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MAJOR ARTICLE

Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia

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Background. Previous reports suggest that community-acquired pneumonia (CAP) is associated with an enhanced risk of cardiovascular complications. However, a contemporary and comprehensive characterization of this association is lacking.

Methods. In this multicenter study, 1182 patients hospitalized for CAP were prospectively followed for up to 30 days after their hospitalization for this infection. Study endpoints included myocardial infarction, new or worsening heart failure, atrial fibrillation, stroke, deep venous thrombosis, cardiovascular death, and total mortality.

Results. Three hundred eighty (32.2%) patients experienced intrahospital cardiovascular events (CVEs) including 281 (23.8%) with heart failure, 109 (9.2%) with atrial fibrillation, 89 (8%) with myocardial infarction, 11 (0.9%) with ischemic stroke, and 1 (0.1%) with deep venous thrombosis; 28 patients (2.4%) died for cardiovascular causes. Multivariable Cox regression analysis showed that intrahospital Pneumonia Severity Index (PSI) class (hazard ratio [HR], 2.45, $P = .027$; HR, 4.23, $P < .001$; HR, 5.96, $P < .001$, for classes III, IV, and V vs II, respectively), age (HR, 1.02, $P = .001$), and preexisting heart failure (HR, 1.85, $P < .001$) independently predicted CVEs. One hundred three (8.7%) patients died by day 30 postadmission. Thirty-day mortality was significantly higher in patients who developed CVEs compared with those who did not (17.6% vs 4.5%, $P < .001$). Multivariable Cox regression analysis showed that intrahospital CVEs (HR, 5.49, $P < .001$) independently predicted 30-day mortality (after adjustment for age, PSI score, and preexisting comorbid conditions).

Conclusions. CVEs, mainly those confined to the heart, complicate the course of almost one-third of patients hospitalized for CAP. More importantly, the occurrence of CVEs is associated with a 5-fold increase in CAP-associated 30-day mortality.

Keywords. pneumonia; cardiovascular events; mortality.

Community-acquired pneumonia (CAP) is the most common infectious disease leading to hospitalization in intensive care units and the most common cause of mortality in patients with infection [1]. CAP is also a serious public health problem as its incidence continues to increase in the elderly, the fastest-growing age group in Western countries, and it is associated with an enhanced risk of morbidity and mortality even after the infection has resolved [2, 3]. In the United States, CAP affects >5 million patients and causes 60 000 deaths every year [4]. Recent studies documented a frequent association between CAP and the occurrence of acute cardiac complications such as heart failure (HF), atrial fibrillation (AF), and myocardial infarction (MI) [5]. Moreover, the occurrence of these complications in patients with CAP has been associated with increased short- and long-term mortality [5–7]. However, there is still uncertainty regarding the actual incidence of these complications as it has varied widely in studies that have used different designs (retrospective vs prospective) and criteria to define these complications [8]. Furthermore, only 1 multicenter study is currently available that described the incidence and timing of cardiac complications in a cohort of patients with CAP recruited between 1991 and 1994 [5]. Finally, the incidence of CAP-associated vascular complications in vascular territories other than the coronaries, such as stroke, deep venous thrombosis (DVT), and pulmonary embolism (PE), is still undefined [9]. We argue that a more comprehensive and contemporary appraisal of the cardiovascular complications that occur during CAP is very important to better appreciate the contribution of these events to the morbidity and mortality associated with CAP, identify patients at higher risk of death during this infection, and design evidence-based strategies to improve their outcomes. Accordingly, we performed a multicenter, prospective study to assess the incidence of cardiac and noncardiac vascular complications, their timing, and their relationship with 30-day mortality in patients with CAP.

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METHODS

Patient Selection

This cohort study recruited patients at 5 medical centers: 3 from the University Hospital Policlinico Umberto I, Sapienza University of Rome, Italy (Department of Internal Medicine and Medical Specialties, Department of Clinical Medicine, Department of Public Health and Infectious Diseases), 1 from the General and University Hospital of Careggi, Florence, Italy (Internal and Emergency Medicine Unit), and 1 from the Ottawa Hospital in Ontario, Canada (Department of Internal Medicine).

All patients with CAP admitted to the 5 units from October 2011 to January 2016 were prospectively recruited and followed up.

After they gave written informed consent, we enrolled 1182 consecutive patients who fulfilled the following criteria in the study: (1) age ≥18 years; (2) clinical presentation of an acute illness with at least ≥2 of the following signs or symptoms of CAP: presence of rales, rhonchi, bronchial breath sounds, dullness, increased fremitus and egophony, fever (>38.0°C), tachycardia, chills, dyspnea, coughing (productive or unproductive cough), chest pain; and (3) presence of new consolidation(s) on chest radiograph [10]. Among patients with preexisting HF, a careful evaluation of clinical and radiological findings as well as of inflammatory markers was performed to differentiate between pneumonia and pulmonary congestion and edema. Pneumonia was considered as CAP if it was diagnosed upon hospitalization and the patient had not been discharged from an acute care facility within 14 days preceding the clinical presentation [11].

Patients were excluded from the study if any of the following criteria applied: radiographic evidence of preexisting infiltrates; immunosuppression (human immunodeficiency virus infection, chemotherapy, high dose of immunosuppressive agents to prevent the rejection of transplanted organs and tissues or to treat autoimmune diseases); presence of malignancy; pregnancy or breastfeeding; documented severe allergy to antibiotics; healthcare-associated pneumonia [11].

The present study was conducted according to the principles stated in the Declaration of Helsinki. The institutional review boards at each institution approved this study.

Baseline Assessment

Data on demographic characteristics and comorbidities were collected. Severity of illness at presentation was quantified by the Pneumonia Severity Index (PSI), a validated prediction score for 30-day mortality [12, 13], and the systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH (SMART-COP) score, a validated score for predicting the need for intensive respiratory or vasopressor support in patients with CAP [14].

Preexistence of type 2 diabetes mellitus, hypertension, dyslipidemia, history of coronary heart disease, chronic obstructive pulmonary disease (COPD), and peripheral artery disease (PAD), HF, and atrial fibrillation were defined as previously described [15–19]. Baseline treatments were defined according to the patients' pharmacological history.

Immediately after diagnosis of CAP, routine blood laboratory tests including serum high-sensitivity cardiac troponin T, a 12-lead electrocardiogram (ECG), and arterial blood gas test were performed. At the Ottawa site, however, troponin assessment was left to the discretion of the treating team.

Assessment of Intrahospital Cardiovascular Events

The primary study outcome was the occurrence of an acute intrahospital cardiovascular event defined as any of the following: (1) non-ST elevation myocardial infarction (NSTEMI); (2) ST elevation myocardial infarction (STEMI); (3) stroke; (4) a new episode of AF; (5) DVT and/or PE; (6) new or worsening HF; or (7) cardiovascular death.

Myocardial infarction, in concordance with the Third Universal Definition of Myocardial Infarction [20], was diagnosed by the detection of a rise of cardiac troponin with at least 1 value above the 99th percentile upper reference limit associated with at least 1 of the following: (1) chest pain; (2) detection of new or presumably new significant ST-segment–T wave changes or new left bundle branch block; (3) development of pathological Q waves in the ECG; (4) de novo imaging evidence of viable myocardium loss or regional wall motion abnormality; (5) identification of an intracoronary thrombus by angiography or autopsy; or (6) cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block. STEMI and NSTEMI were defined as previously reported [20].

The occurrence of stroke was determined on the basis of clinical manifestations and was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) [21].

A new episode of AF was considered a newly recognized episode of AF during the hospitalization in individuals that were in sinus rhythm before hospital admission as documented by medical records, ECGs, rhythm strips, and Holter monitors [22].

DVT or PE was determined on the basis of clinical manifestations and by eco-Doppler ultrasound or angiography CT, respectively [23].

New or worsening HF was considered in patients with worsening signs, symptoms, and supportive findings on ECG and/or chest radiograph consistent with this diagnosis (ie, new or worsening paroxysmal nocturnal dyspnea; neck vein distention on clinical examination; pulmonary rales; radiographic cardiomegaly; radiographic evidence of pulmonary edema; left ventricular ejection fraction <40%; S3 gallop; hepatojugular reflux; bilateral ankle edema; initiation or increase in dosage of loop diuretics, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy, vasodilators, or evidence-based beta blocker therapy for heart failure; weight loss >4.5 kg in 5 days in response to treatment) [5, 18, 24].

Cardiovascular death included fatal MI; fatal stroke; sudden death; death due to cardiogenic shock in patients with New York Heart Association (NYHA) Functional Class IV HF; death related to cardiovascular investigation/procedure/operation; death due to other specified cardiovascular causes.

Assessment of 30-Day Mortality

Thirty-day follow-up data about survival status and/or date of death were obtained by review of hospital databases, medical records, death certificates, or telephone interviews.

Statistical Analysis

All continuous variables were tested for normality with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean and standard deviation (SD) and tested for differences using a *t* test. Nonparametric variables were expressed as median and interquartile range (IQR) and differences tested using the Mann-Whitney *U* test. Categorical variables were expressed as percentages and analyzed by χ^2 test.

Survival curves were formally compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted relative hazards of outcome events by each clinical variable.

Stochastic level of entry into the model was set at $P = .10$, and interaction terms were explored for all the variables in the final model.

Only P values <.05 were regarded as statistically significant. All tests were 2-tailed and analyses were performed using SPSS software, version 22.0 (IBM SPSS, Armonk, New York).

RESULTS

Overall, 1182 patients hospitalized for CAP were recruited (698 males, 484 females; mean age: 73 ± 14 years).

Most patients had arterial hypertension (65%). History of coronary heart disease was present in 38%, history of chronic HF in 29%, and history of stroke in 12%. Type 2 diabetes mellitus was present in 36%, COPD in 33%, dyslipidemia in 31%, and PAD in 11%. A history of paroxysmal AF was present in 19% of patients, whereas 12% were affected by chronic (persistent or permanent) AF, and 13% had chronic kidney disease. At baseline, 35% of patients were treated with 100 mg/day aspirin; 10% with thienopyridines, 31% with statins, 14% with oral anticoagulation.

Cardiovascular Events During the Intrahospital Stay

The median length of the hospital stay was 11 days (IQR, 7–16 days).

During the in-hospital follow-up, 380 (32.2%) patients experienced an intrahospital cardiovascular event (CVE). Specifically, 281 patients (23.8%) met the criteria for new or worsening HF, 109 patients (9.2%) for a new episode of AF, 78 (6.6%) had NSTEMI, 11 (0.9%) STEMI, 11 (0.9%) ischemic stroke, 1 patient (0.1%) DVT/EP, and 28 patients (2.4%) died for cardiovascular causes. CAP patients could also experience >1 CVE; thus, among 281 patients with a new or worsening HF, 55 experienced AF, 45 NSTEMI, 4 STEMI, and 24 cardiovascular death. Furthermore, among 109 patients with a new episode of AF, 13 experienced NSTEMI and 8 died from cardiovascular death. Finally, 2 patients with STEMI and 5 NSTEMI died during the intrahospital stay (Figure 1).

Among patients who experienced an intrahospital CVE, 48% had their CVE within 1 day from enrollment and 61% within 2 days, whereas 90% had CVE within 1 week of enrollment.

Patient Characteristics Associated With Intrahospital Cardiovascular Events

Characteristics of patients with and those without incident CVE are presented in Table 1.

Patients who experienced a CVE were older and had a higher prevalence of diabetes, hypertension, dyslipidemia, PAD, HF, paroxysmal AF, chronic kidney disease, history of coronary

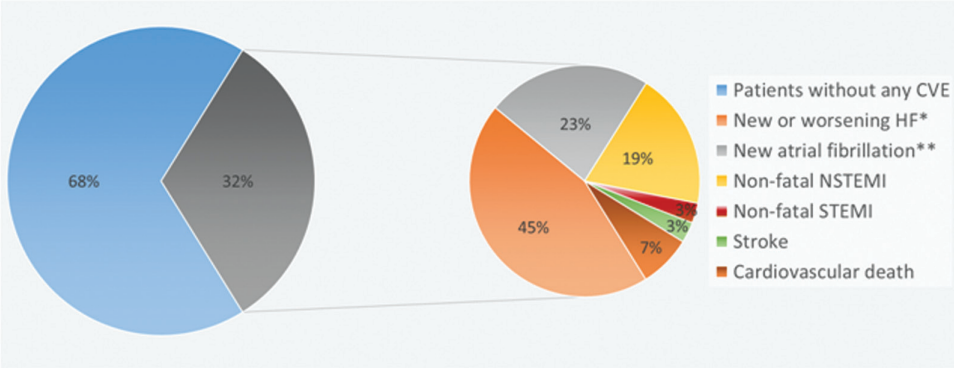

Figure 1. Frequency and type of intrahospital cardiovascular events in patients with community-acquired pneumonia. Abbreviations: CVE, cardiovascular event; HF, heart failure; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST elevation myocardial infarction. *Including only isolated new or worsening heart failure. **Including patients who experienced isolated new atrial fibrillation (AF) or a new AF and new/worsening heart failure.

Table 1. Clinical Characteristics of Patients Who Experienced or Did Not Experience a Cardiovascular Event During the Intrahospital Stay

Characteristic	Overall	Without Intrahospital CVE	With CVE	*P* Value
No.	1182	802	380	
Age, y[a]	73.1 ± 14.1	70.6 ± 14.8	78.3 ± 11.2	<.001
Sex, male/female (%)	41/59	42/58	39/61	.311
Body mass index[a], kg/m^2	26.5 ± 5.0	26.5 ± 5.2	26.6 ± 4.6	.906
Preexisting comorbid conditions				
Smoker	21%	23%	16%	.003
Former smoker	40%	38%	44%	.075
Coronary heart disease	38%	30%	55%	<.001
History of stroke	12%	10%	16%	.003
Liver cirrhosis	4%	4%	3%	.297
Diabetes	36%	34%	40%	.037
Dyslipidemia	31%	28%	41%	<.001
Arterial hypertension	65%	60%	80%	<.001
Chronic renal disease	20%	16%	28%	<.001
COPD	33%	32%	34%	.375
Peripheral artery disease	11%	9%	16%	.001
Congestive heart failure	29%	20%	47%	<.001
Paroxysmal atrial fibrillation	19%	13%	31%	<.001
Chronic atrial fibrillation	10%	9%	11%	.270
Physical examination and laboratory and radiographic findings				
PSI[b]	109 (85–133)	101 (78–122)	127 (104–152)	<.001
PSI class II	13%	19%	2%	<.001
PSI class III	17%	20%	9%	
PSI class IV	43%	43%	44%	
PSI class V	27%	18%	45%	
hs-CRP, mg/L[b]	56 (28–86)	56 (27–86)	56 (33–81)	.909
Pleural effusion	37%	33%	47%	<.001
pO2 <60 mm Hg	26%	22%	36%	<.001
Acute respiratory failure	33%	28%	43%	<.001
Altered mental status	10%	8%	15%	<.001
Hematocrit <30%	8%	6%	12%	<.001
Respiratory rate >30 breaths/min	27%	22%	36%	<.001
Pulse ≥125 beats/min	5%	3%	9%	<.001
SBP <90 mm Hg or DBP <60 mm Hg	3%	2%	6%	<.001
pH <7.35	10%	7%	17%	<.001
Pleural effusion on chest radiograph	37%	33%	47%	<.001
Glucose ≥250 mg/dL	15%	15%	14%	.501
Intrahospital treatments				
Aspirin	35%	32%	42%	<.001
Thienopyridines	10%	9%	13%	.028
Oral anticoagulants	14%	12%	18%	.009
Statins	31%	30%	33%	.360
ACE inhibitors/ARBs	55%	53%	60%	.080
Heparins	30%	23%	44%	<.001
Fluoroquinolones	36%	37%	35%	.446
Macrolides	43%	42%	45%	.322
Cephalosporins	50%	50%	49%	.847
β-lactams	36%	36%	35%	.820
Carbapenems	9%	9%	11%	.223

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; CVE, cardiovascular event; DBP, diastolic blood pressure; hs-CRP, high-sensitivity C-reactive protein; pO2, partial pressure of oxygen; PSI, Pneumonia Severity Index; SBP, systolic blood pressure.

[a]Data are presented as mean ± standard deviation.

[b]Data are presented as median (interquartile range).

heart disease, and stroke; moreover, they were more likely to be treated with antiplatelet drugs or anticoagulants (Table 1).

Furthermore, PSI severity was higher and some components of PSI were more prevalent in patients who experienced a CVE. A progressive increase of CVE incidence was observed across PSI risk classes ($P < .001$, log-rank test) (Figure 2).

A multivariable Cox regression analysis showed that intrahospital PSI classes, together with age and heart failure, independently predicted CVEs, after adjusting for possible confounding factors (Table 2).

To further analyze the relationship between CVEs and severity of CAP, the population was also divided into the

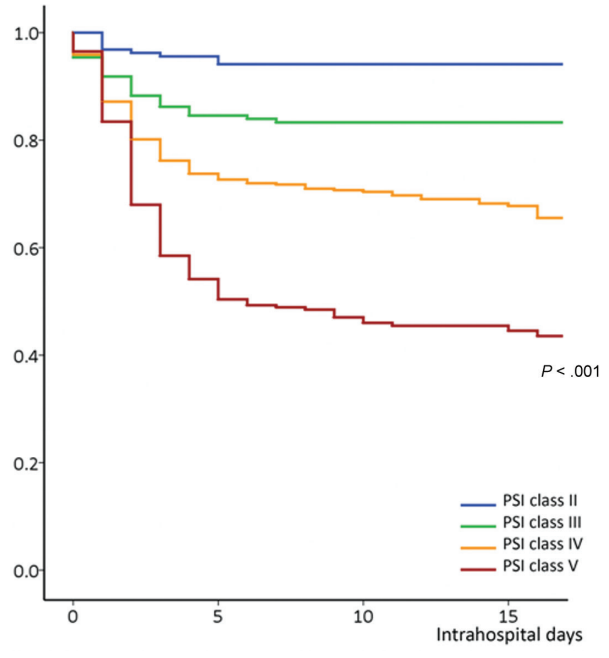

Figure 2. Kaplan–Meier estimates of time to intrahospital cardiovascular event according to Pneumonia Severity Index (PSI) class.

Table 2. Adjusted Hazard Ratios, Based on a Cox Proportional Hazards Model, of Intrahospital Cardiovascular Events According to Selected Variables

Variable	Adjusted HR	95% CI	*P* Value
Age	1.017	(1.007–1.028)	.001
Congestive heart failure	1.848	(1.483–2.304)	<.001
PSI class III vs II	2.454	(1.110–5.426)	.027
PSI class IV vs II	4.229	(2.005–8.919)	<.001
PSI class V vs II	5.959	(2.752–12.900)	<.001

After adjusting for diabetes, hypertension, dyslipidemia, peripheral artery disease, paroxysmal atrial fibrillation, chronic kidney disease, history of coronary heart disease and stroke, antiplatelet drugs, and anticoagulants.

Abbreviations: CI, confidence interval; HR, hazard ratio; PSI, Pneumonia Severity Index.

SMART-COP classes: accordingly, 69% were in the "low risk" class, 21% in the "moderate risk" class, 9% in the "high risk" class, and 1% in the "very high risk" class.

A Cox regression analysis showed that SMART-COP classes (hazard ratio [HR], 1.69 [95% confidence interval {CI}, 1.17–2.43], $P = .020$; HR, 3.24 [95% CI, 1.21–9.12], $P = .020$ for high-risk and very high-risk vs low-risk class, respectively), together with age (HR, 1.03 [95% CI, 1.02–1.05], $P < .001$) and heart failure (HR, 2.70 [95% CI, 1.95–3.74], $P < .001$) independently predicted CVEs, after adjusting for possible confounding factors.

Relationship Between Intrahospital Cardiovascular Events and 30-Day Mortality

Survival status and/or date of death were available for all patients at 30 days.

During the follow-up, 103 patients died (8.7%). Clinical characteristics of CAP patients according to 30-day mortality are represented in Table 3. The 30-day mortality was significantly higher in patients who developed incident CVEs compared with those who did not (17.6% vs 4.5%, $P < .001$) (Figure 3).

A multivariable Cox regression analysis showed that intrahospital CVEs (HR, 5.490 [95% CI, 2.905–10.374], $P < .001$), independently predicted 30-day mortality, after adjusting for age, PSI score, and preexisting comorbid conditions. This result did not change when adjusting for SMART-COP instead of PSI (HR, 5.460 [95% CI, 2.888–10.320], $P < .001$).

DISCUSSION

This large multicenter study of CAP inpatients confirms that cardiovascular complications continue to represent a heavy burden on the course and outcomes of patients admitted to hospital with this infection. Altogether, this study provides the most comprehensive and contemporary landscape of the CVEs that complicate the early and late phases of hospitalization for CAP, confirming that new or worsening HF, AF, and MI are the most common cardiovascular complications associated with this infection (24%, 9%, and 8% of cases, respectively) whereas CVEs in territories outside the heart are far less common. The occurrence of cardiovascular complications substantially increases the risk of death associated with CAP.

In a previous multicenter cohort of 1343 CAP inpatients enrolled between 1991 and 1994, Corrales-Medina and colleagues reported cardiac complications in 27% of these patients [5]. Remarkably, despite the progress in antibiotic therapy, acute medical care, and evidence-based management of CAP in the last 2 decades [25], our study demonstrates that the burden of cardiac complications in patients with CAP (slightly more than 30% in our report) has remained largely unchanged or even increased. In line with previous reports, our study confirms that about 90% of cardiac complications in CAP patients are diagnosed in the first week of hospitalization with most of them occurring in the early phase of the disease, within 2–3 days from hospital admission.

Among cardiac complications, new or worsening HF was the most frequent with an incidence of 24%, which is similar to the 21% previously reported [5]. The second more frequent cardiac complication was new AF, which occurred in approximately 9% of our cohort; however, we cannot exclude that the incidence of AF may be even higher as not all CAP patients were monitored by dynamic Holter. For the same reason, we cannot exclude that CAP patients in our cohort may have experienced other cardiac arrhythmias. It is interesting to note that new episodes of AF occurred in CAP patients with a history of paroxysmal AF, suggesting that infections may represent a trigger for AF, particularly in predisposed patients.

Myocardial infarction was the third cardiac complication in order of incidence, being diagnosed in approximately 8% of our cohort. The incidence of MI in previous cohorts of CAP inpatients has varied widely (from 0.8% to 11%) [9, 26, 27]. There are several reasons potentially accounting for this wide incidence variation of MI, including use of different markers for MI diagnosis and/or MI underestimation because MI can frequently be clinically silent. In concordance with our previous report [27], myocardial ischemia was characterized prevalently by NSTEMI, suggesting that coronary vascular dysfunction rather than coronary thrombosis is prevalently implicated in this phenomenon [4].

Our study is the first to characterize the incidence of vascular events in circulatory districts other than the coronaries in patients with CAP. Here we show that such events are rather infrequent as only about 1% of CAP inpatients experienced ischemic stroke while the rate of symptomatic DVT was 0.1%. This last figure is seemingly surprising as retrospective and case-control studies have previously demonstrated a relationship between acute infections and DVT [9]. We cannot exclude, however, that CAP inpatients in our cohort may have experienced asymptomatic DVT or that infections in other organs may be associated with a higher rate of DVT.

Cardiovascular complications were more frequently detected in older people, patients with atherosclerotic risk factors, and

Table 3. Clinical Characteristics of Patients Who Died During the 30-Day Follow-up

Characteristic	30-d Survivors	CAP Patients Who Died	*P* Value
No.	1079	103	
Age, y[a]	72.3 ± 14.2	81.4 ± 11.0	<.001
Sex, male/female (%)	41/59	45/55	.423
Body mass index[a], kg/m^2	26.6 ± 5.0	25.3 ± 5.1	.257
Preexisting comorbid conditions			
Smoker	21%	15%	.099
Former smoker	41%	33%	.119
Coronary heart disease	37%	47%	.056
History of stroke	11%	23%	<.001
Liver cirrhosis	4%	5%	.524
Diabetes	35%	45%	.046
Dyslipidemia	31%	26%	.456
Arterial hypertension	65%	70%	.549
Chronic renal disease	19%	30%	.007
COPD	33%	24%	.058
Peripheral artery disease	11%	18%	.019
Congestive heart failure	27%	43%	.001
Paroxysmal atrial fibrillation	19%	19%	.896
Chronic atrial fibrillation	10%	8%	.403
PSI, median (IQR)	106 (83–129)	144 (122–174)	<.001

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PSI, Pneumonia Severity Index.

[a]Data are presented as mean ± standard deviation.

in those with a history of cardiac and cerebrovascular disease. In multivariate analysis, however, the strongest predictors were age, history of HF, and severity of infection. In this last regard, it is interesting to note that the progressive increase of CVEs across the PSI risk classes suggests a role for the body's inflammatory to infection in the mechanisms accounting for cardiovascular complications in patients with CAP.

In our cohort, the 30-day CAP-associated mortality was 9%, consistent with other contemporary reports [28, 29]. Mortality was 4-fold higher in patients diagnosed with CVEs during their hospital stay, which is consistent with previous studies that demonstrate the negative impact of cardiovascular complications on the short- and long-term survival of CAP patients and suggesting that the prevention of these events could significantly improve the clinical outcomes of this population [5–7].

Several mechanisms have been proposed to account for the high incidence of cardiovascular complications in CAP patients. For the case of MI, it is still unclear how much true acute thrombotic events (triggered by the rupture of atherosclerotic plaques) contribute to this complication. An alternative mechanism is that stable preexisting coronary artery disease causes myocardial ischemia in CAP patients as a result of the heightened myocardial metabolic demands imposed by the acute infection [4]. Platelet activation may be a potential contributor to both phenomena as, upon activation, platelets release thromboxane A2, which may favor artery thrombosis or impair coronary and cerebral artery flux with its vasoconstrictive property [30]. In accordance with this, markers of in vivo platelet activation are significantly associated with MI in CAP patients [27, 31], who also disclose a significant decrease of CVEs if treated with aspirin [32]. This proposed CAP-induced platelet hyperactivity could also be a contributor to the cases of stroke and DVT associated with this infection.

The high incidence of HF and AF in CAP inpatients suggests that a degree of myocardial injury is common in this population. This myocardial damage may occur independent of myocardial ischemia, as indicated by the detection of isolated elevation of troponin without signs of coronary ischemia [27]. Myocardial injury in the context of CAP may be due to an interaction between specific pathogens and the myocardium or may be related to systemic inflammation as suggested by the significant association between Nox2-related oxidative stress and troponin elevation and by the increased risk of AF in CAP patients with more marked Nox2 activation [22, 33]. However, many other factors, such as fever, diminished oxygen saturation, systemic inflammatory response, and sympathetic activation, may play a role in favoring HF and AF during CAP [4].

This study has important implications. Clinicians should have a high level of suspicion for the occurrence of cardiovascular complications in patients with CAP, especially during the early phase of the disease and because they are associated with an increased risk of mortality. In this context aging, preexisting cardiovascular disease and, overall, infection severity should be regarded as important warning factors for the possibility of these events. As there are no approved therapeutic approaches to counteract this phenomenon, our study may represent a useful tool for the planning of clinical trials to test novel strategies aimed at preventing cardiovascular complications in CAP inpatients. In this context, aspirin could be a promising candidate, but drugs aimed at lowering systemic inflammation, such as drugs inhibiting Nox2-derived oxidative stress, may also be of interest.

Our study was conducted primarily at level 3 urban hospitals with affiliated medical education training programs; this may limit generalizability. Enrollment of most patients comes from Italian hospitals and thus may not be generalizable to other regions of the world. The processes of care may differ among the participating sites, with many potentially being institution specific; therefore, the results may be not generalizable to other healthcare settings.

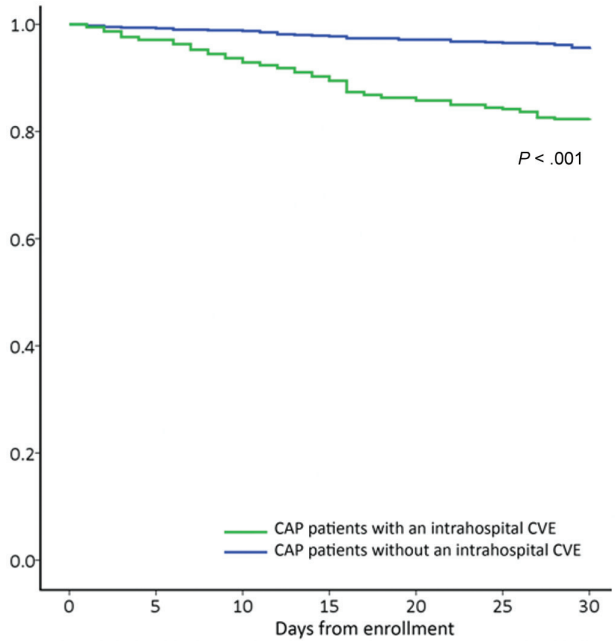

Figure 3. Kaplan–Meier estimates of time to 30-day mortality in patients with community-acquired pneumonia (CAP) who experienced or did not experience a cardiovascular event (CVE) during the intrahospital stay ($P < .001$).

CONCLUSIONS

The present study demonstrates that CVEs complicate a substantial proportion of hospitalized CAP cases and that their occurrence significantly increases the mortality associated with this infection. This suggests that CAP should be regarded not only as a disease limited to the lung but also as a systemic illness that commonly and negatively affects the cardiovascular system. Awareness of this association should prove useful for the clinical management of CAP and for the planning of interventional trials aimed at improving the outcomes of patients with this infection.

Notes

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