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Long-term prognosis in community-acquired pneumonia

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Abstract

Purpose of review—Pneumonia is considered the leading infectious diseases cause of death and the seventh leading cause of death overall in the US. There is significant interest in understanding the relationship between community-acquired pneumonia (CAP) and mortality.

Recent findings—Most clinical studies examining patients with CAP have used an arbitrary in-hospital or 30-day mortality as a short-term mortality clinical end point. However, long-term mortality (arbitrary >3 months) factors, incidence, prediction, and implications on patient care are important issues that require further evaluation in patients with CAP. This review focuses on the most recent literature assessing the importance and the frequency of long-term associated outcomes in patients with CAP, the risk factors, and possible implications for future strategies. Multiple risk factors that include age, sex, comorbid conditions, type of pneumonia, and severity of illness are associated with higher long-term mortality. In addition, several biomarkers were demonstrated to be independently associated with long-term mortality.

Summary—Despite advances in the understanding of long-term mortality among CAP patients, there is still a high unacceptable long-term mortality. Public health programs should address this important gap, considering the high level of complexity factors in patients with CAP.

Keywords

biomarkers; community-acquired pneumonia; outcome

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Conflicts of interest

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INTRODUCTION

Community-acquired pneumonia (CAP) is an important problem with significant morbidity, mortality, and cost. CAP accounts for 3–5 cases per 1000 person-years, particularly in the elderly with a 10-fold increased incidence rate [1–3]. In addition, the incidence of CAP has not decreased over the past few decades, despite advances in supportive care. CAP remains a frequent problem in clinical practice, particularly for those patients who require hospitalization and ICU admission [4]. Approximately 10% of the patients admitted to the hospital with a diagnosis of CAP require ICU care [5,6]. The mortality associated with CAP greatly depends on the clinical setting where it is treated. This mortality is only less than 3% in the outpatient setting, around 5–10% in inpatients not requiring ICU care, as high as 25% in intubated patients, and nearly 50% in ICU patients requiring vasopressors [7,8]. Therefore, the in-hospital case fatality rate for patients with severe disease remains unacceptably high.

Pneumonia is considered the seventh leading cause of death overall, and accounted for more than 59 000 deaths in the year 2008 in the USA [9]. In addition, in 2008, influenza and pneumonia together was the seventh cause of death for those aged 1–24 years and for those aged 65 years or older [9]. The total cost of pneumonia was approximately \$20 billion, including \$14 billion in healthcare expenditures and \$6 billion in lost productivity [9]. Patients with pneumonia are also at risk for developing complications such as requiring mechanical ventilation for hypoxemic respiratory failure, need for vasopressors for hemodynamic instability, and multiorgan system failure [4]. There is significant interest in understanding the relationship between CAP and mortality. Most clinical studies examining patients with CAP have used an arbitrary in-hospital or 30-day mortality as a short-term mortality clinical end point [10–12]. The use of 30-day outcomes in clinical studies may underestimate the morbidity and mortality and may lead to inaccurate inferences [13]. Therefore, the understanding of long-term mortality (arbitrary >3 months) factors, incidence, prediction, and implications on patient care are important issues that require further evaluation in patients with CAP [14,15]. Multiple studies have addressed the association of pneumonia and pneumonia-related factors with long-term mortality [16–20,21,22,23,24,25,26,27,28,29–33,34,35,36–38,39,40,41–51,52,53,54,55–70,71–74,75,76]. This review focuses on the most recent literature assessing the importance and the frequency of long-term associated outcomes in patients with CAP, the risk factors and possible implications for future strategies.

WHAT IS THE LONG-TERM MORTALITY RATE AFTER DEVELOPING COMMUNITY-ACQUIRED PNEUMONIA?

Over the past few decades multiple studies have reported variable long-term mortality rates for patients with CAP [16–20,21,22,23,24,25,26,27,28,29–33,34,35,36–38,39,40,41–51,52,53,54,55–70,71–74,75,76]. The variability in the reports depends on several factors that include: demographic characteristics, comorbid conditions, ambulatory vs. hospitalized patient location, severity of illness at presentation, time to follow-up, and other associated risk factors (Table 1 and Fig. 1). In general there is an incremental risk of death after surviving the pneumonia episode and the hospitalization-related event. In addition, the

excess mortality observed among CAP patients who survived the initial event could be as high as 50% within 5 years after hospital discharge. Despite the higher rates of mortality observed in elderly patients, the unacceptable high long-term mortality persists after adjusting for demographic characteristics (e.g. age), comorbid conditions, and other factors [16,17,25]. Therefore, it is unclear why CAP is not considered a public health threat and major funding is not devoted to this important healthcare problem around the world. Comparing CAP with other important healthcare problems should strengthen the rationale for a call to action on this matter.

IS COMMUNITY-ACQUIRED PNEUMONIA *PER SE* A RISK FACTOR FOR LONG-TERM MORTALITY?

Community-acquired pneumonia alone, without medical complications, may also have significant unappreciated long-term outcomes secondary to effects on various organ systems, especially the cardiovascular system, by possible pathogenetic mechanisms related to causal microorganisms, the bacterial load, the host response, or a combination of these factors. Consequently, several studies have addressed the impact of CAP in comparison with other important conditions. The initial observation by Hedlund *et al.* [59] in 1993 suggested that CAP, particularly in elderly patients (>50 years of age), had a significant mortality during the 3 years following discharge. In addition, the mortality directly associated with CAP was higher compared to other infections. Kaplan *et al.* [18] evaluated 158 960 hospitalized patients with CAP and non-CAP controls. The authors found a 1-year mortality of 41% among the CAP cohort vs. 20% of hospitalized control patients ($P < 0.001$), and among hospital survivors a 1-year mortality of 34 vs. 25% ($P < 0.001$), respectively. The differences among groups were not explained by underlying disease. In addition, Yende *et al.* [20] focused on a high-functioning cohort of older hospitalized patients with CAP. The authors found that CAP was associated with greater long-term mortality (5 years) independent of prehospitalization comorbid conditions. However, CAP long-term mortality rates were similar to other hospital-related chronic diseases, such as heart failure, cerebrovascular disease, and fracture.

These data suggest that CAP carries a significant long-term mortality even when compared to chronic conditions. However, the complex interactions that occur in a patient with an acute condition like CAP, with present chronic comorbid conditions, individual characteristics, and chronic pharmacological therapies may also influence the long-term mortality rate.

WHAT RISK FACTORS ARE ASSOCIATED WITH LONG-TERM MORTALITY IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA?

Multiple studies have reported a series of risk factors deserving further exploration and evaluation that have shown an association with long-term mortality (Table 1).

Age

The aging process is something really alarming in the USA and around the globe. The proportion of US elderly patients (>65 years or older) is expected to increase from 12% in the year 2000 to almost 20% in the year 2030, and will double by the year 2050 [55]. Elderly patients tend to have higher rates of chronic comorbid conditions, poor functional status and disability, and are more likely to require care at a long-term care facility. Several studies have identified that advanced age is associated with higher long-term care mortality as shown in Table 1 [16–18,22,23,24*,25,58]. Klapdor *et al.* [77*] suggested that CAP is a different entity in younger patients due to the lower 6-month mortality compared to older patients with CAP. However, the risk of aging is variable, with a starting risk as early as 50 years of age as reported by Hedlund *et al.* [58] and as late as above 70 years of age as described by Sligl *et al.* [55]. In conclusion, increased age is associated with higher risk of long term-mortality in CAP.

Sex

Several studies [17,18,22,26*,27] identify male sex as an important risk factor associated with higher risk of long-term CAP mortality (Table 1).

Race

A study by Polsky *et al.* [28], in the Medicare Provider Analysis and Review File and the Veterans Administration Patient Treatment File from 1998 to 2002, retrospectively assessed racial differences in mortality at 30 days and up to 2 years following a hospital admission for the elderly (>65 years of age) with common medical conditions. The authors found that by day 90, blacks with CAP had higher mortality compared to whites. In addition, the long-term (1 and 2-year) mortality rate among blacks and whites was unacceptably high (42 and 54% for blacks vs. 40 and 51% for whites, respectively). The long-term mortality at 2 years (54%) was higher among blacks compared to whites with other common admission diagnoses such as heart failure (44%), gastrointestinal bleeding (37%), hip fracture (41%), stroke (42%), and acute myocardial infarction (40%).

Type of pneumonia

A limited number of studies have assessed the association of different types of pneumonia and long-term outcomes in patients with CAP. Cecere *et al.* [25] studied younger adults and patients with health-care-associated pneumonia (HCAP) in comparison with CAP patients. The authors concluded that admission to the hospital for HCAP, and to a lesser degree CAP, was associated with long-term mortality even in young patients. Similar results were reported by Hsu *et al.* [29*], who showed that 1-year HCAP mortality was nearly twice that of CAP, and that HCAP was an independent predictor of 1-year mortality [odds ratio (OR) 1.99, 95% confidence interval (CI) 1.87–2.11]. In addition, HCAP patients incurred significantly higher costs during the initial hospital stay and in the following 12 months. Mortensen *et al.* [22] also showed that patients who required nursing home residence were more likely to have long-term mortality (hazard ratio 1.5, 95% CI 1.1–2.1). Nursing home residence is one of the most common risk factors for HCAP diagnosis [15].

Chronic comorbid conditions

The concurrence of an acute illness such as CAP in patients with chronic conditions may be associated with greater morbidity, mortality, and cost. This interaction of an acute condition with chronic comorbid conditions leads to higher healthcare utilization, particularly among elderly patients [55]. Several comorbid conditions including neurodegenerative disorders, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), malignancy, HIV, and poor nutritional status are some of the most common entities linked to long-term mortality in patients with CAP (Table 1) [16–20,21[■], 22,23,24[■],25,26[■],27,28,29[■]–33[■], 34,35,36[■]–38[■],39,40[■],41–51,52[■],53,54[■],55–70,71[■]–74[■],75,76,78,79[■], 80,83[■],84]. Many studies tend to combine or include the list of associated comorbid conditions in severity of illness scores validated for pneumonia or for chronic comorbid conditions, such as the Charlson comorbidity index [85], in order to predict mortality [22,30[■],55]. Below are a few of the most relevant hot topics regarding the association of long-term mortality in patients with CAP.

Neurodegenerative disorders such as dementia, stroke, and cognitive impairment have been associated with long-term mortality [21[■],27,31[■],32[■],51, 78,79[■]]. Van der Steen *et al.* [31[■]] showed that male nursing home residents with advanced dementia and lower respiratory tract infection (e.g. CAP) had a substantial 6-month mortality (74%) despite antibiotic treatment. Sachs *et al.* [32[■]] evaluated the association between cognitive impairment and increased long-term mortality among primary care patients aged 60 years and older. The authors found a few important notable differences in the causes of death among the groups. Influenza and pneumonia together was the seventh leading cause of death overall, but the fourth leading cause of death for those with moderate to severe cognitive impairment. Similarly, Sligl *et al.* [21[■]] found that prehospital functional dependence was associated with increased 1-year mortality (hazard ratio 3.0, 95% CI 1.5–6.1).

Cardiovascular conditions that include acute coronary syndromes (e.g. acute myocardial infarction), heart failure, arrhythmias, and stroke are associated with higher rates of long-term mortality among CAP patients [37[■],38[■],39,40[■],41,80,83[■]]. A recent *European Respiratory Journal* perspective article by Ewig and Torres [36[■]] compared the similarities between CAP and acute coronary syndromes, and suggested the need for a more aggressive and intensified approach to diagnose, treat, and prevent CAP. Dong *et al.* [83[■]] showed in their meta-analysis that acute respiratory infection was associated with an increased risk of acute coronary syndromes. In addition, a provocative series of articles by Corrales-Medina *et al.* [37[■],38[■],39,40[■],41], which builds on the experience of the association of short-term mortality and acute coronary syndromes in patients with pneumonia, suggests interesting hypotheses on the possible triggering mechanisms of infection.

Pre-existent malignancy at the time of CAP diagnosis, or a new diagnosis of malignancy after initial presentation, is also associated with a higher long-term mortality [24[■],59,84]. Bruns *et al.* [24[■]] reported, in a prospective observational study in a Dutch population, that most CAP patients died because of malignancy (27%), respiratory diseases (27%, COPD the most common respiratory reason in 19%), and vascular diseases (16%). Hedlund *et al.* [59] also reported that after an episode of CAP, the most important causes of death were

cardiovascular diseases and malignancies. Mortensen *et al.* [84] confirmed an important association between post-pneumonia pulmonary malignancy and higher short and long-term mortality, long-term survival, and length of hospital stay. Patients diagnosed with lung cancer had improved survival for the first 90 days postpneumonia hospitalization, but lower survival after 90 days and total survival of less than 2 years. The authors found that the risk factors associated with a new diagnosis of pulmonary malignancy included current tobacco use, any malignancy, metastatic solid tumor, COPD, congestive heart failure, and male sex.

Chronic obstructive pulmonary disease is another risk factor previously mentioned. Bruns *et al.* [24[•]] showed that individuals who recovered from CAP had a four-fold increased risk of dying because of COPD as compared with the general population. This could be a result of statistical confounding, as the prevalence of COPD is higher in the CAP cohort than in population controls. However, other studies have confirmed similar poor survival associated with COPD [43,44].

The above information regarding comorbidities emphasizes the importance of optimal management of chronic conditions in CAP patients. Early recognition and appropriate management of comorbidities may play a role in favorable long-term outcomes.

Severity of illness

Most of the severity risk assessments focus on short-term mortality by measuring the variables involved in organ dysfunction in patients with CAP. Admission to the hospital or the development of moderate to severe pneumonia may influence the risk of long-term mortality [22,42]. In a study by Karhu *et al.* [30[•]], severe CAP (ICU-admitted patients with pneumonia) compared to hospital-acquired and ventilator-associated pneumonia had the lowest 1-year mortality. However, severity of illness was measured by ICU admission and not by any of the validated pneumonia severity of illness scores. The two most widely used and validated methods include the pneumonia severity index score (PSI) and the CURB-65 [10–12]. The PSI is a 20-point score used at the time of clinical presentation that classifies patients into five risk categories. It uses three demographic parameters, five comorbid conditions, five physical examination findings, and seven laboratory/imaging findings to calculate the final score. The number of points for each variable are added and then stratified into the risk categories based on their percentage risk to predict 30-day mortality. PSI is heavily influenced by age, and the large number of variables evaluated makes it complex to use. In contrast are the CURB-65, CURB, and CRB (simpler tool that does not require blood urea nitrogen). CURB-65 is a less complex score derived from the original CURB with the addition of age as a new variable. This score is also based on the 30-day mortality risk and is composed of only five variables (accounting for one point each): confusion, urea, respiratory rate, blood pressure, and age above 65 years of age (CURB-65). Despite the simplicity, the ability of this tool to predict long-term mortality is not adopted in clinical practice. Sligl *et al.* [55] showed that, among several risk factors, high PSI score (modified for age) was associated with higher 1-year mortality. However, most of the studies addressing severity of illness have included inflammatory or infection parameters to assess outcomes, with certain limitations. This is why significant interest has emerged in cardiovascular biomarkers as important predictive tools.

BIOMARKERS

Multiple biomarkers have been studied alone or in combination with severity of illness scores attempting to predict short and long-term outcomes [33,34,35,46,48,49,54,72,73,82]. Several bio-markers were demonstrated in univariate and multivariate analyses to be independently associated with long-term mortality [33,34,35,46,54,72,73,82]. However, routine use of these biomarkers is not widely accepted or utilized and may take some time to become the standard of care. Procalcitonin is a biomarker that has shown benefit in the diagnosis and guidance on discontinuation of antibiotic in patients with CAP [81]. Bello *et al.* [33] performed a prospective study in immunocompetent CAP patients and found that pro-adrenomedullin (proADM) had a high predictive power for short and long-term mortality. Similar results were observed by Kruger *et al.* [34], who showed that midregional-proADM, midregional-pro-antidiuretic peptide (MR-pro-ANP), copeptin, proendothelin 1 (CT-ET-1), and CRB-65 are good predictors for 3-month mortality. Moreover, MR-pro-ADM is a better predictor for 3-month mortality than MR-pro-ANP, copeptin, CT-ET-1, procalcitonin, C-reactive protein, and white blood cell count. These data suggest that the complexity associated with death includes cardiovascular, inflammatory, and infectious processes, better measured by a biomarker.

CONCLUSION

Community-acquired pneumonia is an important problem with significant morbidity, mortality, and cost. There is significant interest in understanding the relationship between CAP and mortality for patients who survive the initial acute event. A better understanding of long-term mortality (arbitrary >3 months) factors, incidence, prediction, and implications on patient care are important issues that require further evaluation in patients with CAP. This review focused on the most recent literature assessing the importance and the frequency of long-term associated outcomes in patients with CAP, the risk factors, and possible implications for future strategies.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 205–206).

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KEY POINTS

- Community-acquired pneumonia is associated with significantly high long-term mortality (>3 months).
- Multiple risk factors that include demographic characteristics, comorbid conditions, location of hospitalization, severity of illness at presentation, and time to follow-up are associated with poor long-term survival among patients with community-acquired pneumonia.
- Several biomarkers have been demonstrated to predict long-term mortality in patients with community acquired pneumonia.

FIGURE 1.

Long-term mortality rates among patients that develop community-acquired pneumonia. The figure represents the long-term mortality rates [◆] among community-acquired pneumonia patients reported in whole cohorts and subgroup analyses by multiple studies available in the literature [16–18,20,21[■],22,23,24[■],25,26[■],27,28,30[■],31[■],33[■],34,35,42,45–47,54[■], 55,57,64,65,70,72[■],73[■],77[■],79[■],82].

Table 1

Risk factors associated with long-term mortality in patients with community-acquired pneumonia

Age (> 65 years of age)	Neurocognitive disorders
Male	Cardiovascular diseases
Black	Chronic obstructive pulmonary disease
Nursing home residence	Preexisting malignancy
High school level or less	Poor nutritional states
Pneumonia characteristics	Charlson comorbidity score
Lack of fever	Pharmacotherapies
Healthcare associated pneumonia	Corticosteroids
Pleural effusion	Immunizations
Gram-negative bacilli infection	Statins
Severity of disease at presentation	Other
Low albumin level	Do not resuscitate order
Inflammatory and cardiovascular biomarkers	Living will

Adapted from multiple sources [4,11,12,13[■],14–20,21[■],22,23,24[■],25,26[■], 27,28,29[■]–33[■],34,35,36[■]–38[■],39,40[■],41–51,52[■],53,54[■],55–70,71[■]–74[■], 75,76,77[■],78,79[■],80,81].