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Risk factors for cardiovascular events in hospitalized patients with community-acquired pneumonia

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SUMMARY

Background: An increased risk of cardiovascular complications has been found in those with community-acquired pneumonia (CAP). Preliminary data suggest that pneumococcal pneumonia, more severe pneumonia, older age, renal disease, hypoalbuminemia, and inpatient sliding scale insulin administration contribute to risk. The objective of this study was to ascertain additional factors influencing cardiovascular events in CAP.

Methods: This investigation was a retrospective cohort study of inpatients with CAP. Outcomes evaluated were development of a cardiovascular event during hospitalization, defined as acute pulmonary edema, cardiac arrhythmia, or myocardial infarction. Those with and without events were compared across cardiovascular- and pneumonia-specific variables by logistic regression to ascertain factors that independently increase risk or reduce risk.

Results: Of 3068 inpatients with pneumonia, 376 (12%) developed a cardiovascular event. Hyperlipidemia, more severe pneumonia, and *Staphylococcus aureus* or *Klebsiella pneumoniae* as etiologies were associated with increased risk, while statin use was associated with decreased risk.

Conclusions: This study highlights variables in CAP patients that should make clinicians vigilant for the development of cardiac complications. Additional research is needed to determine if statins attenuate cardiac risk in CAP.

1. Introduction

While community-acquired pneumonia (CAP) may result in morbidity and mortality as a direct function of an infectious agent's deleterious effects on the respiratory system, those with CAP are known to develop additional complications extraneous to the lungs.[1] These complications may not be directly related to the pathogen itself, but are postulated to be due in part to the inflammatory response that ensues.[2] Among other sequelae, evidence has suggested an increased risk of cardiovascular events, such as myocardial infarction, in those with CAP.[3,4] Preliminary data have demonstrated that infection with the pneumococcus,[5,6] older age, a previous cardiac history, severe pneumonia,[2,6] chronic kidney disease, hypoalbuminemia,[6] and sliding scale insulin administration during a CAP episode[7] may contribute to developing cardiac incidents in CAP. In contrast, other reports have suggested improved outcomes in general in the setting of CAP with medications mitigating cardiovascular disease, such as statins and angiotensin converting enzyme (ACE) inhibitors,[8] but no study has evaluated cardiovascular events in the setting of CAP with reference to such medications. As a result, the objective of this study was to ascertain additional risk factors or protective factors influencing cardiovascular events in CAP, including medications prescribed specifically for cardiovascular diseases, and to clarify previously defined risk factors for such events.

2. Methods

2.1. Study design and population

This study was a secondary analysis of the Community-Acquired Pneumonia Organization (CAPO) database on CAP, a multicenter, retrospective, international cohort study of inpatients from 80 centers in 13 countries. Patients with a confirmed diagnosis of CAP were entered into the database from June 1, 2011 to November 12, 2012. Data procured for CAPO were collected on a case report form, entered into a computer database, and then reviewed for quality assurance before final acceptance into the database. Institutional review board evaluation was performed at each of the sites from which patients were sampled. Informed consent was waived due to the retrospective nature of this investigation.

Inclusion criteria were age ≥16 years and confirmed CAP. CAP was verified if a new infiltrate on chest X-ray was present with any

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of the following: leukocyte count $>10 \times 10^9$ cells/l, $<4 \times 10^9$ cells/ml, or >5% bands; new onset or increased cough; or temperature $\geq$37.8 °C or $\leq$35.6 °C. Patients were excluded if pneumonia developed 48 h or more after admission. CAP severity was ascertained by the Pneumonia Severity Index (PSI).[9] Etiologic organisms of pneumonia were discerned primarily by blood or sputum culture. Some institutions performed urinary antigen testing (*Legionella pneumophila* and *Streptococcus pneumoniae*), PCR testing (*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydia pneumoniae*, and respiratory viruses), and sputum culture on buffered charcoal yeast extract agar (BCYE) or direct fluorescent antibody staining of sputum for *Legionella* species.

2.2. Study definitions

A cardiovascular event was defined as acute pulmonary edema, new onset cardiac arrhythmia, exacerbation of a preexisting arrhythmia, or myocardial infarction. All events were confirmed by an attending physician at the time they transpired and were required to be documented in the medical records to be considered present for this analysis. Pulmonary edema was diagnosed by a combination of clinical exam findings (such as jugular venous distension), radiologic evidence, and/or elevated brain natriuretic peptide levels. For an arrhythmia to be considered exacerbated, new clinical signs or symptoms, such as chest pain, dyspnea, or cardiac arrest, had to accompany the arrhythmia and be deemed by the treating physician to be due to the arrhythmia. Myocardial infarction was verified by electrocardiogram aberrations and elevated cardiac biomarkers including myocardial specific creatine kinase and/or cardiac troponins. To be considered relevant to the current episode of pneumonia, all cardiovascular events had to transpire upon admission for CAP or at some time during the concurrent hospitalization for CAP. If a patient developed more than one cardiac incident during hospitalization, the case in question was counted as a single cardiac event in analyzing the primary outcome. Comorbidities, such as hyperlipidemia or previous cardiac disease, were defined as present if documented in the medical records by a medical provider.

2.3. Study outcomes

The primary outcome assessed in this study was development of a cardiovascular event during admission for CAP. Secondary outcomes included in-hospital mortality and 28-day mortality, the cumulative number of deaths from admission until 28 days after admission, regardless if the patient was discharged from the hospital. Categories of variables collected as potential confounders of cardiovascular events and used in multivariate analyses were: age, sex, history of cardiovascular disease prior to pneumonia admission, history of atrial fibrillation prior to admission, current smoking status, family history of cardiac disease, use of cardiovascular medicines (anticoagulants (heparin or warfarin), aspirin, alternative antiplatelet agents (clopidogrel, ticlopidine), beta-blockers, ACE inhibitors, or statins), genus and species of infecting bacteria, initiation of empiric therapy within 8 h of pneumonia diagnosis, empiric macrolide therapy during pneumonia admission (erythromycin, clarithromycin, or azithromycin), empiric quinolone therapy during pneumonia admission (moxifloxacin, levofloxacin, ciprofloxacin, ofloxacin, gemifloxacin, or lomefloxacin), albumin level on admission, pneumonia severity by PSI, and presence of bacteremia related to pneumonia. For this analysis, use of a medication was defined as use during the current hospitalization for pneumonia or use as an outpatient prior to admission. Empiric antibiotic therapy was denoted as the antibiotic regimen begun within the first 48 h of admission before an etiologic agent was identified.

2.4. Statistical analyses

Chi-square or Fisher's exact tests were used to compare baseline categorical characteristics of those with and without cardiovascular events, while the Mann–Whitney *U*-test was used to compare continuous characteristics between the two groups.

To create a predictive model to evaluate variables significantly associated with cardiovascular events in hospitalized patients with CAP, multivariable logistic regression models were employed. Rather than eliminating patients with missing values for any particular variable, we used bootstrapped additive imputation models to create datasets with complete data for every patient. A total of 20 imputed datasets were created to obtain the most valid variance estimates. In each dataset, all variables were analyzed for collinearity using variance inflation factor and tolerance statistics.

Next, these 20 datasets were each subjected to a purposeful selection algorithm to create a final best-fit predictive logistic regression model.[10] The variables collected as potential confounders of cardiovascular events, as previously elucidated, were the ones included in the purposeful selection algorithm. Briefly, the purposeful selection algorithm initially selects variables with bivariate *p*-values of $\leq$0.25, and fits a model based on backwards elimination. Next, variables eliminated by backwards elimination are further assessed for potential confounding along with the remaining variables, and any included variable with a $\geq$15% change in the regression coefficient is replaced in the model. Finally, variables initially excluded based on the bivariate analysis are further assessed for confounding with the included variables and are similarly added back to the model if the regression coefficients change by $\geq$15%. In this analysis, variables remaining in the purposeful selection of each of the 20 datasets were noted, and any variables remaining in more than 50% of the purposefully selected models were included in a final logistic regression model.

R version 2.15.1[11] and SAS version 9.3 (SAS Inc, Cary, NC) were used for all analyses. The Hmisc package was used for multiple imputation following accepted procedures.[12] Except as specified previously in the initial selection of variables in the purposeful selection algorithm, *p*-values $\leq$0.05 were considered significant.

3. Results

Of 3068 patients with CAP, 376 (12%) presented with at least one cardiovascular event upon admission or subsequently developed an event during hospitalization. However, in total, 435 events occurred, as some patients had more than one cardiovascular incident during hospitalization. The most common event to transpire was exacerbation of a previously diagnosed arrhythmia (Table 1). Those with a cardiac complication were more likely to be older and to have had a preexisting cardiac history, atrial fibrillation, hypertension, or hyperlipidemia. Furthermore, they were more likely to have been administered empiric macrolide therapy or to have been prescribed aspirin or another antiplatelet, beta-blockers, or ACE inhibitors as a

Table 1
Distribution of cardiovascular events by category of event[a]

Event	*n* (%)	Present on admission	Developed during hospitalization
	(*n* = 435)	(*n* = 188)	(*n* = 247)
New onset arrhythmia	179 (41)	70 (37)	109 (44)
New onset pulmonary edema	127 (29)	64 (34)	63 (26)
Worsening of preexisting arrhythmia	73 (17)	28 (15)	45 (18)
Myocardial infarction	56 (13)	26 (14)	30 (12)

[a] All values are given as number (*n*) of events by category (% of total events).

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