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MAJOR ARTICLE

Host- and Pathogen-Related Factors for Acute Cardiac Events in Pneumococcal Pneumonia

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Background. Acute cardiac events (ACEs) are increasingly being recognized as a major complication in pneumococcal community-acquired pneumonia (CAP). Information regarding host- and pathogen-related factors for ACEs, including pneumococcal serotypes and clonal complexes, is scarce.

Methods. A retrospective study was conducted of a prospective cohort of patients hospitalized for CAP between 1996 and 2019. Logistic regression and funnel plot analyses were performed to determine host- and pathogen-related factors for ACEs.

Results. Of 1739 episodes of pneumococcal CAP, 1 or more ACEs occurred in 304 (17.5%) patients, the most frequent being arrhythmia (n = 207), heart failure (n = 135), and myocardial infarction (n = 23). The majority of ACEs (73.4%) occurred within 48 hours of admission. Factors independently associated with ACEs were older age, preexisting heart conditions, pneumococcal bacteremia, septic shock at admission, and high-risk pneumonia. Among 983 pneumococcal isolates, 872 (88.7%) were serotyped and 742 (75.5%) genotyped. The funnel plot analyses did not find any statistically significant association between serotypes or clonal complexes with ACEs. Nevertheless, there was a trend toward an association between CC230 and these complications. ACEs were independently associated with 30-day mortality (adjusted odds ratio, 1.88; 95% CI, 1.11–3.13).

Conclusions. ACEs are frequent in pneumococcal pneumonia and are associated with increased mortality. The risk factors defined in this study may help identify patients who must undergo close follow-up, including heart rhythm monitoring, and special care to avoid fluid overload, particularly during the first 48 hours of admission. These high-risk patients should be the target for preventive intervention strategies.

Keywords. acute cardiac events; community-acquired pneumonia; genotype; pneumococcal pneumonia; serotype.

Acute cardiac events pose a significant challenge in the management of community-acquired pneumonia (CAP) [1–3]. The incidence of acute cardiac events during the course of hospitalization for CAP ranges from 8% to 32% [4–7]. It is increasingly being recognized that the development of acute cardiac events in patients with CAP is an independent predictor of poor outcomes [5, 7]. Moreover, hospitalized patients with CAP have a 2-fold increase in the long-term risk for cardiovascular disease, new-onset heart failure, and mortality compared with the general population [8–11].

Several cohort studies focusing on the overall population of all-cause CAP have identified certain host factors associated with the development of acute cardiac events [4–7, 12, 13]. Importantly, the development of life-threatening acute cardiac events appears to be particularly frequent among patients with pneumococcal CAP [4, 14]. The first study linking acute cardiac events and pneumococcal pneumonia was carried out by Musher and colleagues in 2007 [15]. However, that seminal study reported only 33 cardiac events occurring in 170 patients, precluding an analysis of risk factors. Other researchers have found that pneumococcal bacteremia significantly increased the risk of new-onset heart failure up to 10 years after CAP compared with controls [9].

Interestingly, recent animal experimental models have shown that *Streptococcus pneumoniae* is capable of invading the myocardium and inducing cardiac injury by promoting the formation of microlesions [16–18]. In these studies, bacteremia strongly correlated with increasing levels of cardiac troponin-L and cardiac damage [19, 20]. Pneumolysin, a major virulence factor of *S. pneumoniae*, mediates cardiac damage and depresses cardiomyocyte contractile function [19, 21]. Antimicrobial

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treatment has been associated with cardiac scarring as a result of collagen synthesis in damaged myocardium, which may explain the increased risk for long-term cardiac complications in humans due to the promotion of arrhythmias and/or impairment of left ventricular function [16, 17]. A recent experimental study in a small sample of mice found that cardiac damage is probably dependent on the ability of certain pneumococci to cause high-grade bacteremia and that the type of lesions might be strain-specific [20]. Interestingly, similar cardiac microlesions largely devoid of bacteria were observed in heart sections from 3 rhesus macaques infected with simian immunodeficiency virus that died of pneumococcal pneumonia despite antibiotic therapy, and in 2 out of 9 humans who succumbed to invasive pneumococcal disease [17].

To date, however, no clinical studies have specifically assessed host risk factors for acute cardiac events in pneumococcal pneumonia. Moreover, the potential link between pneumococcal genotypes (clonal complexes) and cardiac complications in humans with pneumococcal CAP has not been explored. Nevertheless, a recent study has found an association between the development of acute cardiac events and pneumococcal serotypes 3 and 9N in 310 patients with invasive pneumococcal disease (of whom 60% had CAP) [22]. An association between any pneumococcal serotype or clonal complex and cardiac events could have important public health implications with regard to the composition of further pneumococcal vaccines.

Here, we aim to assess the host- and pathogen-related factors, more specifically serotypes and genotypes (clonal complexes), related to a high risk of developing acute cardiac events in a large prospective cohort of hospitalized patients with pneumococcal CAP.

METHODS

Setting, Patients, and Study Design

This retrospective cohort study was performed at the Bellvitge University Hospital, a 750-bed tertiary academic hospital for adults in Barcelona, Spain. All nonimmunocompromised patients aged ≥18 years with pneumococcal CAP who were hospitalized through the emergency room from January 1, 1996, to September 30, 2019, were included. Data on all patients were prospectively recorded using a computer-assisted protocol. Patients with neutropenia, HIV infection, or transplantation were not included.

To identify risk factors for acute cardiac events during hospitalization, patients with pneumococcal pneumonia were divided into 2 groups: those who developed acute cardiac events (new-onset or worsening cardiac arrhythmias, new-onset or worsening congestive heart failure and/or myocardial infarction) and those without acute cardiac events during hospital stay. A comparison of *S. pneumoniae* strains isolated from patients with pneumococcal pneumonia and with or without acute cardiac events was performed. Local clinical practices regarding initial microbiological testing and empirical antibiotic therapy are detailed in the Supplementary Data. Serotypes, genotypes (clonal complexes), and penicillin susceptibility of isolated strains were analyzed.

Patients were seen during their hospital stay by 1 or more of the investigators who recorded clinical data, including the occurrence of any acute cardiac event, and microbiological findings in a computer-assisted protocol (case report form, Supplementary Data). Patients were seen at the outpatient clinic 30 days after hospital discharge.

Patient Consent Statement

The study was approved by the Bellvitge University Hospital Ethics Committee. Informed consent was waived because of the observational nature of the study and because the analysis used anonymous clinical data. The STROBE guidelines were used to ensure the reporting of the study (Supplementary Table 1).

Definitions

New-onset or worsening cardiac arrhythmias were considered when they were documented by an electrocardiogram (ECG). New-onset or worsening congestive heart failure was considered when patients fulfilled Framingham criteria [23]. Myocardial infarction was defined as the detection of an increase in cardiac biomarkers (creatine kinase fraction MB and/or troponin) with at least 1 of the following manifestations: symptoms of ischemia, ECG changes (new ST-T changes or a new left bundle branch block), or development of pathological Q waves. Early and overall mortality were defined as death due to any cause ≤48 hours and ≤30 days after hospitalization, respectively. The definitions for pneumococcal CAP and other variables are detailed in the Supplementary Data.

Microbiological Studies

S. pneumoniae was identified using standard microbiological procedures. *S. pneumoniae* urinary antigen detection was performed with a rapid immunochromatographic assay (BinaxNOW *Streptococcus pneumoniae*, Abbott, Lake Bluff, Illinois, USA). Penicillin susceptibility was tested by the microdilution method, following the European Committee on Antimicrobial Susceptibility Testing methods and criteria (EUCAST).

Serotypes were identified using the Quellung reaction at the Spanish Reference Laboratory [24] and/or by conventional polymerase chain reaction following the methodology described by the Centers for Disease Control and Prevention [25]. For genotyping all available strains, pulsed-field gel electrophoresis with multilocus sequence typing (PFGE/MLST) scheme was performed following a previously described methodology [26]. PFGE patterns were visually compared. Representative strains of the main clusters (those accounting for >5 pneumococci) were studied by MLST. Allele numbers and sequence

types (STs) were assigned using the pneumococcal multilocus sequence typing website [27]. Unusual serotype–genotype combinations were retested.

Statistical Analysis

Categorical variables were presented by the number of cases and percentages, and continuous variables by means and SDs or medians and interquartile ranges (IQRs). Continuous variables were compared using the Student *t* test or Mann-Whitney *U* test where appropriate. The Fisher exact test or Pearson χ^2 test was applied to assess the relationship between categorical variables.

To estimate the magnitude of the associations between covariates and the development of acute cardiac events, multivariable adjusted ORs and their corresponding 95% confidence intervals were computed by logistic regression. A potential set of predictors was prespecified based on the literature. The cohort was sampled by bootstrapping with replacement 1000 times. A model was fitted in each sample using stepwise elimination and the Akaike information criterion. Predictors retained in more than 70% of the models were considered for inclusion in the selected model. Factors included in the model are detailed in the Supplementary Data. Comparison of acute cardiac event rates between serotypes and clonal complexes was carried out taking into account the volume of patients at risk and was represented graphically with funnel plots [28]. Using the overall acute cardiac event rate as a benchmark, serotypes or clonal complexes above or below the benchmark's confidence interval would indicate that the risk observed was significantly higher or lower than expected. If the serotypes or clonal complexes were within the benchmark's confidence interval, this would indicate that the risk observed was as expected. Only serotypes and genotypes (clonal complexes) isolated in 10 or more cases were analyzed. As a general strategy, variables with >25% of missing values were not considered. No imputation was performed for missing values, and no sensitivity analysis was carried out. Whenever possible, 95% confidence intervals accompanied point estimators. All analyses were performed with a 2-sided significance level of .05 and were conducted with R Statistical Software, version 3.6.3 [29].

RESULTS

Over the study period, 1739 consecutive adults with pneumococcal pneumonia were included, of whom 304 (17.5%) developed 1 or more acute cardiac events during hospitalization. The most frequent cardiac complications were arrhythmia (n = 207, of which 124 were new-onset atrial fibrillation/flutter), heart failure (n = 135, of which 85 were new-onset heart failure), and myocardial infarction (n = 23), with the majority of events occurring within 48 hours (73.4%) of admission. Details of the microbiological methods used to establish the diagnosis of pneumococcal pneumonia are shown in the Supplementary Table 2. In brief, *S. pneumoniae* was isolated in 1 or more clinical samples in 983 (56.5%) patients, with the remaining patients being diagnosed through antigen testing, and 495 (28.5%) had pneumococcal bacteremia.

Baseline characteristics of patients with pneumococcal pneumonia who developed acute cardiac events and those who did not are detailed in Table 1. Patients who developed acute cardiac events were significantly older, had more preexisting heart conditions, and had more comorbidities such as stroke, dyslipidemia, arterial hypertension, peripheral artery disease, chronic renal disease, and chronic obstructive pulmonary disease. They were more often receiving oral anticoagulants, antiplatelet therapy, statins, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and diuretics. They also had more often pneumococcal bacteremia, a more severe presentation with a higher pneumonia severity index (PSI), and higher rates of septic shock at admission, hypoalbuminemia, and respiratory insufficiency. Patients without acute cardiac events were more likely to have received prehospitalization antibiotic treatment for the acute episode of pneumonia, which was associated with a lower frequency of bacteremia (13.3% vs 30.8%; $P < .001$), a lower proportion of septic shock at admission (7.3% vs 13.3%; $P < .01$), and a lower rate of high-risk pneumonia (PSI classes IV and V, 56% vs 65.6%; $P = .017$). In the adjusted multivariate logistic regression analysis, age, preexisting heart conditions, pneumococcal bacteremia, septic shock at admission, and high-risk pneumonia (PSI classes IV and V) were found to be independent risk factors for the development of acute cardiac complications in pneumococcal CAP (Table 2).

Regarding pathogen-related factors, among 983 pneumococcal isolates, 872 (88.7%) were serotyped and 742 (75.5%) genotyped. A complete distribution of identified serotypes and clonal complexes is detailed in Supplementary Tables 3 and 4. Serotype 3 was the most common, and it was mainly related to clonal complexes CC180 and CC260; the β-lactam-resistant CC156, which included serotypes 9V and 14, was third. A funnel plot analysis (Figure 1) showed a trend toward a higher incidence of acute cardiac complications than expected with serotype 4, whereas serotypes 6A, 5, and 1 had a lower incidence than expected. The clonal complex CC230 showed a trend toward a higher rate of acute cardiac events in the funnel plot analysis (Figure 2), whereas the serotype 5–associated clonal complex CC289 had a lower incidence than expected. No differences in penicillin minimum inhibitory concentration were observed between the 2 groups (Supplementary Table 5).

Initial empirical antibiotic treatment and outcomes are summarized in Table 3. According to our local guidelines for treatment of CAP, combination therapy with β-lactam and fluoroquinolone is recommended for severe pneumonia. Accordingly, it was associated with a higher rate of septic shock, respiratory failure, intensive care unit (ICU) admission, and a higher PSI score. A higher rate of acute cardiovascular events

Table 1. Baseline Characteristics of Patients With Pneumococcal Pneumonia who Developed Acute Cardiac Events and Those who Did Not

Patients (n = 1739)	Pneumococcal Pneumonia With Acute Cardiac Events (n = 304), No. (%)	Pneumococcal Pneumonia Without Acute Cardiac Events (n = 1435), No. (%)	*P* Value
Mean age (SD), y	73.4 (12.6)	65.8 (17.2)	<.001
Age ≥70 y	200/304 (65.8)	710/1435 (49.5)	<.001
Female sex	111/304 (36.5)	509/1435 (35.5)	.78
Vaccination status			
Influenza vaccine (season)	147/256 (48.4)	628/1328 (43.8)	.14
Pneumococcal vaccination (<5 y)	53/245 (21.6)	233/1296 (18)	.21
Current smoker	59/302 (19.5)	407/1431 (28.4)	.002
Heavy alcohol consumption	39/302 (12.9)	244/1429 (17.1)	.091
Underlying disease			
Chronic obstructive pulmonary disease	115/304 (37.8)	434/1435 (30.2)	.012
Cancer	31/304 (10.2)	120/1435 (8.4)	.36
Chronic renal disease	40/304 (13.2)	110/1435 (7.7)	.003
Chronic liver disease	25/304 (8.2)	122/1435 (8.5)	.96
Dementia	13/304 (4.3)	77/1435 (5.4)	.52
Stroke	36/304 (11.8)	112/1435 (7.8)	.029
Peripheral artery disease	23/284 (7.6)	52/1266 (3.6)	.004
Arterial hypertension	126/288 (43.8)	424/1352 (31.4)	<.001
Diabetes mellitus	80/304 (26.3)	303/1435 (21.1)	.056
Dyslipidemia	75/286 (26.2)	264/1342 (19.7)	.017
Preexisting heart conditions	173/304 (56.9)	344/1435 (24)	<.001
Arrhythmia	94/304 (30.9)	162/1435 (11.3)	<.001
Coronary disease	60/304 (19.7)	120/1435 (8.4)	<.001
Congestive heart failure	71/304 (23.4)	98/1435 (6.8)	<.001
Baseline treatment			
Oral anticoagulation	51/281 (18.1)	84/1253 (6.7)	<.001
Antiplatelet therapy	85/283 (30)	267/1266 (21.1)	.002
Statin treatment	61/282 (21.6)	171/1264 (13.5)	.001
Beta-blockers	37/282 (13.1)	101/1266 (7.98)	.009
ACE inhibitor and/or angiotensin II receptor blocker	88/283 (31.1)	286/1266 (22.6)	.003
Diuretic therapy	105/283 (37.1)	256/1266 (20.2)	<.001
Prehospitalization antibiotic treatment	24/287 (8.36)	202/1404 (14.4)	.004
Multilobar pneumonia	97/304 (31.9)	389/1435 (27.1)	.10
Respiratory insufficiency[a]	218/304 (71.7)	847/1435 (59)	<.001
Pleural effusion	38/304 (12.5)	200/1435 (13.9)	.57
Empyema	13/304 (4.28)	79 /1434 (5.5)	.47
Septic shock at admission	60/304 (19.7)	162/1432 (11.3)	<.001
Hypoalbuminemia (<30 g/L)	129/259 (49.8)	512/1225 (41.8)	.021
Pneumococcal bacteremia	121/304 (39.8)	374/1435 (26.1)	<0.001
High-risk pneumonia (PSI >90 points, classes IV and V)	259/304 (85.2)	866/1433 (60.3)	<.001

Abbreviations: ACE, acute cardiac event; PSI, pneumonia severity index.

[a]Respiratory insufficiency defined as PaO2 <60 mmHg or peripheral oxygen saturation <90%.

Table 2. Adjusted Multivariate Logistic Regression for Acute Cardiac Events in 1739 Episodes of Pneumococcal Pneumonia

Variable	Odds Ratio for Acute Cardiac Events (95% CI)	*P* Value
Age	1.02 (1–1.03)	.009
Preexisting heart disease	3.45 (2.54–4.71)	<.001
Pneumococcal bacteremia	2.52 (1.86–3.42)	<.001
Septic shock at admission	1.77 (1.21–2.59)	.003
High-risk pneumonia (PSI >90 points, classes IV and V)	2.33 (1.56–3.54)	<.001

Abbreviation: PSI, pneumonia severity index.

was observed in patients who were empirically treated with β-lactam and fluoroquinolone combination therapy in the univariate analysis; however, fluoroquionolone exposure (either as mono- or combination therapy) was not. Patients with pneumococcal pneumonia with acute cardiac events had a greater need for ICU admission, mechanical ventilation, and a longer hospital stay. Among the 304 patients with pneumococcal pneumonia with acute cardiac events, the 30-day mortality was 13.9%, compared with 4.7% among those patients without cardiac complications (P = .001). Acute cardiac events were

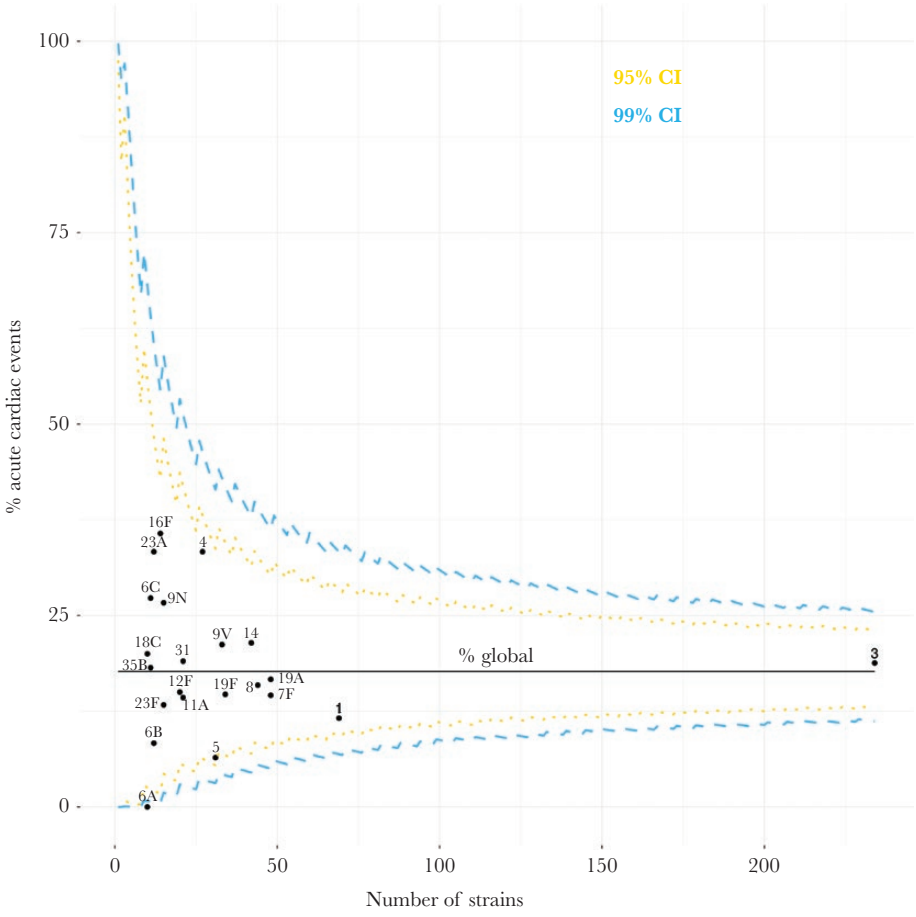

Figure 1. Funnel plot analysis of serotypes and acute cardiac events.

independently associated with 30-day mortality (adjusted odds ratio, 1.88; 95% CI, 1.11–3.13; $P = .017$).

DISCUSSION

This retrospective study of a large cohort of patients with pneumococcal pneumonia defined several host factors associated with the development of acute cardiac events. We also studied a possible link between both pneumococcal serotypes or clonal complexes and the risk of developing cardiac complications.

The host factors we found to be independently associated with acute cardiac events in pneumococcal pneumonia were older age, preexisting heart conditions, pneumococcal bacteremia, septic shock at admission, and high-risk pneumonia. A finding of interest in our study is the fact that prehospitalization antibiotic treatment for the acute episode of pneumococcal pneumonia tended to display a protective effect for acute cardiac events, although it did not reach statistical significance in the multivariate analysis. Interestingly, experimental animal studies have shown a significant positive correlation between pneumococcal blood load and cardiac damage [17, 20]. In addition, pneumococcal bacteremia has been shown to be an important trigger for the development of acute cardiac events in CAP patients [31]. We found a lower incidence of bacteremia and a less severe clinical presentation in patients with prehospitalization antibiotic treatment, which may, to some extent at least, explain the lower incidence of cardiac complications.

Previous information regarding characteristics of pneumococcal strains and cardiac complications is derived from 2 studies [20, 22]. An experimental study evaluating not more than 6 mice per strain showed that only serotypes able to cause high-grade bacteremia, such as serotypes 2, 3, 4, and 6A, produced cardiac damage [20]. Moreover, for the serotypes that could invade the heart, the type of cardiac damage was strain specific. In addition, a recent study of 310 patients with invasive pneumococcal disease, of whom 71 presented an acute cardiac event, found an association between serotypes 3 and 9N [22]. In that study, clonal complexes were not analyzed. In contrast, in our study, which included a large number of patients, we did not find any significant association of serotypes 3 and 9N with acute cardiac events. Our study, analyzing serotypes isolated from 872 patients and clonal complexes from 742, found a negative trend linking acute cardiac events with some highly clonal serotypes, such

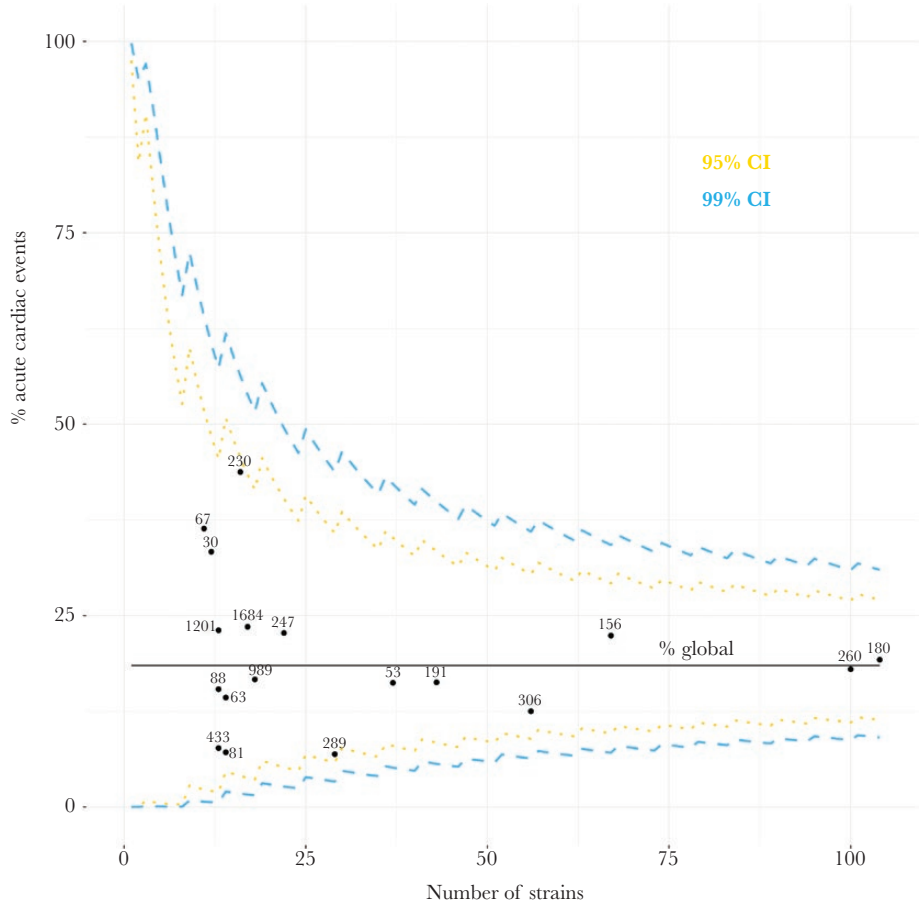

Figure 2. Funnel plot analysis of genotypes (clonal complexes) and acute cardiac events.

Table 3. Treatment and Outcomes of Pneumococcal Pneumonia in Patients who Developed Acute Cardiac Events and Those who Did Not

Patients (n = 1739)	Pneumococcal Pneumonia With Acute Cardiac Events (n = 304), No. (%)	Pneumococcal Pneumonia Without Acute Cardiac Events (n = 1435), No. (%)	*P* Value
Initial antibiotic treatment			
β-lactam monotherapy	131/304 (43.1)	700/1435 (48.8)	.082
β-lactam + macrolide	5/304 (1.6)	32/1435 (2.2)	.672
Fluoroquinolone monotherapy	24/304 (7.9)	140/1435 (9.8)	.37
β-lactam + fluoroquinolone	134/304 (44.1)	525/1435 (36.6)	.017
Fluoroquinolone (alone or any combination)	158/304 (52)	669/1435 (46.6)	.102
Macrolide (alone or any combination)	6/304 (2)	37/1435 (2.6)	.68
Other	10/304 (3.3)	37/1435 (2.6)	.62
Door-to-needle antibiotic time, median (IQR[a]), h	5 (3.00–8.00)	5 (3.00–7.00)	.72
Intensive care unit admission	79/304 (26)	147/1435 (10.2)	<.001
Need for mechanical ventilation[b]	74/304 (24.3)	111/1435 (7.7)	<.001
Length of hospital stay, median (IQR), d	10 (7.00–18.2)	8 (5.00–11.00)	<.001
Early mortality (≤48 h)	8/304 (2.6)	22/1435 (1.71)	.24
30-d mortality	42/304 (13.8)	68/1435 (4.7)	<.001

Abbreviation: IQR, interquartile range.

[a]Data missing in 482 patients.

[b]Includes invasive and noninvasive mechanical ventilation.

as 5 (CC289) or 1 (CC306). Moreover, clonal complex CC230 tended to be associated with a higher incidence of acute cardiac events. This finding, although not statistically significant in the funnel plot, may be clinically relevant. In our study, clonal complex CC230 was mainly related to serotypes 19A and 24F. Serotype 19A was not associated with acute cardiac events, suggesting that genetic background, and not serotype, could play a major role in these serious complications. Importantly, while serotype 19A is included in both conjugated and polysaccharide pneumococcal vaccines, serotype 24F is not covered by the current vaccines or by any of those under development. It is plausible that certain strains disproportionally impact individuals who have risk factors for ACEs—older age, preexisting heart disease. Multivariate analyses that include serotype-specific information should be performed in future investigations.

Our finding that CC230 tends to be associated with a higher incidence of acute cardiac events is hypothesis-generating and should be explored in further multicenter studies in other geographical areas and including a higher number of pneumococcal strains. Our study also opens up avenues for further research exploring the association of the pneumococcal serotypes and genotypes and long-term risk of serious cardiac events.

Despite a number of strengths, our study has some limitations that should be acknowledged. First, the study involved a cohort of adults with pneumococcal pneumonia recorded over more than 20 years at a single center. This may limit the extrapolation of our results to other geographical areas where other serotypes and clonal complexes may be more prevalent [30]. Second, serotyping and genotyping were not performed in all isolates; however, serotypes and genotypes were determined in the majority of the 983 isolates (89% and 76%, respectively). Third, the small number of some serotypes and clonal complexes limited the analysis of their potential relationship with acute cardiac complications. Lastly, worsening of preexisting heart conditions was included as an acute cardiac event and may have confounded the results; however, analyzing exclusively new-onset arrhythmia, new-onset heart failures, and myocardial infarction yielded similar results.

In summary, acute cardiac events are frequent and confer worse clinical outcomes in pneumococcal pneumonia. Although CC230 tends to be associated with a higher incidence of acute cardiac events, host factors appear to be more important than pathogen-related factors for developing these life-threatening complications. The host factors defined in this study may help identify the patients who require close follow-up including heart rhythm monitoring and special care to avoid fluid overload, particularly within the first 48 hours of admission. These high-risk patients should be the target for urgent preventive intervention strategies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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