ORIGINAL ARTICLE

Declining mortality among hospitalized patients with community-acquired pneumonia

A. F. Simonetti[1], C. Garcia-Vidal[1,2], D. Viasus[3], D. García-Somoza[4], J. Dorca[5], F. Gudiol[1,2,6] and J. Carratalà[1,2,6]

1) *Department of Infectious Diseases, Hospital Universitari de Bellvitge—IDIBELL, Barcelona,* 2) *Spanish Network for the Research in Infectious Diseases (REIPI), Madrid, Spain,* 3) *Division of Health Sciences, Faculty of Medicine, Universidad del Norte, and Hospital Universidad del Norte, Barranquilla, Colombia,* 4) *Department of Microbiology, Hospital Universitari de Bellvitge, Barcelona,* 5) *Department of Respiratory Diseases, Hospital Universitari de Bellvitge Barcelona and* 6) *Department of Clinical Sciences, University of Barcelona, Barcelona, Spain*

Abstract

Little information is available on the changes over time in community-acquired pneumonia (CAP) management and their impact on 30-day mortality in hospitalized patients. We performed a prospective, observational study of non-severely immunosuppressed hospitalized adults with CAP from 1995 to 2014. A total of 4558 patients were included. Thirty-day mortality decreased from 9.6% in the first study period (1995–99) to 4.1% in the last period (2010–14); with a progressive downward trend (−0.2% death/year; p for trend = 0.003). Over time, patients were older (p 0.02), had more co-morbidities (p 0.037), more frequently presented severe illness according to the Pneumonia Severity Index (p <0.001) and septic shock (p <0.001), and more often required intensive care unit admission (p <0.001). Combination antibiotic therapy (p <0.001) and fluoroquinolone use (p <0.001) increased. Factors independently associated with 30-day mortality were increasing age (OR 1.04; 95% CI 1.03–1.05), co-morbidities (OR 1.48; 95% CI 1.04–2.11), shock at admission (OR 4.95; 95% CI 3.49–7.00), respiratory failure (OR 1.89; 95% CI 1.42–2.52), bacteraemia (OR 2.16; 95% CI 1.58–2.96), Gram-negative bacilli aetiology (OR 4.79; 95% CI 2.52–9.10) and fluoroquinolone use (OR 0.45; 95% CI 0.29–0.71). When we adjusted for a propensity score to receive fluoroquinolones, the protective effect of fluoroquinolone use was not confirmed. In conclusion, 30-day mortality decreased significantly over time in hospitalized patients with CAP in spite of an upward trend in patient age and other factors associated with poor outcomes. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes.

Keywords: Antibiotics, community-acquired pneumonia, management, prognosis, time-trends
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Corresponding author: C. Garcia-Vidal, Department of Infectious Diseases, Hospital Universitari de Bellvitge—IDIBELL, Feixa Llarga s/n, 08907, L'Hospitalet de Llobregat, Barcelona, Spain
E-mail: carolgv75@hotmail.com

Introduction

Community-acquired pneumonia (CAP) is the leading infectious cause of death and the fourth cause of global mortality in the world [1]. Mortality in patients hospitalized for CAP ranged from 10% in patients in conventional wards to >30% in those admitted to the intensive care unit (ICU) [2–4]. The current Infectious Diseases Society of America/American Thoracic Society guidelines on the management of CAP in adults state that rates of mortality due to pneumonia have not decreased significantly since penicillin became routinely available [5]. However, our understanding of CAP has improved substantially in recent decades. Helpful tools in site-of-care decision-making such as prognostic severity scores, several new diagnostic tests for early aetiological diagnosis of CAP, and improved management in critical care have been introduced in routine clinical practice. At the same time, the use of new antibiotic agents and

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new combinations of antibiotics for treating CAP and strategies for its prevention such as pneumococcal vaccination have been implemented.

Although some studies have shown the benefit of specific interventions for improving the outcomes of CAP patients [6–8], the impact of the widespread use of these strategies on mortality has not been extensively measured. Interestingly, recent studies based on administrative data reported falls in in-hospital mortality over time among this population [9,10]. Nevertheless, clinical studies of the changes over time in CAP management and their impact on 30-day outcomes in patients hospitalized with CAP are lacking.

The aim of this study was to analyse trends of mortality in a large cohort of adult patients with CAP documented over a 20-year period. We analysed factors related with overall mortality and explored changes over time in the characteristics of patients and CAP management. Finally, we evaluated the relationship between these changes and trends of mortality in CAP patients.

Material and Methods

Setting, population studied and design

This observational study was conducted at a 700-bed university hospital for adults in Barcelona, Spain. All patients admitted to the hospital with CAP via the emergency department from 1 February 1995 through to 31 December 2014 were prospectively recruited and followed. Immunosuppressed patients (those with neutropenia, HIV infection, transplantation or splenectomy, and those receiving immunosuppressants and/or >15 mg/day of prednisone or its equivalent) were excluded. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the hospital's ethics committee.

Clinical evaluation and follow-up

Patients were seen daily during the hospital stay by one or more of the investigators, who recorded clinical, laboratory and microbiological data in a computer-assisted protocol. The Pneumonia Severity Index (PSI) was used to stratify patients according to risk [2].

Before starting empirical antibiotic therapy, patients underwent a complete clinical history and physical examination. Basic laboratory tests and chest radiography were performed. Two sets of blood samples were obtained and cultured and, when available, a sputum sample was evaluated by Gram staining and culture. Urinary antigen detection tests for *Streptococcus pneumoniae* and *Legionella pneumophila* were performed if indicated by the attending physician. Paired serum samples obtained during the acute and convalescent phases of infection (separated by a 3- to 8-week interval) were also obtained for serological studies.

Antibiotic therapy was administered according to the hospital guidelines, which recommended the administration of a β-lactam (ceftriaxone or amoxicillin-clavulanate) with or without a macrolide (erythromycin or clarithromycin) or a fluoroquinolone with or without a β-lactam.

All patients were prospectively followed up during hospitalization and attended a long-term follow-up visit 1 month after discharge. Admission criteria, variables collection, clinical evaluation and follow up of patients with CAP did not change during the study period. The primary outcome (30-day mortality) was assessed by a specific search for each patient in the Health-Care Database (SAP) of the Catalan Health Service. The Catalan region provides universal health coverage. All beneficiaries are registered in the SAP, with a unique lifetime personal health number.

Definitions

Community-acquired pneumonia was defined as an acute illness associated with two or more of the following signs and symptoms: new cough with or without sputum production, pleuritic chest pain, dyspnoea, fever or hypothermia, altered breath sounds on auscultation, leucocytosis, and the presence of a new infiltrate on a chest radiograph.

A co-morbid condition was defined as the presence of one or more of the following underlying diseases: diabetes mellitus, chronic cardiopathy, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, cerebral vascular disease and dementia. Initial inappropriate therapy was defined as the absence of antimicrobial agents directed at a specific type of organism or administration of an antibiotic to which the organism was resistant, according to susceptibility test criteria for lower respiratory tract pathogens. Overall mortality was defined as death from any cause within 30 days after hospital admission. Other definitions are described in Appendix 1.

Microbiological studies

Pathogens in blood, pleural effusion, sputum and other samples were investigated using standard microbiological procedures. Isolation of *Legionella* was attempted in sputum and other respiratory samples by using selective media (buffered charcoal yeast extract α). The *S. pneumoniae* antigen in urine was detected by using a rapid immunochromatographic assay (NOW Assay; Binax Inc., Portland, ME, USA). *Legionella pneumophila* Serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW Legionella Urinary Antigen Test; Binax Inc.) or by ELISA (ELISA-Bartels, Trinity

Biotech, Wicklow, Ireland). Both antigens in urine were used routinely from 2000. Serological methods were used both on admission and 3–4 weeks thereafter, to determine antibodies against the following pathogens: *Mycoplasma pneumoniae*, *Chlamydophila psittacci*, *Chlamydophila pneumoniae*, *Coxiella burnetii*, *L. pneumophila*. Real-time PCR were performed to identify influenza A and B viruses from 2009 onwards. Antimicrobial susceptibility was tested by the microdilution method, following the Clinical Laboratory Standard Institute methods and criteria [11].

Statistical analysis

Data are presented as percentages and numbers, means with SDs, medians and interquartile ranges (IQRs), or proportions and 95% CIs. Accordingly, chi-squared tests for equal proportion, *t* tests, or the Mann–Whitney *U* test were used to test differences. To reduce the variability and noise of random in year by year data, we divided the study periods into 5-year blocks, defining 1995–99 as the reference period.

To assess whether 30-day mortality has changed over time, a logistic regression model was used with period of admission as numerical independent variable. Then we multiplied the adjusted ORs for each subsequent period with the observed survival rate for the reference period (1995–99) to obtain risk-adjusted survival rates. These rates represent what the survival would be for each 5-year period if the patient case-mix was identical to that of the reference period. Our models adjusted for patients' characteristics and severity of disease that in a univariate analysis were related with 30-day mortality: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia.

Trends of factors related with demographics, clinical condition, diagnosis, aetiology, treatment and outcome of CAP were analysed using the Mantel–Haenszel test of trend for categorical variables and linear regression for continuous variables.

We analysed the impact of initial treatment strategy on mortality, assessing predictors for overall mortality in the entire study population by using a logistic regression model. Associations are given as ORs with 95% CIs. In a secondary analysis, we calculated the propensity to receive a fluoroquinolone as empiric antibiotic treatment given the patient's observed pre-treatment characteristics. We limited the analysis from 2000 onwards (year of introduction of fluoroquinolones for CAP in our institution). The propensity score was estimated using a logistic regression model including variables associated with fluoroquinolone use as empiric treatment ($p \leq 0.05$ in the univariate analysis) as: year of admission, patient characteristics (age >65 years, presence of cancer or dementia) and clinical features (sudden onset, purulent sputum, diarrhoea, headache, arthralgia, multilobar pneumonia or pleural effusion on a chest radiograph, more than 12 000 leucocytes in peripheral blood sample), the fit of which was assessed by the Hosmer–Lemeshow test (p 0.878). Then we carried out a case–control matched analysis on propensity score (1: 1) to reduce the selection bias by factors associated with initial antibiotic therapy.

A value of $p < 0.05$ was considered statistically significant. All reported p values are two-tailed. All statistical calculations were performed using the Statistical Package for the Social Sciences (Version SPSS 15.01s) for Windows.

Results

Trends of mortality and main causes of death

A total of 4558 patients were hospitalized with CAP during the study, 47 of whom were lost to follow up. Overall mortality (≤30 days) was 7.3% (330 of 4511 patients); in patients hospitalized in conventional wards mortality was 5.4% (219 of 4063 patients) whereas in patients admitted to the ICU it reached 24.8% (111 of 448 patients).

During the study period, unadjusted rates of 30-day mortality decreased from 9.6% in the first 5 years (1995–99) to 4.1% in the last 5 years (2010–14); with a progressive significant downward trend (−0.2% death/year; *p* for trend 0.003) (Fig. 1).

In a secondary analysis, we adjusted rates of mortality for patient characteristics and severity of disease found to be related with 30-day mortality by univariate analysis: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia (Table 1). Risk-adjusted rates of mortality decreased in a greater way over the study period (p <0.001).

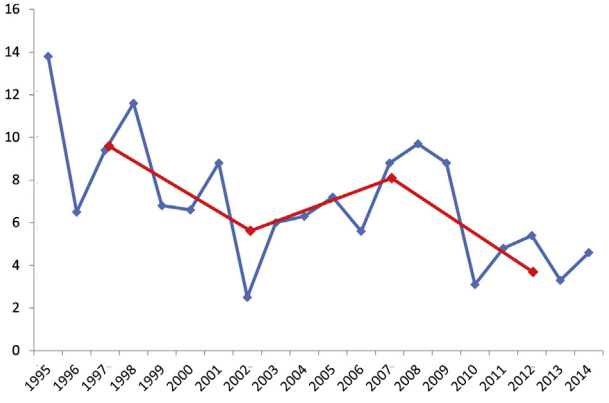

FIG. 1. Trends in 30-day mortality in hospitalized patients with community-acquired pneumonia from 1995 to 2014 (distribution by year and by period).

TABLE 1. Thirty-day mortality per 5-year period

Period	Unadjusted rate (%)	Adjusted rate (%)	Ratio	p value for trend
1995–99	9.6			<0.001
2000–04	5.9	5.1	0.533	
2005–09	8.2	5.6	0.585	
2010–14	4.1	2.8	0.292	

Multivariable analysis adjusted for: β-lactam monotherapy, inadequate empiric treatment.
Rates are adjusted for: age, presence of co-morbidity, septic shock at admission, respiratory failure, Gram-negative bacilli aetiology and presence of bacteraemia.

Acute respiratory failure secondary to pneumonia (n = 168; 51.8%), multiorgan failure associated with septic shock (n = 92; 25.9%) and acute cardiac events related with pneumonia (n = 20; 5.6%) were the most frequent causes of death.

Changes over time in the characteristics of patients and CAP management

Table 2 shows the principal changes in characteristics and management of patients over the study period. Over time, patients were more likely to be older, to present some co-morbidity, and to have received previous pneumococcal and influenza vaccination. Conversely, there were fewer current smokers and alcohol abusers. The percentage of patients with high-risk pneumonia according to PSI, pleural empyema and septic shock at admission increased significantly over time.

Streptococcus pneumoniae caused 33.8% of CAP cases, being the most frequent pathogen. The diagnosis of pneumococcal pneumonia increased significantly mainly due to the introduction of the pneumococcal urine antigen test (routinely available

TABLE 2. Characteristics of 4558 patients with community-acquired pneumonia divided by study period

Variable	1995–99 (n = 1121)	2000–04 (n = 1064)	2005–09 (n = 1634)	2010–14 (n = 739)	p value
Age, years (median, IQR)	69 (57–78)	68 (57–79)	71 (57–80)	71 (55–80)	0.002[a]
Male sex, (%)	69.8	70.4	66.7	65.9	0.02
Current smoker, (%)	28.8	25.5	25.5	24.2	0.02
Heavy drinking, (%)	19.5	14.9	17.9	11.0	<0.001
Influenza vaccine (season), (%)	41.9	48.4	53.7	52.4	<0.001
Pneumococcal vaccine, 5-year, (%)	4.7	18.6	23.0	25.0	<0.001
Underlying disease, (%)	72.4	72.5	77.7	73.7	0.03
COPD	23.8	29.9	27.8	34.1	<0.001
Diabetes mellitus	17.1	18.2	24.5	25.2	<0.001
Cerebral vascular disease	1.5	6.5	12.6	7.3	<0.001
Chronic renal disease	4.0	3.8	10.2	13.0	<0.001
Chronic heart disease	21.1	30.1	22.5	23.0	0.83
Chronic liver disease	6.2	4.3	7.9	7.3	0.02
Dementia	3.4	4.1	6.9	7.0	<0.001
High severity risk PSI classes (IV–V), (%)	55.0	54.6	63.4	60.5	<0.001
Clinical features, (%)					
Respiratory failure	60.5	54.4	59.7	59.7	0.74
Pleural effusion	19.4	16.7	16.0	16.9	0.06
Empyema	2.9	3.0	5.8	4.5	0.002
Bacteraemia	12.9	10.9	15.0	13.1	0.20
Altered mental status	14.3	11.2	16.9	14.3	0.11
Septic shock at admission	3.2	4.6	11.2	11.5	<0.001
Aetiology, (%)					
Streptococcus pneumoniae	23.5	29.5	44.5	31.8	<0.001
Pneumococcal bacteraemia	10.1	8.6	10.9	8.3	0.73
Legionella pneumophila	6.6	7.7	3.9	2.4	<0.001
Haemophilus influenzae	6.2	6.6	3.8	4.7	0.009
Aspiration pneumonia	7.0	6.6	8.1	7.2	0.42
Atypical agents	5.6	4.8	2.9	3.8	0.003
Gram-negative bacilli[b]	1.3	1.5	1.7	2.7	0.04
Virus	1.3	1.1	4.5	6.1	<0.001
Mixed pathogens	3.5	2.4	5.0	5.5	0.002
Unknown aetiology	49.3	43.0	31.9	39.8	<0.001
Treatment, (%)					
Overall β-lactam treatment	85.1	75.1	84.9	85.8	<0.043
Penicillin/Amoxicillin (± clavulanate)	30.3	15.5	18.7	17.3	<0.001
Cephalosporin	53.9	58.4	63.9	64.4	<0.001
β-lactam monotherapy	67.1	47.0	39.3	29.0	<0.001
Fluoroquinolone monotherapy	0.4	20.5	11.1	10.4	<0.001
Overall fluoroquinolone treatment	0.5	44.3	57.3	66.0	<0.001
Overall macrolide treatment	29.7	6.3	0.9	1.1	<0.001
Combination therapy	23.7	29.3	48.6	59.7	<0.001
Combination β-lactam and macrolide	17.2	4.4	0.7	0.8	<0.001
Combination β-lactam and fluoroquinolone	0.1	23.2	43.5	52.9	<0.001
Overall oseltamivir	0	0	4.7	5.5	<0.001
Inadequate empirical antibiotic therapy	4.6	4.2	4.2	2.4	0.04
Timing of antibiotic administration $\leq$ 4h	ND	39.1	37.0	46.0	0.016
Outcomes					
Mechanical ventilation, (%)	4.4	5.3	7.0	6.9	0.003
Non-invasive ventilation, (%)	0	1.3	5.9	10.0	<0.001
ICU admission, (%)	7.3	9.0	11.1	12.0	<0.001
Length of hospital stay, days (median, IQR)	9 (6–12)	8 (6–12)	7 (5–11)	8 (5–12)	0.002[a]
Early mortality (<48 h), (%)	3.2	1.5	2.1	0.7	<0.001
30-day mortality, (%)	9.6	5.9	8.2	4.1	0.002

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; PSI, Pneumonia Severity Index; ICU, intensive care unit.
[a]Kruskas–Wallis test.
[b]Of the 4558 CAP episodes, 83 were due to Gram-negative bacilli. 13 episodes (15.7%) had mixed infection. The Gram-negative bacilli were: *Pseudomonas aeruginosa* (43), *Escherichia coli* (18), *Klebsiella pneumoniae* (13), others Enterobacteraceae (5), *Acinetobacter baumanii* (2), *Stenotrophomonas maltophila* (1). Twelve isolates (14%) were resistant to quinolones. There was no relationship between quinolone resistance and mortality.

from 2000); meanwhile the number of CAP with unknown aetiology decreased. We also observed a significant reduction in rates of diagnosis of *L. pneumophila* and other atypical pathogens as causes of CAP. In contrast, there was a significant increase in CAP due to Gram-negative bacilli. After the introduction of PCR for influenza virus during the 2009 pandemic, we found a substantial increase in viral pneumonia, along with higher rates of mixed infections. The percentage of patients with bacteraemia did not significantly change during the study period. Penicillin resistance of invasive *S. pneumoniae* strains changed from 18.6% in the first period to 8.2% in the last period, while susceptibility to cephalosporins and quinolones did not show major changes. Over time there was an increase in patients requiring ICU admission and patients who underwent invasive and non-invasive mechanical ventilation.

Regarding empirical antibiotic therapy, combination therapy increased, the use of β-lactam monotherapy as well as the use of macrolides fell but there was a huge increase in the use of fluoroquinolones, and initial inappropriate therapy decreased slightly over time. The proportion of patients who received their first antibiotic dose within 4 h from admission increased over time (data available from 2000).

Factors associated with mortality

In a multivariable analysis (Table 3) factors independently associated with 30-day mortality were: increasing age, presence of some co-morbidity, shock at admission, respiratory failure, bacteraemia, Gram-negative bacilli aetiology, and period of admission. Conversely, the use of fluoroquinolones as empiric treatment, either in monotherapy or in combination, was the only factor significantly associated with lower mortality. In a secondary analysis, we calculated the propensity to receive a fluoroquinolone as empiric antibiotic treatment, and performed a case–control matched analysis on propensity score (1: 1 matching with replacement). After applying the propensity score, the protective effect of fluoroquinolone use was not confirmed. (OR 0.317, 95% CI 0.069–1.448; p 0.138).

TABLE 3. Factors independently associated with mortality during the period studied in a multivariable analysis

Variable	OR	95% CI	p value
Year of admission	0.962	0.936–0.989	0.006
Age	1.039	1.029–1.050	<0.001
Presence of co-morbidity	1.481	1.040–2.110	0.02
Shock at admission	4.945	3.494–6.997	<0.001
Respiratory failure	1.890	1.420–2.515	<0.001
Bacteraemia	2.162	1.579–2.960	<0.001
Gram-negative bacilli	4.792	2.523–9.103	<0.001
Fluoroquinolone treatment [a]	0.452	0.289–0.707	0.001

Multivariable analysis adjusted for: β-lactam monotherapy, inadequate empiric treatment.
[a]When a propensity score for receiving fluoroquinolone as empiric treatment was added to the multivariable analysis, fluoroquinolone treatment was not associated with mortality (OR 0.317, 95% CI 0.069–1.448; p 0.138).

Discussion

This observational study of a large prospective cohort of adults hospitalized with CAP found a substantial decrease in 30-day mortality over a period of 20 years, in spite of an upward trend in several factors with negative prognostic influence.

A similar downward trend in mortality due to CAP has been reported in two previous studies [9,10] using US national databases, where mortality due to CAP fell from 8.9% in 1993 to 4.1% in 2005 (p <0.001) in hospitalized patients [9] and from 13.5% in 1987 to 9.7% in 2005 in a population of elderly inpatients and outpatients with CAP [10].

Interestingly, two recent studies have also found reductions in mortality among CAP patients [12,13]. The first study [12], which compared patients with CAP admitted to the ICU in two periods (1995–2000 versus 2005–10), suggests that the decrease in mortality observed may be related to the implementation of a sepsis management bundle derived from the Surviving Sepsis Campaign. Among other interventions, the bundle included the combined use of levofloxacin and a third-generation cephalosporin for the initial empirical antimicrobial regimen. The second study [13], a matched case–control study that compared two periods (2000–02 versus 2008–13) found a 15% decrease in mortality among patients with pneumococcal pneumonia admitted to the ICU. Early antibiotic administration and combination antibiotic therapy were independently associated with better outcomes.

In our cohort, we observed over time some important changes in the management of CAP patients that could have caused the better outcomes observed, including the rise in patients who underwent mechanical (either invasive or non-invasive) ventilation or who were admitted to ICU, and a huge change in empirical antibiotic choice, with an increase in fluoroquinolone use, either alone or in combination with β-lactams.

Several randomized controlled trials have demonstrated a non-inferiority of fluoroquinolone monotherapy when compared with either β-lactams alone or β-lactams plus macrolide regimens in treating patients with CAP [14–18]. Furthermore, fluoroquinolones have also been associated with improvement of other outcomes, such as lower risk of treatment failure, shorter duration of intravenous treatment and hospital stay, a faster clinical improvement and a decrease in the number of admissions of low-risk patients [18–21]. In our cohort the use of fluoroquinolones was the only factor associated with decreased mortality over time in a multivariable analysis. However, after matching patients by means of a propensity score for receiving quinolones, the beneficial effect of fluoroquinolone use on mortality was not confirmed.

In recent years, the possible beneficial effect of combination therapy with β-lactams and macrolides on patient outcomes has been the subject of active debate. Although the use of combination therapy has been linked to better outcomes in some observational studies, especially in patients with severe CAP [22], this benefit has not been found in randomized controlled trials [23,24]. In a large meta-analysis of almost 10 000 critically ill patients with CAP, when broadly guideline-concordant regimens were compared (β-lactams plus macrolides versus β-lactams plus fluoroquinolones), no significant difference in mortality was found [25]. Similarly, we did not observe better outcomes in patients who received the β-lactams plus macrolides regimen.

The strengths of this study include the prospective nature of the cohort, the comprehensive data collection over a period of 20 years, the large number of a wide spectrum of hospitalized patients with CAP and the application of a propensity analysis. There are, however, some limitations that should be acknowledged; the study was conducted at a single centre and the extrapolation of our results to other settings should be done with care.

In summary, 30-day mortality significantly decreased over time in hospitalized CAP patients in spite of an upward trend in patient age and other factors associated with poor outcomes. Several changes in the management of CAP and a general improvement in global care over time may have caused the observed outcomes. In fact, during the past decades mortality has declined for a variety of conditions, including sepsis, myocardial infarction and stroke [26–28], suggesting an overall better clinical management and a general improvement of healthcare systems.

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Author Contributions

AFS, CGV, JC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of the manuscript. AFS, CGV, DV, DGS, JD, FG and JC contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. Study concept and design: CGV, AFS, JC. Acquisition of the data: AFS, CGV, DV, DGS, JD. Analysis and interpretation of the data: AFS, CGV, DV, FG, and JC. Drafting of the manuscript: CGV, AFS, JC. Critical revision of the manuscript for important intellectual content: DV, DGS, JD, FG, JC. Statistical analysis: CGV, AFS. Study supervision: FG, JC.

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Transparency Declaration

All authors have no conflicts of interest to disclose.

Appendix 1. Definitions

Cerebrovascular disease a clinical diagnosis of stroke or transient ischaemic attack or stroke documented by magnetic resonance imaging or computed tomography.

Chronic cardiopathy chronic heart disease was defined as evidence in records or treatment for coronary artery disease, arrhythmia, or congestive heart failure, or the presence of valvular heart disease.

Chronic liver disease a clinical or histological diagnosis of cirrhosis or another form of chronic liver disease, such as chronic active hepatitis.

Chronic obstructive pulmonary disease the coexistence of chronic and progressive symptoms such as dyspnoea, cough and sputum and airflow obstruction diagnosed by spirometry.

Chronic renal failure included pre-existing renal disease with documented abnormal serum creatinine levels outside the pneumonia episode (glomerular filtration rate <60 mL/min/1.73 m^2).

Current smoker patients who had smoked more than ten cigarettes per day for at least 1 year preceding the study were classified as current smokers.

Diabetes mellitus diagnosis was based on a previous clinical and/or biochemical diagnosis of diabetes mellitus and/or treatment with oral anti-diabetic agents or insulin.

Heavy drinking consumption of more than 40 g alcohol per day for women (more than three standard drinks) and more than 60 g per day for men (more than four standard drinks).

Influenza and pneumococcal vaccine status assessed from interviews with the patients or their relatives and from reviews of hospital and personal health records (vaccination card). Patients were considered to be pneumococcus-vaccinated if the pneumococcal vaccine had been administered in the 5 years before admission, and influenza-vaccinated if seasonal influenza vaccine had been administered during the year before admission.

Respiratory failure a Pao_2/Fio_2 ratio <300.

Septic shock diagnosis of septic shock was based on a systolic blood pressure of <90 mmHg, and diagnosis of peripheral hypoperfusion on the need for vasopressors.

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