Vascular complications are associated with poor outcome in community-acquired pneumonia

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Summary

Background: Recognition of cardiovascular risk factors is important for primary and secondary prevention strategies. Recent evidence has linked lower respiratory tract infections with the development of acute myocardial infarction.

Aim: The aim of this study was to determine the frequency of cardiovascular and cerebrovascular events and the clinical outcomes, during hospitalization for community-acquired pneumonia (CAP).

Design: We performed a retrospective study of 4408 patients with CAP presenting to five hospitals over a 2-year period. Clinical information, co-morbidities, cardiovascular events and 90-day mortality were collected from review of medical case notes. The relationship between cardiovascular events and outcomes were analysed using multivariable logistic regression.

Results: From a total of 4408 patients, 2.2% developed stroke, 5% acute coronary syndrome or myocardial infarction and 9.3% new onset atrial fibrillation. These were associated with increased 90-day mortality [odds ratio (OR), 1.49 95% CI 1.18–1.87, \( P = 0.0006 \)]. Vascular events were independently associated with increased length of hospital stay—median 12 days (IQR 5–22), compared to patients with no vascular events 8 days (IQR 3–17 days, \( P < 0.0001 \)).

Conclusions: Cardiovascular and cerebrovascular events are common during hospitalization for CAP and are associated with increased 90-day mortality.

Introduction

Community-acquired pneumonia (CAP) is the most common infectious disease requiring hospitalization in western countries and a major cause of morbidity and mortality worldwide.\(^1\) It is known that 50% of all deaths in patients with pneumonia, and more than a quarter of deaths within 30 days are related to co-morbidities such as vascular disease (including acute coronary syndrome, decompensated cardiac failure and stroke).\(^2\)

There is an established link between vascular events following acute infection and this is particularly augmented in the first few days but persisting for several weeks following an acute infection.\(^3\)\(^-\)\(^5\)

To date, there have been no studies of arrhythmias, transient ischaemic attack (TIA) and stroke in CAP and limited small retrospective studies of acute coronary syndrome in patients with CAP.\(^6\)\(^,\)\(^7\)

The aim of our study was to describe the frequency of cardiovascular and cerebrovascular events in patients admitted with CAP and to assess whether these events are independently associated with poor outcome.

Methods

We conducted a retrospective study of patients admitted to five hospitals in South East Scotland...
over a 2-year period from 2005 to 2007. Lothian Research Ethics Committee approved the study.

Identification of cases of CAP

Patients aged ≥18 years were identified from an administrative database of hospital admissions to five National Health Service hospitals in the East of Scotland. ICD-10 codes were used to identify all adult patients with a primary diagnosis of pneumonia (ICD-10 codes J12–J18). Patients were excluded if they did not have clinical or radiological features consistent with CAP or had any of the following exclusion criteria: hospital-acquired pneumonia; admission or transfer from a health-care facility; post-operative pneumonia; HIV; age <18 years.

The use of International classification of diseases (ICD) codes in combination with medical chart review has been shown to have good accuracy for identifying cases of CAP. ICD codes, including the ICD-10 codes used in this study are widely used in epidemiological and prognostic studies of CAP.

Medical records of those identified by ICD-10 to have a vascular event were reviewed retrospectively to obtain details of clinical and demographical characteristics in addition to confirmation of the vascular events.

Identifying cardiovascular complications

From review of medical case notes and laboratory results, the incidences of four vascular complications—ST elevation myocardial infarction (STEMI), acute coronary syndrome, new onset atrial fibrillation (AF) and cerebrovascular events were recorded. We have defined vascular events to include any of the four vascular complications. STEMI diagnosis was based on reported ST elevation on ECG along with positive cardiac troponin result and a clinical diagnosis of STEMI. Acute coronary syndrome was defined as acute non-ST elevation myocardial infarction (compatible ECG changes along with positive Troponin I and a clinical diagnosis of non-STEMI or unstable angina (clinical diagnosis of non-myocardial infarction acute coronary syndrome comprising chest pain with one of the ECG abnormalities, positive cardiac specific troponin or a clinical diagnosis of cardiac ischaemia)). In the absence of the above, chest pain occurring during hospitalization was not regarded as constituting acute coronary syndrome. An elevated cardiac specific troponin may occur in CAP in the absence of an acute coronary syndrome and hence an elevated troponin in the absence of a compatible clinical history was not regarded as an acute cardiovascular event.

New onset atrial fibrillation was diagnosed in a patient without a prior history of AF in whom the attending physician made a diagnosis of AF based on ECG findings. Stroke was defined as a new onset neurological deficit lasting >24 h with a confirmatory CT or MRI.

Outcomes

The primary outcome was 90-day mortality. The secondary outcome measured was length of hospital stay.

Statistical analysis

All data were analysed using Graphpad prism (Graphpad software, San Diego, CA, USA). For demographic and clinical variables, data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables unless otherwise stated. Survival curves were constructed by Kaplan–Meier analysis and curves compared using the Log-rank test. Adjustment for potential confounders was achieved using multivariable logistic regression. Multivariable regression models were constructed by including demographic (age, gender, co-morbidities, smoking history—as listed in Table 1) and clinical characteristics (site of care, including admission to intensive care unit) with cardiovascular or cerebrovascular events as

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<th>Table 1 Demographics of the study population</th>
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<td>Baseline characteristics</td>
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<td>Age (years)</td>
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<td>Gender: male (%)</td>
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<td>Previous myocardial infarction (%)</td>
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independent variables. As this was a retrospective study, full data to calculate severity scores such as CURB65 and PSI were not available for all patients. Therefore these were not included in the logistic regression analysis. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test ($P > 0.05$ indicates adequate model fit). To analyse factors associated with length of stay, multiple linear regression was performed using the above co-variates in addition to cardiovascular events as independent variables.

Results are presented as adjusted odds ratio (AOR) with 95% CIs. A $P$-value of <0.05 was considered statistically significant for each analysis.

**Results**

After removing patients with a diagnostic code corresponding to an exclusion criterion, 5034 patients were identified. After reviewing medical records for these patients a further 626 patients were excluded, leaving a study cohort of 4408 patients.

In this cohort, median age was 73 years (interquartile range 58–82 years). About 65.6% of the patients were aged ≥65 years (age range 18–105 years). About 52.0% of the patients were female and 48.0% were male. Median duration of admission was 8 days (IQR 3–17 days)—range 0–272 days. Ninety-day mortality was 13.9%.

ICU admission was required for 172 patients (3.9%) of the study population.

Baseline characteristics of the study population are shown in Table 1.

### Frequency of cardiovascular and cerebrovascular events in patients with CAP

Acute myocardial infarction associated with ST elevation occurred in 1.8% patients during hospitalization. Acute coronary syndrome incorporating non-ST elevation myocardial infarction and unstable angina occurred in 3.2% patients. Cerebrovascular events occurred in 2.2% of the patients (0.5% developed haemorrhagic stroke and 1.7% developed ischaemic stroke) and new onset atrial fibrillation occurred in 9.3% of patients during hospitalization.

The frequency of myocardial infarction ($P < 0.0001$), NSTEMI and acute coronary syndrome ($P < 0.0001$), atrial fibrillation ($P < 0.0001$) and cerebrovascular events ($P < 0.0001$) were all increased in patients aged ≥65 years.

In a multivariable logistic regression model, factors significantly associated with acute myocardial infarction were age, previous acute myocardial infarction, COPD and chronic renal disease. Only age was independently associated with acute coronary syndrome diagnosis (Table 2).

Age, diabetes mellitus and prior myocardial infarction were associated with increased risk of atrial fibrillation.

Finally, cerebrovascular events were associated with increasing age and a prior history of cerebrovascular disease but having prior COPD was protective.

### Outcomes of patients with cardiovascular and cerebrovascular events

#### Ninety-day mortality

Ninety-day mortality was 13.9%. Figure 1 shows the outcome of patients with each cardiovascular complication and cerebrovascular event compared with outcome in patients with no history of these events.

Kaplan–Meier survival analysis showed increase in 90-day mortality in patients with vascular events during hospitalization (Figure 1E) (log-rank test $\chi^2$ 19.1, $df = 1$, $P < 0.0001$). Acute myocardial infarction (log-rank test $\chi^2$ 6.4, $df = 1$, $P = 0.01$), acute coronary syndrome (log-rank test $\chi^2$ 4.37, $df = 1$, $P = 0.04$), stroke (log-rank test $\chi^2$ 15.8, $df = 1$, $P < 0.0001$) and new onset atrial fibrillation (log-rank test $\chi^2$ 4.46, $df = 1$, $P = 0.03$) were all associated with increased 90-day mortality.

In multivariable analysis, stroke during hospitalization (AOR 1.79, 95% CI 1.51–2.12, $P < 0.0001$), acute myocardial infarction during hospitalization
(AOR 1.93, 95% CI 1.60–2.33, \( P < 0.0001 \)) and new onset atrial fibrillation during hospitalization (AOR 2.39, 95% CI 1.65–2.19, \( P < 0.0001 \)) were all associated with increased 90-day mortality. Acute coronary syndrome (AOR 1.46, 95% CI 0.82–2.76, \( P = 0.2 \)) was not significant in this model.

Length of stay
Median duration of admission for the population as a whole was 8 days (IQR 3–17 days).

The duration of stay for acute myocardial infarction was 12 days (interquartile range 8–23 days, \( P < 0.0001 \)), new onset atrial fibrillation was 12 days (6–23, \( P = 0.008 \)) and stroke 14 days (6–33, \( P < 0.0001 \)), were all associated with increased length of stay. Patients with acute coronary syndrome did not have significantly prolonged length of stay (median 10 days, 4–18, \( P = 0.07 \)).

Overall, patients with one or more vascular events had a higher median length of stay of 12 days (IQR 5–22), compared to patients with no vascular events 8 days (IQR 3–17 days, \( P < 0.0001 \)).

In a linear regression analysis, stroke (coefficient 7.58 SE 2.91, \( P = 0.0009 \)), atrial fibrillation (coefficient 3.91 SE 1.45, \( P = 0.007 \)) and myocardial infarction during hospitalization (coefficient 7.16 SE 2.46, \( P = 0.004 \)) were associated with increased length of stay, independent of confounders. Acute coronary syndrome was not independently associated with increased length of stay (coefficient 0.08 SE 3.41, \( P = 0.9 \)).

### Discussion
This large study involving 4408 patients has shown that vascular events are common in patients admitted with CAP. About 16.5% patients developed STEMI, acute coronary syndrome, new onset atrial fibrillation and/or cerebrovascular event. Among these events, the most frequent was new onset atrial fibrillation. Vascular events were associated with increased 90-day mortality.

The association between respiratory infections and cardiovascular events has been the subject of extensive recent study. Although some studies in hospitalized patients have shown an association between acute infections and increased cardiovascular events and stroke,\(^4,12,13\) there is a paucity of data in patients admitted with CAP. It is known that cardiovascular events peak during the winter when respiratory infections are also most frequent.\(^14,15\)

There have been three major primary care studies comprising a total of 33 563 patients with first acute myocardial infarction and 28 271 with first stroke\(^3,5,16\) following respiratory tract infection. The risk of a vascular event persists for up to 90 days after infection. In our study, we have shown a similar association in patients admitted with CAP.

In a retrospective study conducted in the USA, Ramirez et al.\(^6\) showed that a combined diagnosis of CAP and acute myocardial infarction is common among hospitalized patients with severe CAP (15% of 86 patients), and in cases in which the clinical course of a hospitalized patient with CAP is...
complicated by clinical failure (development of respiratory failure or shock), acute myocardial infarction should be considered as a possible aetiology. Another retrospective study, by Musher et al. also conducted in the USA found in 170 patients admitted with pneumococcal pneumonia, 19.4% had one or more cardiac events (myocardial infarction, atrial fibrillation or ventricular tachycardia, or new onset or worsening congestive heart failure) which was associated with higher mortality.

The present study confirms the findings of these smaller studies that vascular events are common in patients with CAP and are associated with prolonged length of hospital stay and increased risk of 90-day mortality.

Potential mechanisms that result in increased 90-day mortality in patients admitted with CAP include the degree of hypoxia, pyrexia, systemic inflammation, acidosis, coagulopathy and metabolic disturbance. Both pneumonia and acute coronary syndromes are associated with major systemic inflammation and activation of coagulation pathways. CAP leads to elevation in pro-inflammatory cytokines such as C-reactive protein, Interleukin 6, Tumour Necrosis Factor-α and Interleukin 8 and also induces a marked pro-thrombotic state associated with elevation of thrombotic markers such as fibrinogen, factor IX, thrombin–anti-thrombin complex and D-dimer. In a recent study, Milbrandt et al. identified significant pro-thrombotic effects and elevation of coagulation markers during hospital admission with CAP. The combination of systemic inflammation and thrombosis are highly conducive to plaque rupture and clot formation.

Figure 1. Ninety-day mortality rates and the development of cardiovascular complications. (A) Acute myocardial infarction, (B) Acute coronary syndrome, (C) Stroke, (D) New onset atrial fibrillation and (E) all vascular events.
It is known that acute respiratory infections are associated with reduced myocardial contractility, increased myocardial oxygen demand and reduced myocardial oxygen delivery. Cytokines (Interleukin 1, Tumour Necrosis Factor-α, Interleukin 6), prostanoids, endothelin-1 and nitric oxide produced in sepsis are all known to depress myocardial contractility. Several clinical and scientific studies have shown that decreased systolic and diastolic ventricular contractility in septic patients results in reduced coronary perfusion pressure. Associated arrhythmias may also be a risk factor for the development of a TIA or ischaemic stroke. The coagulopathy associated with severe pneumonia may also be a potential risk factor for cerebral haemorrhage.

Limitation
This study has limitations. First, it is a retrospective study using ICD-10 codes to identify cases of CAP and vascular events. These codes have modest sensitivity and specificity and it is likely that some cases of pneumonia admitted during the study period were missed. In addition, we did not have the data to calculate severity scores such as CURB65/PSI or data on prior secondary prevention treatment, which would ideally have been added to the multi-variable model. Although, we reviewed clinical data, ECG, troponin testing and brain imaging to diagnose vascular events, a prospective study would be desirable to better characterize the patients in terms of both cardiovascular events and severity of CAP.

Conclusion
Cardiovascular events and stroke are common during hospitalization for CAP and are associated with increased length of hospital stay and 90-day mortality. Further prospective studies are needed to define the pathogenesis of this association and possible therapeutic modalities to prevent these vascular events.

Conflict of interest: None declared.

References


