Burden of pneumococcal disease: 8-year retrospective analysis from a single centre in Hong Kong

MY Man *, HP Shum, Judianna SY Yu, Alan Wu, WW Yan

ABSTRACT

Purpose: *Streptococcus pneumoniae* is a common pathogen involved in community-acquired pneumonia. Invasive pneumococcal disease is often associated with higher co-morbidity rates, but mortality-related findings have been inconclusive. This study investigated predictors of 30-day mortality and invasive pneumococcal disease.

Methods: This retrospective analysis included adults with pneumococcal disease who were admitted to Pamela Youde Nethersole Eastern Hospital from 1 January 2011 to 31 December 2018. Demographics, microbiological characteristics, and outcomes were compared between 30-day survivors and non-survivors, and between patients with invasive disease and those with non-invasive disease. Intensive care unit (ICU) subgroup analysis was performed. The primary outcome was 30-day all-cause mortality; secondary outcomes were ICU and hospital mortalities, and ICU and hospital lengths of stay.

Results: In total, 792 patients had pneumococcal disease; 701 survived and 91 (11.5%) died within 30 days. Notably, 106 (13.4%) patients had invasive pneumococcal disease and 170 (21.5%) patients received intensive care. Vasopressor use (odds ratio [OR]=4.96, P<0.001), chronic kidney disease (OR=3.62, P<0.001), positive urinary antigen test results (OR=2.57, P=0.001), and advanced age (OR=2.19, P=0.010) were independent predictors for 30-day mortality by logistic regression analysis. Among critically ill patients, chronic kidney disease (OR=4.64, P<0.001), higher APACHE IV score (OR=3.73, P=0.016), and positive urinary antigen test results (OR=2.94, P=0.008) were predictors for 30-day mortality. Logistic regression analysis revealed that chronic kidney disease (OR=3.10, P<0.001) was a risk factor for invasive pneumococcal disease.

Conclusion: Advanced age, vasopressor use, chronic kidney disease, and positive urinary antigen test results were independent predictors for 30-day mortality in patients with pneumococcal disease.

Hong Kong Med J 2020;26:372–81
https://doi.org/10.12809/hkmj208373

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This article was published on 9 Jul 2020 at www.hkmj.org.

New knowledge added by this study

- This is one of the largest studies thus far regarding pneumococcal infection in Hong Kong; it also includes an analysis of critically ill patients.
- Invasive pneumococcal disease was associated with greater disease severity and higher rates of invasive organ support. Positive urinary pneumococcal antigen test results were associated with increased 30-day mortality rates in all patients, as well as patients in the intensive care unit.
- The 30-day mortality predictors of pneumococcal disease included vasopressor use, chronic kidney disease, positive urinary antigen test results, and advanced age.

Implications for clinical practice or policy

- Invasive pneumococcal disease is associated with more severe disease and higher mortality rates. Rapid identification and treatment can improve patient outcomes.
- Increasing use of the urinary antigen test was observed during the study period. A positive urinary antigen test result can serve as an independent predictor for 30-day mortality in all patients, as well as patients in the intensive care unit.

Introduction

Streptococcus pneumoniae causes a wide range of diseases that include middle ear infection, sinusitis, pneumonia, and meningitis. As one of the most common pathogens in community-acquired pneumonia (especially in Western countries),

S pneumoniae infection contributed to 1.6 million deaths in 2010 and 3.7 million severe pneumococcal infections worldwide in 2015.[1-3]

Streptococcus pneumoniae is a gram-positive encapsulated bacterium that colonises human nasopharynx and is mainly transmitted via respiratory droplets, which cause middle ear and respiratory tract infection. Thus far, more than 90 serotypes of *S pneumoniae* have been identified. *Streptococcus pneumoniae* infection can be stratified into invasive and non-invasive disease.[4,5] Invasive pneumococcal disease (IPD) is a notifiable disease in Hong Kong. In 2019, there were 187 cases; the incidence has remained similar over the past few years.[6] Worldwide, there is growing concern regarding drug-resistant *S pneumoniae* strains (eg, strains resistant to macrolide, penicillin, and/or fluoroquinolone). However, drug-resistant strains have not been associated with higher mortality rates.[7] The prevalence of drug-resistant *S pneumoniae* is lower in Southeast Asia than in Western countries.[1] Despite inconclusive evidence in the literature regarding its association with mortality, IPD is often associated with more severe disease and requires more invasive organ support.[8]

In this study, we aimed to identify the predictors for 30-day mortality in patients with *S pneumoniae* infection, as well as predictors for IPD. We also performed subgroup analysis of patients in the intensive care unit (ICU) and identified risk factors for 30-day mortality and IPD in those patients, as well as all patients with *S pneumoniae* infection.

肺炎鏈球菌：八年回顧研究

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目的：肺炎鏈球菌是引致社區肺炎最常見的病菌之一。有關入侵性肺炎鏈球菌的文獻甚多，但鮮有關於死亡率的研究。這項研究的目的在於找出30天死亡率及入侵性肺炎鏈球菌的誘因。

方法：這項回顧研究納入2011年1月1日至2018年12月31日在東區尤德夫人那打素醫院留醫的肺炎鏈球菌患者。本研究就30天存活者和死者的人口統計資料和微生物學特徵，以及肺炎鏈球菌患者與入侵性肺炎鏈球菌患者作出比較。

結果：研究期間，792名病人患有肺炎鏈球菌。701人存活，91人（11.5%）於30天內死亡。當中106人（13.4%）為入侵性肺炎鏈球菌患者，170人（21.5%）須接受危重治療。邏輯迴歸分析顯示使用血管加壓藥（比值比=4.96，P<0.001）、慢性腎病（比值比=3.62，P<0.001）、尿液肺炎鏈球菌快速抗原檢測呈陽性（比值比=2.57，P=0.001）及老年患者（比值比=2.19，P=0.010）是30天死亡率的獨立預測因子。在重症患者中，慢性腎病（比值比=4.64，P<0.001）、APACHE IV評分較高（比值比=3.73，P=0.016）和尿液肺炎鏈球菌快速抗原檢測呈陽性（比值比=2.94，P=0.008）是30天死亡率的獨立預測因子。邏輯迴歸分析顯示慢性腎病（比值比=3.10，P<0.001）是入侵性肺炎鏈球菌疾病的危險因素。

結論：老年患者、使用血管加壓藥、慢性腎病及尿液肺炎鏈球菌快速抗原檢測呈陽性均為肺炎鏈球菌患者在30天內死亡的最重要誘因。

Methods

Study design and data collection

This retrospective cohort study included adults who were admitted to Pamela Youde Nethersole Eastern Hospital, Hong Kong, with pneumococcal infection from 1 January 2011 to 31 December 2018. Patients who were aged <18 years or had incomplete data were excluded.

Patient medical records and data were extracted from clinical management systems and clinical information systems (IntelliVue Clinical Information Portfolio; Philips Medical, Amsterdam, The Netherlands). Baseline demographics, clinical characteristics, and microbiological data were identified. For patients in the ICU, disease severity was quantified using APACHE (Acute Physiology and Chronic Health Evaluation) IV scores. The use of invasive organ support was recorded, including continuous renal replacement therapy, inotropes, invasive mechanical ventilation, and extracorporeal membrane oxygenation. The primary outcome was 30-day all-cause mortality; secondary outcomes were ICU and hospital mortalities, ICU and hospital length of stay (LOS), and ICU ventilator days.

Definitions

Pneumococcal infection was determined by positive culture of *S pneumoniae*. Invasive pneumococcal disease was defined as the presence of *S pneumoniae* in sterile sites (eg, pleural fluid, cerebrospinal fluids, and blood).[4,8] Non-invasive pneumococcal disease was defined as the presence of *S pneumoniae* in non-sterile sites, or a positive urinary antigen test (UAT) result. Medical co-morbidities (eg, diabetes mellitus, chronic kidney disease, heart failure, and haematological malignancies) were coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification. Smokers were defined as those who had ever smoked. Advanced age was defined as age >65 years.

Microbiology

Antibiotic resistance was determined based on Clinical and Laboratory Standards Institute testing criteria for minimal inhibitory concentrations. Breakpoints adopted for determination of parenteral penicillin resistance in non-meningitis *S pneumoniae* isolates were susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistance, ≥8 μg/mL.[9] Breakpoints adopted for determination of parenteral penicillin resistance in meningitis *S pneumoniae* isolates were susceptible, ≤0.06 μg/mL and resistance,

≥0.12 μg/mL; breakpoints adopted for determination of levofloxacin resistance in *S pneumoniae* were susceptible, ≤2 μg/mL; intermediate, 4 μg/mL; and resistance, ≥8 μg/mL.[9]

Urinary antigen test (Alere 710-012 BinaxNOW *Streptococcus*) results were evaluated in accordance with the manufacturer's instructions.

Statistical analysis

Characteristics and clinical parameters were compared between patients with IPD and those with non-invasive pneumococcal disease, as well as between 30-day survivors and non-survivors. Results were expressed as median (interquartile range) or as numbers (percentages) of cases, as appropriate. For univariate analysis, categorical variables were compared by Pearson Chi squared tests or Fisher's exact test, as appropriate; continuous variables were compared by using the Mann-Whitney *U* test. Variables with P<0.2 in univariate analysis or with known clinical significance from previous studies were entered into multivariate analysis. Independent predictors for 30-day mortality and independent predictors for IPD were assessed by logistic regression analysis.[8,10-12] Subgroup analysis was performed regarding IPD and disease severity among patients in the ICU. Hosmer-Lemeshow test was performed for goodness-of-fit for logistic regression models. Kaplan-Meier survival plots were used to compare cumulative survival between patients with IPD and those with non-invasive pneumococcal disease. SPSS (Mac version 24.0; IBM Corp, Armonk [NY], United States) was used for all statistical analyses.

Results

Patient demographic and clinical characteristics, including co-morbidities and use of invasive organ support, are shown in Table 1. In total, 792 patients with pneumococcal disease were identified during the 8-year study period. The median age was 73 years; patients were predominantly men. Most patients exhibited respiratory tract infection (96.1%) and approximately one quarter of patients had asthma/chronic obstructive pulmonary disease (24.4%). In total, 170 patients received intensive care and 14.1% required invasive mechanical ventilation; 28% required vasopressor use. Invasive pneumococcal disease was present in 13.4% of the patients. The overall hospital mortality rate was 11.2%, while the mortality rate among patients in the ICU was 22.9%.

Invasive pneumococcal disease was associated with a higher 30-day mortality rate (28.6% vs 11.4%, P<0.001); a positive UAT result was also associated with a higher 30-day mortality rate (36.3% vs 12.7%, P<0.001). Logistic regression analysis identified statistically significant predictors for 30-day mortality, which are shown in Table 1. Patients with vasopressor use (odds ratio [OR]=4.96, P<0.001), chronic kidney disease (OR=3.62, P<0.001), a positive UAT result (OR=2.57, P=0.001), and older age (OR=2.19, P=0.010) exhibited comparatively higher 30-day mortality rates; however, asthma/chronic obstructive pulmonary disease was not an independent predictor for mortality in logistic regression analysis. The Figure depicts the results of Kaplan-Meier survival analysis comparing patients with IPD and those with non-invasive pneumococcal disease.

Table 2 shows the characteristics of patients with IPD and those with non-invasive pneumococcal disease. More patients with asthma/chronic obstructive pulmonary disease exhibited non-invasive pneumococcal disease (26.5% vs 10.4%, P<0.001). Invasive pneumococcal disease was more likely to be associated with renal failure (27.4% vs 9.6%, P<0.001) and haematological malignancy (5.7% vs 1.7%, P=0.012). Additionally, IPD was associated with higher rates of ICU admission (33.0% vs 19.7%, P=0.002), renal replacement therapy (16.0% vs 4.8%, P<0.001), and vasopressor use (93.4% vs 17.9%, P<0.001). Patients with IPD had a higher 30-day mortality rate (24.5% vs 9.5%, P<0.001) and longer hospital LOS (8 vs 4 days, P<0.001). Independent risk factors for IPD by logistic regression analysis are shown in Table 2, along with their ORs. Notably, chronic kidney disease (OR=3.10, P<0.001) was the sole independent predictor for IPD.

The results of ICU subgroup analysis are shown in Table 3. Respiratory tract infection constituted 93.5% of all *S pneumoniae* infections. The rate of IPD was 20.6% among patients in the ICU with *S pneumoniae* infection, which was higher than the rate among all patients with *S pneumoniae* infection. Further analysis revealed that IPD was associated with higher rates of complications and invasive organ support; in particular, more patients with IPD required renal replacement therapy (48.6% vs 24.4%, P=0.005) and vasopressor use (100% vs 88.9%, P=0.039). Additionally, more patients with IPD tended to exhibit pleural effusion/empyema, although this difference was not statistically significant. Patients who required invasive mechanical ventilation (76.0% vs 57.5%, P=0.023), extracorporeal membrane oxygenation (14.0% vs 5.0%, P=0.044), renal replacement therapy (48.0% vs 21.7%, P=0.001), and vasopressor use (98.0% vs 88.3%, P=0.043) exhibited significantly higher 30-day mortality rates. Logistic regression analysis showed that chronic kidney disease (OR=4.64, P<0.001), higher APACHE IV score (OR=3.73, P=0.016), and a positive UAT result (OR=2.94, P=0.008) were independent predictors for 30-day mortality among patients in the ICU who had IPD (Table 3).

TABLE 1. Clinical predictors of 30-day mortality in patients with pneumococcal disease*

Characteristics	Total (n=792)	30-Day non-survivors (n=91)	30-Day survivors (n=701)	P value	Odds ratio (95% CI)
Age (years)	73 (61-81)	79 (68-85)	72 (61-81)	<0.001	
Advanced age (>65 years)	554 (69.9%)	72 (79.1%)	482 (68.8%)	0.043	2.19 (1.21-3.99)†
Sex				0.849	
Male	581 (73.4%)	66 (72.5%)	515 (73.5%)		
Female	211 (26.6%)	25 (27.5%)	186 (26.5%)		
Ever smoker	200 (25.3%)	9 (9.9%)	191 (27.2%)	<0.001	
Sources of admission				0.318	
AED	734 (92.7%)	82 (90.1%)	652 (93.0%)		
Clinical/transfers	58 (7.3%)	9 (9.9%)	49 (7.0%)		
Sources of infection				0.409	
CNS	3 (0.4%)	1 (1.1%)	2 (0.3%)		
MSK	2 (0.3%)	0	2 (0.3%)		
Respiratory	761 (96.1%)	86 (94.5%)	675 (96.3%)		
Septicaemia	10 (1.3%)	1 (1.1%)	9 (1.3%)		
Skin	5 (0.6%)	0	5 (0.7%)		
Others	11 (1.4%)	3 (3.3%)	8 (1.1%)		
Co-morbidities					
Heart failure	31 (3.9%)	8 (8.8%)	23 (3.3%)	0.011	
Asthma/COPD	193 (24.4%)	8 (8.8%)	185 (26.4%)	<0.001	
Chronic kidney disease	95 (12.0%)	40 (44.0%)	55 (7.8%)	<0.001	3.62 (2.04-6.42)†
Cirrhosis	10 (1.3%)	0	10 (1.4%)	0.615	
Haematological malignancy	18 (2.3%)	4 (4.4%)	14 (2.0%)	0.142	
Metastatic cancer	2 (0.3%)	0	2 (0.3%)	1.000	
Chemotherapy	68 (8.6%)	6 (6.6%)	62 (8.8%)	0.471	
Diabetes mellitus	131 (16.5%)	14 (15.4%)	117 (16.7%)	0.752	
Immunocompromised status	9 (1.1%)	2 (2.2%)	7 (1.0%)	0.277	
Complications and invasive organ support					
Intensive care	170 (21.5%)	50 (54.9%)	120 (17.1%)	<0.001	
Pleural effusion/empyema	40 (5.1%)	6 (6.6%)	34 (4.9%)	0.475	
Invasive mechanical ventilation	112 (14.1%)	40 (44.0%)	72 (10.3%)	<0.001	
ECMO	13 (1.6%)	7 (7.7%)	6 (0.9%)	<0.001	
Viral co-infection	22 (2.8%)	2 (2.2%)	20 (2.9%)	1.000	
RRT	50 (6.3%)	24 (26.4%)	26 (3.7%)	<0.001	
Vasopressor use/septic shock	222 (28.0%)	65 (71.4%)	157 (22.4%)	<0.001	4.96 (2.86-8.60)†
Microbiology					
Invasive pneumococcal disease	106 (13.4%)	26 (28.6%)	80 (11.4%)	<0.001	
Positive UAT	122 (15.4%)	33 (36.3%)	89 (12.7%)	<0.001	2.57 (1.49-4.43)†
Outcomes					
Hospital LOS (days)	5 (2-11)	5 (2-14)	5 (3-10)	0.873	
Hospital mortality	89 (11.2%)	80 (87.9%)	9 (1.3%)	<0.001	

Abbreviations: 95% CI = 95% confidence interval; AED = accident and emergency department; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; LOS = length of stay; MSK = musculoskeletal; RRT = renal replacement therapy defined as intermittent and continuous replacement; vasopressor = dopamine, adrenaline, or noradrenaline; UAT = urinary antigen test

* Data are shown as median (IQR) or No. (%), unless otherwise specified. Hosmer-Lemeshow goodness-of-fit test was performed for logistic regression analysis (χ^2=6.433; degrees of freedom=7; P=0.490)

† P<0.05 in logistic regression analysis

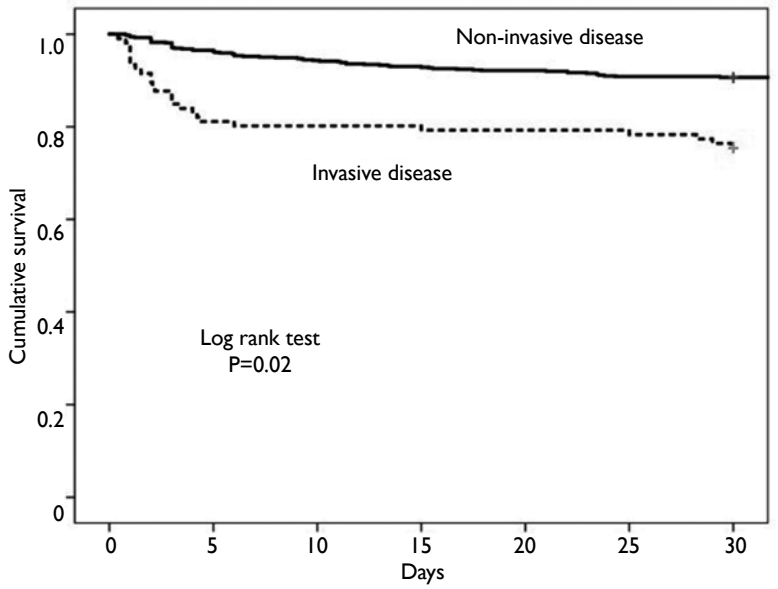

FIG. Kaplan-Meier survival plot of invasive pneumococcal disease

Discussion

Medical co-morbidity and mortality

The overall mortality rate was 28.6% for patients with IPD and 11.4% for patients without IPD. The case fatality rate in our cohort was higher than that in a previous cohort from the Netherlands, but similar to the rate in a previous study from Korea.[5,13] A higher number of co-morbid diseases, worse immune function, impaired mucociliary clearance, and older age are associated with a higher risk of mortality in patients with pneumococcal infection.[4]

Chronic conditions such as chronic lung disease, heart failure, and diabetes, as well as smoking status, were previously shown to be associated with pneumococcal disease and IPD.[10,11] Consistent with the results of prior studies, we found that patients with heart failure (8.8% vs 3.3%, P=0.011) and haematological malignancies (5.7% vs 1.7%, P=0.012) exhibited significantly higher 30-day mortality rates in univariate analysis. Surprisingly, we found a negative association between chronic lung disease and mortality. In post-hoc analysis, we found that patients with chronic lung disease (ie, asthma/chronic obstructive pulmonary disease) also had a lower rate of invasive organ support (15.0% vs 32.7%, P<0.001). This group of patients may be under constant medical surveillance; thus, they may seek medical attention and receive antibiotics earlier than patients without chronic lung disease. Importantly, we did not examine the management and status of underlying lung conditions, which may have affected mortality in these patients.

Pneumococcal urinary antigen test

In our cohort, 122 patients were diagnosed with pneumococcal infection by using the UAT. In our hospital, the first patient was diagnosed by using the UAT in 2015. Use of the UAT in diagnosing community-acquired pneumonia has since increased; thus, in 2018, 71 of 146 patients (48.6%) were diagnosed by using the UAT. A positive UAT result was a consistent independent predictor for 30-day mortality among patients in the ICU, as well as among all patients. Post-hoc analysis showed that a positive UAT result was significantly associated with ICU admission (34.7% vs 10.1%, P<0.001). However, it was not significantly associated with ICU LOS (6.16 vs 8.43 days, P=0.515) or hospital LOS (21.46 vs 29.78 days, P=0.415).

The pneumococcal UAT assay detects the C-polysaccharide antigen of *S pneumoniae*, which is present in all serotypes, from urine samples.[14] Fluorescence immunoassay and immunochromatographic test methods provide similar results in terms of diagnosing pneumococcal disease.[15] While the UAT result remains positive for up to 3 days after initiation of antibiotic treatment, the UAT increases the diagnostic yield of pneumococcal disease relative to the yield of sputum culture of *S pneumoniae*; notably, the yield of such sputum cultures markedly decreases after initiation of antibiotic treatment.[16] This test provides a rapid and simple method for diagnosis of patients with suspected *S pneumoniae* infection; it is particularly helpful in the diagnosis of patients who cannot produce sputum for cultures. The test sensitivity and specificity were approximately 60% and 99%, respectively.[16] Because of the high test specificity, the UAT helps to reduce the costs of further diagnostic tests and aids in selection of empirical antibiotic treatment. It is recommended in the Infectious Diseases Society of America/American Thoracic Society guidelines for aiding the rapid identification of pneumococcal disease in adults.[17] Urinary antigen tests were also found to predict the severity and outcomes of pneumonia. A Korean group found that patients with positive UAT results exhibited greater severity of disease; however, the test results were associated with rates of ICU admission and mortality.[14]

Counterindications for the UAT include recent pneumococcal disease within 3 months; moreover, it may cross-react with antigens from other streptococcal bacteria.[16,18] Patients with acute kidney injury due to sepsis, as well as those with oliguria or anuria of various aetiologies may not be able to provide urine samples for use in the UAT.

TABLE 2. Clinical characteristics of patients with invasive and non-invasive pneumococcal disease*

Characteristics	Total (n=792)	Invasive (n=106)	Non-invasive (n=686)	P value	Odds ratio (95% CI)
Age (years)	73 (61-81)	72.5 (61-81)	73 (61-81)	0.678	
Advanced age (>65 years)	554 (69.9%)	69 (65.1%)	485 (70.7%)	0.241	
Sex				0.021	
Male	581 (73.4%)	68 (64.2%)	513 (74.8%)		
Female	211 (26.6%)	38 (35.8%)	173 (25.2%)		
Ever smoker	200 (25.3%)	11 (10.4%)	189 (27.6%)	<0.001	0.35 (0.18-0.67)†
Sources of infection				<0.001	
CNS	3 (0.4%)	3 (2.8%)	0		
MSK	2 (0.3%)	2 (1.9%)	0		
Respiratory	761 (96.1%)	86 (81.1%)	675 (98.4%)		
Septicaemia	10 (1.3%)	10 (9.4%)	0		
Skin	5 (0.6%)	2 (1.9%)	3 (0.4%)		
Others	11 (1.4%)	3 (2.8%)	8 (1.2%)		
Co-morbidities					
Heart failure	31 (3.9%)	4 (3.8%)	27 (3.9%)	1.000	
Asthma/COPD	193 (24.4%)	11 (10.4%)	182 (26.5%)	<0.001	
Chronic kidney disease	95 (12.0%)	29 (27.4%)	66 (9.6%)	<0.001	3.10 (1.88-5.13)†
Hepatic failure/cirrhosis	10 (1.3%)	0	10 (1.5%)	0.374	
Haematological malignancy	18 (2.3%)	6 (5.7%)	12 (1.7%)	0.012	
Metastatic cancer	2 (0.3%)	0	2 (0.3%)	1.000	
Chemotherapy	68 (8.6%)	9 (8.5%)	59 (8.6%)	0.97	
Diabetes mellitus	131 (16.5%)	14 (13.2%)	117 (17.1%)	0.321	
Immunocompromised status	9 (1.1%)	2 (1.9%)	7 (1.0%)	0.344	
Complications and invasive organ support					
Intensive care	170 (21.5%)	35 (33.0%)	135 (19.7%)	0.002	
Pleural effusion/empyema	40 (5.1%)	9 (8.5%)	31 (4.5%)	0.082	
Invasive mechanical ventilation	112 (14.1%)	26 (24.5%)	86 (12.5%)	0.001	
ECMO	13 (1.6%)	10 (9.4%)	3 (0.4%)	0.399	
Viral co-infection	22 (2.8%)	1 (0.9%)	21 (3.1%)	0.217	
RRT	50 (6.3%)	17 (16.0%)	33 (4.8%)	<0.001	
Vasopressor use/septic shock	222 (28.0%)	99 (93.4%)	123 (17.9%)	<0.001	
Outcomes					
30-Day mortality	91 (11.5%)	26 (24.5%)	65 (9.5%)	<0.001	
Hospital LOS (days)	5 (2-11)	8 (4-18)	4 (2-9)	<0.001	
Hospital mortality	89 (11.2%)	26 (24.5%)	63 (9.2%)	<0.001	

Abbreviations: 95% CI = 95% confidence interval; CNS = central nervous system; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; IQR = interquartile range; LOS = length of stay; MSK = musculoskeletal; RRT = renal replacement therapy defined as intermittent and continuous replacement; vasopressor = dopamine, adrenaline, or noradrenaline

* Data are shown as median (IQR) or No. (%), unless otherwise specified

† P<0.05 in logistic regression analysis

TABLE 3. Clinical predictors for 30-day mortality in the intensive care unit subgroup*

Characteristics	Total (n=170)	30-Day deaths (n=50)	30-Day survivors (n=120)	P value	Odds ratio (95% CI)
Age (years)	68 (59-78)	75.5 (63-80)	67 (59-78)	0.015	
Advanced age (>65 years)	107 (62.9%)	36 (72.0%)	71 (59.2%)	0.114	
Sex				0.949	
Male	115 (67.6%)	34 (68.0%)	81 (67.5%)		
Female	55 (32.4%)	16 (32.0%)	39 (32.5%)		
Ever smoker	24 (14.1%)	4 (8.0%)	20 (16.7%)	0.156	
Sources of infection				0.819	
CNS	3 (1.8%)	1 (2.0%)	2 (1.7%)		
Respiratory	159 (93.5%)	47 (94%)	112 (93.3%)		
Septicaemia	1 (0.6%)	0	1 (0.8%)		
Skin	2 (1.2%)	0	2 (1.7%)		
Others	5 (2.9%)	2 (4.0%)	3 (2.5%)		
Co-morbidities					
Heart failure	7 (4.1%)	2 (4.0%)	5 (4.2%)	1.000	
Asthma/COPD	23 (13.5%)	3 (6.0%)	20 (16.7%)	0.084	
Chronic kidney disease	71 (41.8%)	35 (70.0%)	36 (30.0%)	<0.001	4.64 (2.09-10.32)†
Cirrhosis	3 (1.8%)	0	3 (2.5%)	0.556	
Haematological malignancy	10 (5.9%)	4 (8.0%)	6 (5.0%)	0.482	
Metastatic cancer	2 (1.2%)	0	2 (1.7%)	1.000	
Chemotherapy	14 (8.2%)	3 (6.0%)	11 (9.2%)	0.760	
Diabetes mellitus	39 (22.9%)	9 (18.0%)	30 (25.0%)	0.323	
Immunocompromised status	9 (5.3%)	2 (4.0%)	7 (5.8%)	1.000	
Complications and invasive organ support					
Intensive care	35 (20.6%)	12 (24.0%)	23 (19.2%)	0.478	
Pleural effusion/empyema	16 (9.4%)	5 (10.0%)	11 (9.2%)	1.000	
Invasive mechanical ventilation	107 (62.9%)	38 (76.0%)	69 (57.5%)	0.023	
ECMO	13 (7.6%)	7 (14.0%)	6 (5.0%)	0.044	
RRT	50 (29.4%)	24 (48.0%)	26 (21.7%)	0.001	
Vasopressor use/septic shock	155 (91.2%)	49 (98.0%)	106 (88.3%)	0.043	
APACHE IV score	91 (63.75-117.5)	112.00 (95.00-144.50)	81.00 (59.00-98.75)	<0.001	3.73 (1.27-10.90)†
Microbiology					
Invasive pneumococcal disease	35 (20.6%)	12 (24.0%)	23 (19.2%)	0.478	
Viral co-infection	8 (4.7%)	1 (2.0%)	7 (5.8%)	0.439	
Positive UAT	56 (32.9%)	22 (44.0%)	34 (28.3%)	0.048	2.94 (1.32-6.55)†
Outcomes					
Hospital LOS (days)	14.5 (7-29)	10.00 (3.00-18.00)	16.50 (9.25-35.75)	<0.001	
Hospital mortality	53 (31.2%)	48 (96.0%)	5 (4.2%)	<0.001	
ICU LOS (days)	4.05 (1.89-9.36)	3.75 (1.58-8.27)	4.07 (1.90-9.56)	0.394	

Abbreviations: 95% CI = 95% confidence interval; APACHE IV = Acute Physiology and Chronic Health Evaluation (APACHE IV); CNS = central nervous system; COPD = chronic obstructive pulmonary disease; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay; RRT = renal replacement therapy, defined as intermittent and continuous replacement; vasopressor = dopamine, adrenaline, or noradrenaline

* Data are shown as median (IQR) or No. (%), unless otherwise specified. Hosmer-Lemeshow goodness-of-fit test was performed for logistic regression analysis (χ^2=2.324; degrees of freedom=5; P=0.803)

† P<0.05 in logistic regression analysis

Invasive pneumococcal disease

In our cohort, IPD was associated with a higher 30-day mortality rate; however, this association did not remain statistically significant in logistic regression analysis. Consistent with the results of previous studies,[8,12] we found that patients with IPD exhibited more severe disease and worse outcomes. Moreover, IPD was associated with higher rates of ICU admission, invasive organ support (ie, vasopressor use), and renal replacement therapy, as well as longer hospital LOS. The findings might be explained by the higher bacterial load in patients with IPD, which may lead to worse outcomes.

Similar to the study by Ceccato et al,[8] we did not identify a positive relationship between smoking and IPD. Thus far, results regarding the relationship of smoking with IPD have been inconsistent; the association varies according to local smoking prevalence.[11] With the implementation of effective smoking cessation programmes and corresponding legislation in Hong Kong, approximately 10% of individuals >15 years of age report daily cigarette consumption; this is markedly lower than the rates in other countries.[19,20] In our study, smoking status information was extracted from patient records stored in the Hospital Authority Clinical Management System and nursing notes; thus, we may have underestimated the number of smokers in this cohort. Other important aspects of smoking (eg, number of pack-years and passive smoking) were not available for inclusion in this analysis.

Chronic kidney disease has been consistently associated with IPD. A large retrospective observational cohort of 36 million adults revealed a risk ratio of 21.67 for development of IPD among patients with chronic kidney disease.[21] A Japanese registry showed that the relative risk for IPD among patients with chronic kidney disease ranged from 12.4 to 51.3.[10] Notably, chronic kidney disease was consistently one of the most important predictors for 30-day mortality among all patients (OR=3.62, P<0.001) and among patients in the ICU (OR=4.64, P<0.001).

Intensive care subgroup

Patients with IPD tended to experience a higher rate of complications and require higher rates of invasive organ support. In particular, patients with IPD more frequently exhibited pleural effusion/empyema; they also more frequently required invasive mechanical ventilation, extracorporeal membrane oxygenation, renal replacement therapy, and vasopressor use. Our sample size may not have been sufficiently powered to demonstrate statistically significant results regarding the ICU subgroup; thus, future studies focused specifically on patients in the ICU may be needed. Other aspects of IPD and use of rescue therapies for acute respiratory distress syndrome (eg, prone ventilation, muscle paralytic agents, and inhaled nitrogen oxide) should be investigated in the future.

Drug non-susceptible *Streptococcus pneumoniae* and viral co-infection

Penicillin non-susceptible *S pneumoniae* was not common in the present study; it was only observed in 2.4% of patients. Non-susceptibility to levofloxacin was observed in 0.9% of patients. Drug non-susceptible *S pneumoniae* were not significantly associated with 30-day mortality (penicillin non-susceptible *S pneumoniae* was present in two non-survivors and 14 survivors, P=0.641; levofloxacin non-susceptible *S pneumoniae* was present in zero non-survivors and six survivors, P=1.000). However, these results should be carefully interpreted, because of the small number of drug non-susceptible *S pneumoniae* in our cohort. According to a recent study in Hong Kong, the penicillin resistance rate was approximately 7% and the levofloxacin resistance rate was 0%.[22]

Viral-bacterial interactions have been described with respect to pneumococcal disease.[23] An epidemiological study regarding the 2009 H1N1 influenza pandemic period showed a significant increase in the number of pneumococcal pneumonia hospitalisations.[24] However, viral co-infection was not associated with IPD or mortality in our findings. Notably, an age-specific interaction was described between influenza and IPD; specifically, patients aged 5 to 19 years were significantly more frequently affected, compared with other age-groups.[24,25]

Strengths and limitations

Thus far, this is the first and largest study regarding pneumococcal disease in adults in Hong Kong; it provides clinical and outcome data in both general ward and intensive care subgroups to allow a comprehensive overview of pneumococcal disease in the locality. It is a standard practice in our centre to check urinary antigens and perform blood cultures for nearly all patients with suspected pneumonia to facilitate accurate diagnosis and avoid missed diagnoses. By including data regarding invasive organ support and ICU admission, we were able to identify and describe complications of pneumococcal disease and determine the broader clinical characteristics of affected patients.

However, because of changes in vaccination programmes, the influenza and pneumococcal vaccination statuses were not available for analysis in the current study. Because of the limited number of patients with drug non-susceptible *S pneumoniae* in the present cohort, further robust analyses regarding antibiotic sensitivity patterns and appropriateness of antimicrobial treatment could

not be performed. Furthermore, capsular serotypes of *S pneumoniae* among patients in our cohort were not available for analysis. Future studies focused on capsular subtypes of *S pneumoniae* will facilitate understanding of pneumococcal disease. Because this was a retrospective study, it was subject to potential confounding factors. Finally, the results of this single-centre study may not be generalisable to other countries with higher prevalences of drug non-susceptible *S pneumoniae* infection.

Conclusion

Pneumococcal disease is associated with high rates of morbidity and mortality. In this cohort, vasopressor use, chronic kidney disease, advanced age, and positive UAT results were predictors for 30-day mortality.

Author contributions

Concept or design: MY Man, HP Shum.
Acquisition of data: MY Man, HP Shum.
Analysis or interpretation of data: MY Man, HP Shum.
Drafting of the manuscript: MY Man, A Wu.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Declaration

The abstract of this study was accepted as an oral presentation at the Annual Scientific Meeting of the Hong Kong Society of Critical Care Medicine on 8 December 2019.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

This study was approval by the Hospital Authority Hong Kong East Cluster Research Ethics Committee (Ref HKECREC-2019-065). The requirement for written informed consent was waived.

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