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ORIGINAL ARTICLE

Mortality and costs of pneumococcal pneumonia in adults: a cross-sectional study

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ABSTRACT

Objective: Pneumococcal pneumonia is a significant cause of morbidity and mortality among adults. The study's main aim was to evaluate the in-hospital mortality and related costs of community-acquired pneumococcal pneumonia in adults. **Methods:** This cross-sectional study used medical records of adult patients with pneumococcal pneumonia hospitalized in a university hospital in Brazil from October 2009 to April 2017. All patients aged ≥ 18 years diagnosed with pneumococcal pneumonia were included. Risk factors, intensive care unit admission, length of hospital stay, in-hospital mortality, and direct and indirect costs were analyzed. **Results:** In total, 186 patients were selected. The mean in-hospital mortality rate was 18% for adults aged < 65 years and 23% for the elderly (≥ 65 years). Bacteremic pneumococcal pneumonia affected 20% of patients in both groups, mainly through chronic respiratory disease (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01). Over 7 years, annual total direct and indirect costs were USD 28,188 for adults < 65 years (USD 1,746 per capita) and USD 16,350 for the elderly (USD 2,119 per capita). **Conclusion:** Pneumococcal pneumonia remains an important cause of morbidity and mortality among adults, significantly affecting direct and indirect costs. These results suggest the need for prevention strategies for all adults, especially for patients with chronic respiratory diseases.

Keywords: Pneumococcus; Pneumococcal disease; Pneumonia; Hospital costs; Mortality.

INTRODUCTION

Pneumococcal infection is a significant cause of morbidity and mortality worldwide. *Streptococcus pneumoniae*, or pneumococcus, is the main etiologic agent of community-acquired pneumonia (CAP) in children and adults.[1,2] Elderly people, patients with chronic conditions (chronic obstructive pulmonary disease, bronchial asthma, chronic cardiovascular disease, cerebrovascular disease, chronic renal disease, chronic liver disease, or diabetes mellitus), and immunosuppressed persons are at risk for pneumococcal pneumonia (PP) and bacteremic pneumococcal pneumonia (BPP).[3-7]

Ruiz et al. carried out a study published in 2017 comparing adults aged 18–64 years and elderly people (aged ≥ 65 years) who were diagnosed with PP. The authors found that patients aged ≥ 65 years had a higher 30-day mortality rate; however, elderly patients were less frequently admitted to intensive care units (ICUs) and had shorter hospital stays.[8] Epidemiological data from Europe revealed 21,118 confirmed cases of pneumococcal disease in 2015, with a mortality rate of 14% (1,312 patients) and hospital costs for PP and BPP of approximately 13,611 euros (EUR) per hospitalized patient.[9]

Hospitalizations of patients aged over 50 years have a greater economic impact, compared with hospitalizations of individuals aged 18 years or younger (average cost per episode of EUR 5,000 vs. EUR 2,750, respectively).[10,11] These rates of mortality and costs are higher in developing countries, and published data on PP in adults and its impact on health systems in these contexts are scarce.[11] The present study adds to the literature on the in-hospital mortality from PP and related direct and indirect costs, comparing elderly and younger adult patients in a university hospital in Brazil.

METHODS

Study design and population

This cross-sectional study used the medical records of adult patients diagnosed with PP hospitalized at the Hospital Geral de Caxias do Sul, Brazil. The study period spanned from October 2009 to April 2017, and all patients aged ≥ 18 years diagnosed with PP or BPP were enrolled. Ethical approval for analysis of the hospital records was obtained from the University of Caxias do Sul Research Ethics Committee (2.360.724).

Clinical and microbiological diagnosis of PP and BPP

CAP was diagnosed based on radiographic findings (new infiltrates compatible with a diagnosis of pneumonia on chest x-ray, tomography, or magnetic resonance imaging) and clinical findings (acute-onset clinical symptoms suggestive of a lower respiratory tract infection, such as cough, sputum production, fever, pleural chest pain, or dyspnea).

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Microscopy and phenotypic tests were used to identify *Streptococcus pneumoniae*.[12] PP was defined as at least one positive result for *S. pneumoniae* in sputum, tracheal bronchial aspirate, and/or bronchoalveolar lavage (BAL) associated with clinical and radiographic features of CAP. Sputum specimens with < 10 squamous epithelial cells, > 25 polymorphonuclear cells per low-power field (magnification, ×100) and predominant presence of Gram-positive diplococci were considered of sufficient quality for diagnosis. Semi-quantitative cultures of > 10^5 colony/mL for tracheal aspiration specimens and > 10^4 colony/mL for BAL samples were considered significant for PP. BPP was diagnosed based on isolating *S. pneumoniae* from blood cultures obtained before the parenteral administration of antibiotics in a patient with CAP.

Variables analyzed and covariates

The impact of mortality associated with PP among adults (aged < 65 years and aged ≥ 65 years) was evaluated by demographic (gender, age, occupation, and income) and clinical characteristics. Dependent patients were those who reported not having their own source of income (unemployed patients, students, and people living with relatives); low-income patients were those who declared monthly earnings of USD 1,190 or less; average-income patients were those who earned up to USD 2,975 monthly; and high-income patients were those who reported more than USD 2,975 in monthly income).[13] The following clinical covariates were analyzed: diagnosis of bacteremic and non-bacteremic pneumonia, admission and length of hospitalization for treatment in the ICU, total length of hospital stay, and related deaths, as well as the comorbidities of chronic cardiovascular disease (ischemic heart disease, coronary disease, heart failure, arrhythmia), chronic respiratory disease (chronic obstructive pulmonary disease, bronchial asthma), chronic liver disease (cirrhosis, chronic viral hepatitis), renal failure (acute kidney injury, chronic kidney disease), chronic neurological disease (stroke, dementia), immunosuppression (change in immunity caused by medication or disease other than acquired immunodeficiency syndrome), diabetes mellitus, smoking, human immunodeficiency virus (HIV, living with acquired immunodeficiency syndrome virus and CD4 ≤ 200 cells/mm^3) and alcohol abuse (daily alcohol intake of 80 g for men or 60 g for women, during at least the 12 months prior to inclusion in the study).[1,4,5]

Direct and indirect cost analysis

The cost per hospital stay was analyzed as the direct cost to the Brazilian Health System, defined by the length of hospital stay, medicines, laboratory and imaging exams, surgical procedures and bronchoscopy, daily ICU cost, medical costs, and other health care costs. Indirect costs were the patient's and/or caregiver's costs associated with absence from work and the related impact. The total cost was defined as follows: total cost = direct costs + indirect costs.[14]

Data on the direct per-patient cost of hospitalization were provided by the hospital's financial sector and were adjusted for the 2017 payment rate. Indirect costs were calculated considering the costs of the patient's and/or caregiver's productivity loss, multiplying the number of days by the average job salary, according to each profession declared at hospital admission. Dependent patients had a primary caregiver, with a longer follow-up period in the hospital, whose hours of work-related absence were considered in the indirect cost analysis. The mean national salary rate was obtained from the General Register of Employees and Unemployment of the Brazilian Ministry of Labor and Employment.[15] The amounts in Brazilian real (BRL) were converted into US dollars (USD) at the rate of 1 USD = BRL 3.18.

Statistical analysis

Statistical analyses were performed on the demographic and clinical variables, and the results are presented as frequencies and percentages, means and standard deviations, or medians and interquartile ranges. Patient characteristics were compared between the two groups (younger adults vs. elderly patients), as were variables related to PP, comorbidities, length of hospital stay, ICU admission, and outcomes. The Kaplan–Meier method was used to determine associations between age groups and survival. Chi-square tests or Fisher's exact tests were used for the comparison of qualitative variables, and Student's *t*-test was used for quantitative variables. Multivariate analyses are reported as odds ratios (ORs) and 95% confidence intervals (CIs), with the younger patients (age < 65 years) as the reference group. The statistical model was estimated using logistic regression with the backward Wald method. The final models were created to predict in-hospital death and pneumococcal bacteremia assessing the general performance of the models, that is, the variation in the predicted outcome explained by the model independent variables, using Cox and Snell R-squared values (adjusted R^2). *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using R software, version 3.3.3 for Windows.

RESULTS

In total, 186 patients with PP or BPP criteria were included in the study, and none had previously been vaccinated with any pneumococcal vaccine. Of these patients, 127 were adults aged 18 to 64 years, and 59 were elderly people aged 65 years or older. The mean age for adults aged < 65 years was 46 ± 11.5 years, and the mean age for the elderly group was 70 ± 4.8 years. Most elderly patients were dependent or low-income. Table 1 summarizes all patients' baseline characteristics, stratified by age.

Table 1. Characteristics of patients with pneumococcal pneumonia.

Characteristic	Age < 65 years (n = 127)	Age ≥ 65 years (n = 59)	*P* value
Male, n (%)	78 (62.4)	40 (67.8)	0.40
Age (in years), mean (SD)	46 (36-55)	70 (67-72)	0.001
Average income, n (%)			
Dependent	38 (30)	17 (29)	0.30
Low	80 (63)	42 (71)	
Average	9 (7)	0 (0)	
High	0 (0)	0 (0)	
Pneumonia, n (%)			
Pneumococcal pneumonia	102 (80)	48 (81)	0.86
Bacteremic pneumococcal pneumonia	25 (20)	11 (19)	
Comorbidities, n (%)			
Chronic heart disease	36 (28.3)	31 (52.5)	< 0.01
Chronic respiratory disease	47 (37.0)	35 (59.3)	< 0.01
Chronic liver disease	11 (8.6)	0 (0)	< 0.01
Chronic renal disease	11 (8.6)	3 (5.0)	< 0.01
HIV	29 (22.8)	0 (0)	< 0.01
Chronic neurological disease	8 (6.3)	5 (8.5)	0.60
Immunosuppression	19 (14.9)	17 (28.8)	0.02
Diabetes mellitus	6 (4.7)	4 (6.7)	0.50
Smoking	46 (36.2)	24 (40.6)	0.60
Alcohol abuse	25 (19.7)	10 (16.9)	0.60
ICU admission, n (%)	33 (25.6)	17 (28.8)	0.10
Mean length of stay (days)			
Total	10 (7-15)	14 (5-22)	0.46
ICU	3 (0-5)	2 (0-3)	0.40
Death, n (%)	23 (18.1)	14 (23.7)	0.34

SD: standard deviation, HIV: human immunodeficiency virus, ICU: intensive care unit.

The institutional antimicrobial treatment protocol for CAP was based on the Brazilian Thoracic Association guideline, obtaining full compliance by verification of the Infection Control Service. All clinical cases are discussed on a daily basis with this team, both in intensive care units, as well as in the clinical and emergency departments. The empirical hospital therapy for CAP, adjusted for local epidemiology, includes the use of penicillins with beta-lactamase inhibitors or third generation cephalosporins, with or without macrolide association, depending on the severity of the patient. All strains of pneumococcus isolated from both respiratory tract and blood cultures were sensitive to penicillins, cephalosporins, quinolones and vancomycin. However, 12% resistance to erythromycin and 33% resistance to sulfamethoxazole/trimethoprim were observed in respiratory tract strains. Thus, the empiric antimicrobial treatment did not show impact on mortality in the different age groups of the study population due to the low rate of bacterial resistance to the standard treatment for PP and BPP.

BPP affected 20% of the selected patients, with no difference between the two age groups (p = 0.86). Comorbidities such as chronic heart disease, chronic respiratory disease, and immunosuppression were more prevalent in the elderly population (p < 0.01), whereas chronic liver disease, chronic renal disease, and HIV infection were more frequently observed in the younger adult population (p < 0.01). Chronic neurological disease, diabetes mellitus, smoking, and alcohol abuse did not differ significantly between the two age groups.

A total of 25.6% patients younger than 65 years and 28.8% of the elderly patients were admitted to the ICU with a mean length of stay of 3 days for both groups. The mean total length of hospital stay was 10 days for younger adults and 14 days for the elderly. During the study period, 37 patients died (19.9%), accounting for 18.1% of the younger adults and 23.7% of the elderly patients. The Kaplan–Meier curve presented in Figure 1 shows the patients' survival curve according to age and length of hospital stay. Both groups had similar results until the 20th day of hospitalization, after which there was a decrease in the survival of the elderly patients.

Regarding the risk of in-hospital death because of PP, ICU admission was associated with a higher mortality rate (OR: 156.3, 95% CI: 34.1–715.9, p < 0.001), with no difference in mortality between the two age groups

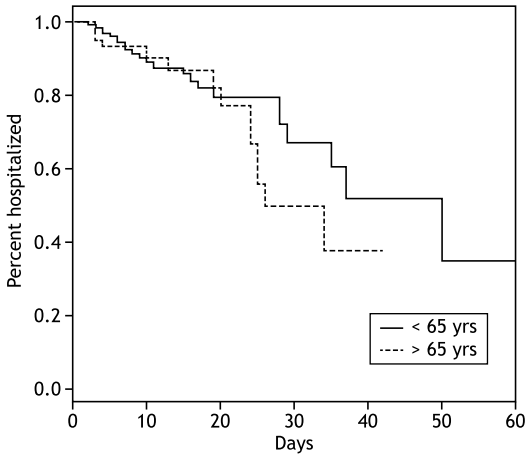

Figure 1. Kaplan-Meier curve on hospital survival analysis of adult (<65 years) and elderly (≥ 65 years) patients with pneumococcal pneumonia.

(OR: 1.41, 95% CI: 0.66–2.98, p = 0.40), as shown in Table 2. Of the comorbidities evaluated for BPP, in both age groups only chronic respiratory disease had an impact (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01) (Table 3).

The costs related to PP and BPP are described in Table 4. The average amount spent on direct and indirect costs annually was USD 28,188 for adult patients aged < 65 years and USD 16,350 for patients aged ≥ 65 years. During the 7-year study period, the total annual direct cost for PP was USD 24,458 for adults aged < 65 years and USD 14,676 for the elderly. The costs per hospitalized patient, considering both direct and indirect costs, were USD 1,746 for adults aged < 65 years and USD 2,119 for the elderly. The Brazilian Ministry of Health spent USD 1,515 on direct costs for each hospitalized adult aged < 65 years with PP and USD 1,902 on direct costs per patient aged ≥ 65 years.

Table 2. Multivariate logistic regression analysis predicting hospital mortality associated with pneumococcal pneumonia.

Risk factor	OR	95% CI	*P* value
Aged ≥ 65 years	1.41	0.66-2.98	0.40
Chronic respiratory disease	0.40	0.18-0.88	0.02
Chronic heart disease	1.10	0.52-2.32	0.80
Chronic liver disease	1.56	0.39-6.20	0.50
Chronic renal disease	2.43	0.76-7.74	0.15
HIV	0.60	0.20-1.85	0.35
Chronic neurological disease	1.89	0.55-6.50	0.31
Immunosuppression	0.97	0.39-2.52	0.94
Smoking	1.17	0.56-2.43	0.70
Alcohol abuse	1.52	0.60-3.60	0.35
Diabetes mellitus	0.43	0.05-3.52	0.40
Bacteremic pneumonia	0.57	0.25-1.32	0.20
ICU mortality	156.3	34.1-715.9	< 0.001

HIV: human immunodeficiency virus, ICU: intensive care unit, OR: odds ratio, CI: confidence interval.

Table 3. Multivariate logistic regression analysis predicting risk factors associated with bacteremic pneumococcal pneumonia.

Risk factor	Adjusted OR	95% CI	*P* value
Aged ≥ 65 years	0.77	0.32-1.90	0.58
Chronic respiratory disease	3.07	1.23-7.65	0.01
Chronic heart disease	0.88	0.36-2.16	0.77
Chronic liver disease	0.76	0.16-3.23	0.68
HIV	1.16	0.37-3.64	0.80
Chronic neurological disease	1.87	0.35-9.89	0.43
Immunosuppression	2.55	0.80-8.18	0.09
Diabetes mellitus	0.60	0.13-2.81	0.53

HIV: human immunodeficiency virus, OR: odds ratio, CI: confidence intervals.

Table 4. Costs related to hospitalization for pneumococcal pneumonia.

Costs	Aged < 65 years	Aged ≥ 65 years
Direct costs per capita	USD 1,515	USD 1,902
Indirect costs per capita	USD 231	USD 216
Total cost per capita	USD 1,746	USD 2,119
Total annual cost	USD 28,188	USD 16,350

USD: United States dollar.

DISCUSSION

Pneumococcal disease has a high incidence among adults aged < 65 years and among the elderly, contributing significant direct and indirect costs to the public health system. Although PP mainly affects patients with comorbidities, there was no observed difference in mortality between patients aged < 65 years and those aged ≥ 65 years. Patients with chronic respiratory diseases were at higher risk for bacteremic pneumonia, but these patients' mortality risk was not higher, compared with patients without this comorbidity.

Our study population was stratified into a younger adult group (aged 18 to 64 years) and an elderly group (aged ≥ 65 years). We found no statistical difference for in-hospital mortality between the two groups, demonstrating the significance of this disease for adult patients of all ages. In a study conducted in 2017, elderly patients had a higher 30-day mortality (OR: 6.83; 95% CI: 1.22–38.22; p = 0.028) than younger adults. This outcome may be related to immunosenescence because the participants were healthy and functional elderly people.[8]

The presence of chronic diseases influences both the chance of acquiring PP because of changes in immune response and the severity of the disease and its outcomes. Patients with comorbidities have a high rate of pneumococcal disease-related mortality in short- (30 days) and long-term (1 year) periods. The comorbidities associated with PP are chronic heart, respiratory, and liver diseases; acute or chronic renal failure; immunosuppression; chronic neurological diseases (among institutionalized patients); HIV; diabetes mellitus; smoking; and alcohol abuse.[16,17]

In the present study, heart disease occurred in 52.5% of elderly patients (p < 0.01) and did not have an impact on mortality in either age group (OR: 1.1, 95% CI: 0.52–2.32, p = 0.8). Musher et al. demonstrated that 19.4% of patients admitted to the hospital with PP had more than one cardiac event during the hospitalization.[18] According to Corrales-Medina et al., patients with heart disease account for a quarter of patients with CAP and have a 60% risk of 30-day mortality, especially in cases of heart failure (OR: 4.3), arrhythmia (OR: 1.8), or coronary disease (OR: 1.5).[19]

Torres et al., in their review of risk factors for pneumococcal disease, showed that chronic lung disease was an independent risk factor for pneumococcal CAP, especially in the elderly.[16] Chronic obstructive pulmonary disease and bronchial asthma were the most prevalent comorbidities found in both age groups of our studied population, with increased risk for bacteremic pneumonia (adjusted OR: 3.07, 95% CI: 1.23–7.65, p < 0.01). Patients with chronic obstructive pulmonary disease have lung architectural changes that predispose them to respiratory infections, and adults with asthma have a 12% to 17% attributable risk of acquiring invasive pneumococcal infections, especially if there are frequent asthma exacerbations.[20,21]

Pneumococcal disease has previously been identified as a significant cause of morbidity in cirrhotic patients. However, in our study only 11 patients aged < 65 years had liver disease, with no impact of this condition on mortality (OR: 1.56: 95% CI: 0.39–6.20, p = 0.5). A study published in 2011 showed that cirrhotic patients had a higher risk for CAP (46.3% vs. 33%, p = 0.007).[22] In a Spanish study, patients aged 18–64 years with liver disease had a higher index of hospitalization for PP (OR: 56.3, 95% CI: 49.1–64.6) than patients aged ≥ 65 years (OR: 15.0, 95% CI: 13.1–17.2).[23]

Chronic renal disease is an important cause of mortality worldwide, and the incidence of pneumonia in dialysis patients is 27.9/100 persons/year, with a 1-year survival rate of 0.51.[24] In our study, chronic renal failure was more prevalent in the population aged < 65 years (p < 0.01), but there was no impact of this condition on mortality (p = 0.15). Several studies have suggested a relationship between chronic renal disease and PP, although the pathophysiological mechanisms involved are not well understood.[25]

Several existing studies have suggested that a high risk of pneumococcal disease is associated with primary immunodeficiency due to B cell defects.[26] Solid tumors and hematological malignancies also predispose individuals to infections, especially by gram-positive bacteria.[27] In the studied population, immunosuppression was more prevalent in the elderly (p = 0.02).

HIV infection was also a relevant risk factor for PP (p < 0.01) in the younger adult group, with no impact in mortality or BPP. The risk of invasive pneumococcal disease has been shown to be elevated in patients living with HIV, especially those with CD4 < 200 cells/mm^3, even with the adequate use of antiretroviral therapy.[28,29]

Studies have evaluated the relationship between smoking and pneumococcal disease in adults. Chun et al. published a study in 2015 on the association between passive smoking and invasive pneumococcal disease in 171 children; they found no association with PP.[30] Nuorti et al. found that active smoking was a strong risk factor for invasive disease in immunocompetent adults (OR: 4.1, 95% CI: 2.4–7.3).[31] In another study published in 2017, smoking was associated with a decreased risk of mortality (OR 0.52, CI 0.31 – 0.87).[32] In our study, tobacco use had no impact on PP or BPP among the age groups evaluated.

Alcohol abuse has been linked to the independent risk of acquiring CAP.[33] In a study of 19,000 subjects followed for 10 years, the overall mortality attributed to PP among alcohol users was 30%, compared with 17% among non-users of alcohol.[34] In our study, 25 (19.7%) adults aged < 65 years and 10 (16.9%) elderly patients were classified as suffering from alcohol abuse. We found no impact of alcohol abuse on mortality during hospital stay (p = 0.35). Chronic neurological diseases and diabetes mellitus also had no impact on mortality. Whereas chronic neurological diseases have a higher incidence in the elderly,

diabetes mellitus has been linked to PP in patients aged <40 years, with an increased risk for bacteremic pneumonia (ORs: 1.4 to 4.6).[16]

We observed BPP to affect 20% of the selected patients, with no difference between the age groups (p = 0.86), and there was no impact on the length of stay or in-hospital mortality. This incidence of BPP corresponds to previously published data showing that 25% to 30% of patients with PP had concomitant bacteremia and that approximately 75% of all pneumococcal diseases were non-bacteremic PP.[35] The length of hospital stay because of PP or BPP was higher for elderly patients (mean: 14 days), as was the rate of ICU admission (28.8% among the elderly vs. 25.6% among younger adults). A study conducted in the Netherlands in 2016 had similar results, with an average length of hospital stay of 12 days.[10] Ruiz et al. identified a mortality risk in the ICU of 4.2 (p = 0.10);[8] however, in our study, the in-hospital mortality was higher (OR: 156.3) because all 37 patients who died were in the ICU.

In terms of costs related to PP and BPP, the average amount spent annually on direct and indirect costs was higher in the population aged < 65 years (USD 28,188 for younger adults vs. USD 16,350 for the elderly) because of the number of adults in the younger age group enrolled and the related indirect costs of hospitalization of the economically active population. In the per capita analysis, however, the cost was higher for the elderly population (USD 2,119 vs. USD 1,746 for adults aged < 65 years) because of the direct costs of prolonged hospitalization and the incidence of comorbidities. A European study showed the average direct costs of CAP treatment to be EUR 196 in the outpatient setting and EUR 1,553 in the hospital setting. A Japanese study demonstrated an average patient treatment cost of USD 4,851.[36,37]

The limitations of our study included the lack of data on 30-day outpatient mortality, on the association with mortality and pneumococcal serotypes, and on patients' influenza vaccine status. Data on outpatient follow up would be relevant to evaluate quality of life after hospital discharge, as well as the association of the serotype and impact of pneumococcal vaccination in this population. Despite the lack of data on influenza vaccination, no co-infection with the virus was diagnosed in the study population.

In conclusion, despite being a monocentric study, the results demonstrate an important cost impact and mortality among the analyzed adult population. The incidence of disease and mortality was similar in the two age groups studied, regardless of the comorbidities, with a slight increase of PP in the population that has chronic respiratory diseases. The economic impact affects both the public health system in direct costs, and the society through indirect costs. Therefore, preventive measures should be urgently encouraged in all age groups, and cost-effectiveness studies should be conducted to assess the possible impact of preventive strategies, such as the pneumococcal vaccine, for all the adult population.

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