 and PPSV23. Pneumococcal serotypes covered by these vaccines have been shown to be well matched to those circulating in the Singapore population. 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. 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. Although the overall incidence in younger adults is lower than in older age groups, the increased susceptibility of adults <65yrs with chronic diseases suggests that targeted efforts to vaccinate this population might be beneficial in reducing IPD incidence.

Currently, 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. Vaccination should also be provided by primary care practitioners as part of chronic disease management and alongside other preventive services such as health screening.

Our study, however, did not demonstrate any significant effect of PCV13 vaccination on reducing risk of pneumococcal disease, likely due to the low proportion of patients in our study with a clearly
documented history of PCV13 vaccination. 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. Singapore introduced PCV7 into the National Childhood Immunisation Programme (NCIP) in October 2009, and this was switched to PCV13 in December 2011. The cost-effectiveness of childhood vaccination in the Singapore setting has been demonstrated by Tyo et al. 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. Furthermore, we followed up the patients longitudinally to the point of discharge from the hospital. Our study population is likely representative of patients hospitalised for pneumococcal disease in Singapore, as our hospital has a large catchment area which is not geographically restricted and patients from anywhere in Singapore may be admitted. Our findings are useful to guide the identification of patients at high risk of in-hospital mortality from the disease. They also support current recommendations to vaccinate at-risk individuals to prevent IPD.

Our study also has some limitations. Selection bias might have been present as clinicians may have preferentially ordered streptococcal urinary antigen and sterile site cultures for certain groups of patients, such as those who were elderly, with co-morbidities, or without records of recent vaccinations. However, at the time of the study, we had verified that there were no clinical protocols mandating such tests to be done for any particular patient groups. 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. Sterile site cultures from multiple possible sources (e.g. blood, joint fluid, or pleural fluid) will also have varying microbial culture methods with different sensitivity and specificity. Some cases of pneumococcal disease may hence have been misclassified as controls (i.e. false negatives). However, 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 (e.g. 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 study groups. We were unable to capture data for some known risk factors, such as smoking history and socioeconomic status. Our analysis of IPD cases was limited by the relatively small numbers, especially when divided into subgroups. 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 6, 10, 27, which we believe to be applicable to our study population. 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 against IPD was estimated to be about 80%, and should be encouraged among high-risk patients, including those from younger age groups.

Declarations
Ethics Approval and Consent to Participate: Ethics approval for this study was obtained from the Domain-Specific Review Board of the National Healthcare Group (NHG DSRB No: 2017/00347).
Consent for Publication: Not applicable.
Availability of 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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Authors’ Contributions: TC and MZT analysed and interpreted the data collected for this study, and contributed to the writing of the manuscript. WMK and AC contributed to study design, interpretation of data, and critically reviewed the manuscript. HJH conceived the study, analysed and interpreted the data, and was a major contributor in writing the manuscript. All authors approved the final version of the manuscript for submission.

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Tables
Table 1. Demographic and clinical characteristics and outcomes of hospitalised patients with pneumococcal disease. SD = standard deviation; PCV13 = 13-valent pneumococcal conjugate vaccination; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; IQR = inter-quartile range; ICU = intensive care unit.

| Characteristics | Pneumococcal disease (N=496), N(%) |
|-----------------|----------------------------------|
| Age, mean (yrs) ± SD | 69.1 ± 15.4 |
| Age group             | Count (Percentage) |
|----------------------|--------------------|
| <65yrs               | 170 (34.3)         |
| 65-74yrs             | 125 (25.2)         |
| 75-84yrs             | 131 (26.4)         |
| ≥85yrs               | 70 (14.1)          |

| Gender = male            | 325 (65.5)        |

| Ethnicity          | Count (Percentage) |
|--------------------|--------------------|
| Chinese            | 359 (72.4)         |
| Malay              | 61 (12.3)          |
| Indian             | 39 (7.9)           |
| Others             | 37 (7.5)           |

| Nursing home residence | 4 (0.8) |

| Vaccination status (received ≥14 days prior to admission) | Count (Percentage) |
|----------------------------------------------------------|--------------------|
| PCV13                                                     | 6 (1.2)            |
| PPSV23                                                    | 78 (15.7)          |
| Any pneumococcal vaccination                             | 80 (16.1)          |
| Influenza vaccination in past 1 yr                       | 75 (15.1)          |

| Co-morbidities                                             | Count (Percentage) |
|------------------------------------------------------------|--------------------|
| Charlson's score, median (IQR)                             | 2 (1 - 4)          |
| Charlson's score >3                                        | 137 (27.6)         |
| Myocardial infarction/Congestive heart failure             | 143 (28.8)         |
| Cerebrovascular disease                                    | 66 (13.3)          |
| Dementia                                                   | 54 (10.9)          |
| Chronic pulmonary disease                                  | 149 (30.0)         |
| Liver disease                                              | 27 (5.4)           |
| Diabetes mellitus                                          | 147 (29.6)         |
| Renal disease                                              | 93 (18.8)          |
| Any malignancy                                             | 53 (10.7)          |
| Hemiplegia                                                 | 18 (3.6)           |
| Peripheral vascular disease                                | 22 (4.4)           |
| Peptic ulcer disease                                       | 17 (3.4)           |
Connective tissue disease 8 (1.6)
AIDs 3 (0.6)

**Primary diagnosis**

Pneumonia 347 (70.0)
Sepsis 63 (12.7)
Meningitis 5 (1.0)
Other respiratory diseases 73 (14.7)
Other diagnoses 8 (1.6)

**Outcomes**

ICU admission 54 (11.0)
Length of stay (days), median (IQR) 8 (5 - 14)
Length of stay >7 days 275 (55.4)
In-hospital mortality 70 (14.1)
30-day in-hospital mortality 33 (6.7)

**Readmission for any pneumococcal infection**

Within 30 days from discharge date 1 (0.2)
Anytime during study period 6 (1.2)

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Table 2. Univariate and multinomial logistic regression analysis of demographic and clinical characteristics of hospitalised patients with invasive, non-invasive, and non-pneumococcal disease. Variables included in the final multivariable analysis were age group, gender, any pneumococcal vaccination, influenza vaccination, and Charlson’s score >3. IPD = invasive pneumococcal disease; RRR = adjusted relative risk ratio; CI = confidence interval; SD = standard deviation; PCV13 = 13-valent pneumococcal conjugate vaccination; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; IQR = inter-quartile range; ICU = intensive care unit.

| Characteristics                        | IPD (N= 92), N(%) | Non-IPD (N= 404), N(%) | Non-pneumococcal disease (N= 9181), N(%) | p value for trend |
|----------------------------------------|-------------------|-------------------------|------------------------------------------|-------------------|
| Age, mean (yrs) ± SD                   | 61.5 ± 16.3       | 70.8 ± 14.7             | 72.2 ± 16.1                              | <0.001            |
| Age group                              |                   |                         |                                          | <0.001            |
| <65yrs                                 | 50 (54.4)         | 120 (29.7)              | 2449 (26.7)                              |                   |
| Age Group     | PCV13  | PPSV23 | Any Pneumococcal Vaccination | Influenza Vaccination |
|---------------|--------|--------|------------------------------|-----------------------|
| 65-74yrs      | 1 (1.1)| 5 (1.2)| 1695 (18.5)                 | 1392 (15.2)           |
| 75-84yrs      | 2 (2.2)| 76 (18.8)| 5035 (54.8)            | 601 (6.6)             |
| ≥85yrs        | 3 (3.3)| 77 (19.1)| 6 (6.5)                | 69 (17.1)             |

| Co-morbidities | Charlson's score, median (IQR) | Charlson's score >3 | Myocardial infarction / Congestive heart failure | Cerebrovascular disease |
|----------------|--------------------------------|---------------------|-----------------------------------------------|-------------------------|
| 65-74yrs       | 1 (0 - 4)                      | 26 (28.3)           | 31 (33.7)                                   | 6 (6.5)                |
| 75-84yrs       | 2 (1 - 4)                      | 111 (27.5)          | 112 (27.7)                                 | 60 (14.9)              |
| ≥85yrs         | 3 (1 - 5)                      | 3753 (40.9)         | 2718 (29.6)                                | 1737 (18.9)            |

| Outcomes | ICU admission | Length of stay (days), median (IQR) |
|----------|---------------|------------------------------------|
| 65-74yrs | 19 (20.7)     | 9 (8 - 17)                         |
| 75-84yrs | 35 (8.7)      | 8 (5 - 14)                         |
| ≥85yrs   | 574 (6.3)     | 8 (5 - 13)                         |

**Notes:**
- PCV13: Pneumococcal vaccine type 13
- PPSV23: Pneumococcal polysaccharide vaccine type 23
- Any Pneumococcal Vaccination: Any pneumococcal vaccine received
- Influenza Vaccination: Any influenza vaccine received
- Charlson's score: A measure of comorbidity
- Myocardial infarction / Congestive heart failure: History of myocardial infarction or congestive heart failure
- Cerebrovascular disease: History of cerebrovascular disease
- Dementia: History of dementia
- Chronic pulmonary disease: History of chronic pulmonary disease
- Liver disease: History of liver disease
- Diabetes mellitus: History of diabetes mellitus
- Renal disease: History of renal disease
- Any malignancy: History of any malignancy
- Outcomes: ICU admission and length of stay

**Significance Levels:**
- <0.001: Highly significant
- <0.001: Highly significant
- 0.001: Significant
- 0.001: Significant
- 0.039: Marginally significant
- 0.667: Not significant
- <0.001: Highly significant
- 0.247: Not significant
- 0.003: Significant
- 0.202: Not significant
- 0.861: Not significant
- 0.492: Not significant
- 0.001: Significant
- 0.001: Significant
- 0.201: Not significant
- 0.001: Significant
- 0.003: Significant
Length of stay >7 days  
71 (77.2)  
204 (50.5)  
4918 (53.6)  
<0.001

In-hospital mortality  
24 (26.1)  
46 (11.4)  
836 (9.1)  
<0.001

30-day in-hospital mortality  
8 (8.7)  
25 (6.2)  
465 (5.1)  
0.096

Readmission for any pneumococcal infection

Anytime during study period  
0 (0.0)  
6 (1.5)  
16 (0.2)  
0.001

Within 30 days from discharge date  
0 (0.0)  
1 (0.25)  
2 (0.02)  
0.146

Table 3: Univariate and multiple logistic regression analysis of demographic and clinical factors associated with all-cause mortality among pneumococcal disease patients. Variables included in the final multivariable analysis were age group, gender, Charlson’s score >3, diagnosis of invasive pneumococcal disease, and intensive care unit admission. OR = odds ratio; CI = confidence interval; AOR = adjusted OR; SD = standard deviation; IQR = inter-quartile range; ICU = intensive care unit.

| Characteristics                          | Died (N= 70), N(%) | Survived (N= 426), N(%) | OR (95%CI) |
|------------------------------------------|--------------------|-------------------------|------------|
| Age, mean (yrs) ± SD                     | 74.4 ± 14.3        | 68.2 ± 15.4             |            |
| **Age group**                            |                    |                         |            |
| <65yrs                                    | 16 (22.9)          | 154 (36.2)              | Ref        |
| 65-74yrs                                  | 18 (25.7)          | 107 (25.1)              | 1.62 (0.79-3.32) |
| 75-84yrs                                  | 16 (22.9)          | 115 (27.0)              | 1.34 (0.64-2.79) |
| ≥85yrs                                    | 20 (28.6)          | 50 (11.7)               | 3.85 (1.85-8.00) |
| Gender = male                             | 45 (64.3)          | 280 (65.7)              | 0.94 (0.55-1.59) |
| **Ethnicity**                             |                    |                         |            |
| Chinese                                   | 51 (72.9)          | 308 (72.3)              | Ref        |
| Malay                                     | 9 (12.9)           | 52 (12.2)               | 1.05 (0.49-2.25) |
| Indian                                    | 7 (10.0)           | 32 (7.5)                | 1.32 (0.55-3.15) |
| Others                                    | 3 (4.3)            | 34 (8.0)                | 0.53 (0.16-1.80) |
| **Vaccination status (received ≥14 days prior to admission)** | | | |
| Any pneumococcal vaccination              | 7 (10.0)           | 73 (17.1)               | 0.54 (0.24-1.22) |
| Influenza vaccination in past 1 yr        | 8 (11.4)           | 67 (15.7)               | 0.69 (0.32-1.51) |
| **Co-morbidities**                        |                    |                         |            |
| Condition                              | Category 1 | Category 2 | p-value or Odds Ratio |
|----------------------------------------|------------|------------|-----------------------|
| Charlson's score, median (IQR)         | 1 (0-4)    | 2 (1-4)    |                       |
| Charlson's score >3                    | 30 (42.7)  | 107 (25.1) | 2.24 (1.33-3.77)      |
| Myocardial infarction / Congestive heart failure | 30 (42.9)  | 113 (26.5) | 2.08 (1.24-3.49)      |
| Cerebrovascular disease                | 17 (24.3)  | 49 (11.5)  | 2.47 (1.33-4.60)      |
| Dementia                               | 16 (22.9)  | 38 (8.9)   | 3.03 (1.58-5.79)      |
| Chronic pulmonary disease              | 16 (22.9)  | 133 (31.2) | 0.65 (0.36-1.18)      |
| Liver disease                          | 3 (4.3)    | 24 (5.6)   | 0.75 (0.22-2.56)      |
| Diabetes mellitus                      | 24 (34.3)  | 123 (28.9) | 1.29 (0.75-2.20)      |
| Renal disease                          | 16 (22.9)  | 77 (18.1)  | 1.34 (0.73-2.47)      |
| Any malignancy                         | 12 (17.1)  | 41 (9.6)   | 1.94 (0.97-3.91)      |
| Invasive pneumococcal disease          | 24 (34.3)  | 68 (16.0)  | 2.75 (1.57-4.80)      |
| **Outcomes**                           |            |            |                       |
| ICU admission                          | 31 (44.3)  | 23 (5.4)   | 13.93 (7.40-26.1)     |
| Length of stay (days), median (IQR)    | 7 (4 - 21) | 8 (6-15)   |                       |
| Length of stay >7 days                 | 33 (47.1)  | 242 (56.8) | 1.08 (0.90-1.29)      |