Review Article

Early, short and long-term mortality in community-acquired pneumonia

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Abstract: Community-acquired pneumonia (CAP) is a public health problem. Mortality associated with CAP remains high, even after excluding patients from nursing homes or those bedridden before CAP. According to the available studies, we can classify the timing of mortality of hospitalized patients with CAP as (I) early mortality (generally within the first 48 hours to 7 days after hospital admission); (II) short-term mortality (frequently measured in the first 28–30 days after diagnosis or during hospital admission); and (III) mortality occurring months or years after hospital discharge (long-term mortality). A considerable number of recognizable factors may impact CAP mortality. Importantly, the associated risk factors and the causes of mortality of patients with CAP can vary according to the time in which mortality is evaluated. Better understanding of predictors and causes may improve strategies for management and follow-up of CAP. In this article, we performed a narrative review about frequency, associated risk factors and causes of early, short and long-term mortality in CAP.

Keywords: Community-acquired pneumonia (CAP); mortality; risk factor; causes

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Introduction

Community-acquired pneumonia (CAP) poses as a health concern for society. Studies have reported that the annual occurrence of CAP ranges from 1.2 to 48 cases per 1,000 inhabitants, being higher in older patients (1,2). However, the incidence in CAP differs by region, season and population characteristics. Moreover, CAP is a frequent reason for hospitalization—typically nearly 20–25% require inpatient treatment. Severe CAP, classified by patient's admission into the intensive care unit (ICU), develops in about 10–20% of hospitalized patients (3,4). Expenses related to CAP are high. It was estimated that healthcare costs per inpatient admission for CAP ranged from U$11,148 to U$51,219 (5). The overall burden of CAP is expected to increase as the incidence and size of the elderly population grow over coming decades (2).

Mortality associated with CAP remains high, even after excluding patients living in nursing homes or those confined to bed prior to onset of CAP. CAP mortality rate matches with those of other known medical emergency diseases such

as ST-elevation myocardial infarction (6). Therefore, it has been stated that CAP should be recognized as a medical emergency due to it being one of the major contemporary acute life-threatening conditions (6,7). However, no effort has been made to organize public health systems in order to reduce short and long-term mortality associated to CAP.

A considerable number of recognizable risk factors may impact CAP mortality. Importantly, associated risk factors and causes of mortality of patients with CAP can vary according to the time in which mortality is evaluated. Factors that may impact mortality within the beginning days could vary from those related to mortality taking place at a later time. According to the available studies, we can classify the timing of mortality of hospitalized patients with CAP as (I) early mortality (generally within the first 48 hours to 7 days after hospital admission); (II) short-term mortality (frequently measured in the first 28–30 days after diagnosis or during hospital admission); and (III) mortality occurring months or years post hospital discharge (long-term mortality). Early mortality has not been evaluated to a great extent as a clinical outcome. However, the majority of studies have centered on short-term adverse events related to CAP. Importantly, studies evaluating short-term mortality also include patients with early mortality. Likewise, throughout the last thirty years, numerous studies have stated variable long-term mortality rates for patients suffering from CAP (8).

In this article, we performed a narrative review about frequency, associated risk factors and causes of early, short and long-term mortality in CAP.

Early mortality (within the first 48 hours to 7 days after hospital admission)

Information about the causes and factors as per mortality within the first 48 hours to 7 days of CAP is scarce. The classic concept is that very early deaths are not as dependent on antimicrobial efficacy as on other factors, including inadequate host response (9-11).

The rate of early mortality has been reported in some CAP studies. Mortensen *et al.* (11) performed a study, which involved 787 patients from two hospitals. The mean age of CAP patients was 60 years; 79% were male, 84% were admitted through the emergency department, and 20% were admitted to the ICU within the first 24 hours post admission. Mortality stood at 2.5% upon 48-hour mark. Similarly, Garcia-Vidal *et al.* (9) documented 57 (2.3%) early deaths (<48 hours) among 2,457 hospitalized patients with CAP. Finally, 7 (26.9%) of 26 patients with CAP died within 7 days of admission in another study in which investigators aimed to determine the impact of inflammatory biomarker levels on early mortality (12).

Risk factors associated with early mortality

In a study performed by Bacci *et al.* (12), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) levels were related with early death, which was defined as death occurring within 7 days of admission. However, C-reactive protein, IL-1 and homocysteine were not associated with this outcome. Moreover, Garcia-Vidal *et al.* (9) documented that the demographic and clinical aspects of early deaths (<48 hours) describe a group with more severe pneumonia, as shown by the fact that most cases were categorized in the pneumonia severity index (PSI) high severity risk classes. In this study, factors related with early mortality were increased age, altered mental status, multilobar pneumonia, shock upon admission, pneumococcal bacteraemia and discordant empiric antibiotic therapy. This last finding was supported almost exclusively by cases of discordant antimicrobials for patients with *P. aeruginosa* pneumonia. Altered mental status, multilobar pneumonia, shock upon admission are closely related with an unbalanced inflammatory response to infection.

Although many reports have shown that prescribed empiric antimicrobial regimens are related with reduced mortality at 30 days, there exists a debate about whether appropriate antibiotic selection offers a favorable impact on mortality within the first 48 hours after admission. Mortensen *et al.* (11) documented in the univariate analysis that variables significantly associated with mortality at 48 hours included living in a nursing home, admission to the ICU within 24 hours, need for mechanical ventilation, altered mental status at onset, arterial hypoxia, and arterial pH 7.35 or less. Furthermore, increasing PSI risk class was associated with increased mortality at 48 hours. After adjusting for potential confounders using the propensity score, use of guideline concordant antibiotics was related with decreased mortality at 48 hours. *Table 1* summarizes the factors related with early mortality.

Causes of early mortality

Causes of early mortality were not reported in most

Table 1 Risk factors associated with early (within the first 48 hours to 7 days after hospital admission) mortality in CAP

First author	Year	Associated with higher mortality	Not related with mortality
Bacci *et al.* (12)	2015	IL-6; TNF-α	IL-1; C-reactive protein; homocysteine
Garcia-Vidal *et al.* (9)	2008	Increased age; altered mental status; multilobar pneumonia; shock at admission; pneumococcal bacteraemia; discordant empiric antibiotic therapy	–
Mortensen *et al.* (11)	2006	Use of guideline concordant; antibiotics	–

CAP, community-acquired pneumonia.

Table 2 Causes of early (within the first 48 hours to 7 days after hospital admission) mortality in CAP

First author	Year	Causes
Garcia-Vidal *et al.* (9)	2008	Acute respiratory failure (66.6%); septic shock/multiorgan failure (24.6%); congestive heart failure or cardiac arrhythmia (7%); diabetic ketoacidosis (1.7%)

CAP, community-acquired pneumonia.

studies (*Table 2*). Acute respiratory failure (66.6%), septic shock/multiorgan failure (24.6%), congestive heart failure or cardiac arrhythmia (7%), and diabetic ketoacidosis (1.7%) were the causes of early death (<48 hours) documented in non-immunocompromised adults hospitalized with CAP (9). The authors indicated that the great portion of deaths were pneumonia-related, within the environment of an unbalanced inflammatory response.

Short-term mortality (28 or 30-day or in-hospital mortality)

During the last decades, the short-term prognosis of patients with CAP has been assessed in a great number of studies: a wide range in mortality and differing predictors of mortality were documented (13). Overall short-term mortality rate for CAP patients is dependent on the type of patient in the evaluated cohort. Thus, lower short-term mortality rates have been documented in younger or ambulatory patients, while higher short-term mortality rates in hospitalized or bacteremic patients, and patients requiring ICU admission.

Risk factors associated with short-term mortality

Demographic and clinical features

Fine *et al.* (13) performed a meta-analysis about the prognosis and outcomes of patients with CAP. Seventeen factors were significantly related with higher risk of mortality (male sex, altered mental status, dyspnea, tachypnea, hypotension, hypothermia, congestive heart failure, alcohol abuse, diabetes mellitus, immunosuppression, neoplastic disease, coronary artery disease, neurologic disease, leukopenia, bacteremia, multilobar radiographic pulmonary infiltrate, and azotemia). However, two factors were related to a lower risk of mortality: chills and pleuritic chest pain. Via multivariate statistical analyses, all of these factors have been recorded as upholding an independent relationship with mortality in one or more individual studies (14-16).

Premorbid poor functional status also has been related with a poor prognostic factor in CAP patients. Functional status has been evaluated by the Eastern Cooperative Oncology Group (ECOG) scale (17), Lawton index (18), Katz index (19) and Barthel index (18,20). Functional status predicted 30-day mortality and improved discrimination and reclassification in consecutive CAP patients (17). Similarly, studies have documented that mortality rate is higher in patients who had acute cardiovascular events (new onset or worsening of cardiac arrhythmias, new onset or worsening of congestive heart failure, stroke and/or myocardial infarction) during an episode of CAP (21-23). Intra-hospital cardiovascular events independently predicted 30-day mortality after adjustment for age, PSI score, and pre-existing comorbid conditions (22,23).

CAP-specific scores

International guidelines recommend varied scores in

order to back grading of CAP severity and mortality risk. CURB65 and the PSI are the most widely recommended severity scores. Fine *et al.* (24) derived a prediction rule (PSI) that classifies patients into five categories as it relates to risk of death within 30 days. The prediction rule assigns points based on age and the presence of coexisting disease, abnormal physical findings and abnormal laboratory findings at presentation. The prediction rule accurately identifies the patients with CAP who are at low risk for death and other adverse events. Similarly, Lim *et al.* (25) identified prognostic variables using multiple logistic regression with 30-day mortality as the outcome measure. The author developed a score that includes variables of prognostic importance, easily measurable upon initial assessment. A six-point score, one point for each: confusion, urea >7 mmol/L, respiratory rate ≥30 times/min, low systolic (<90 mmHg) or diastolic (≤60 mmHg) blood pressure, age ≥65 years (CURB-65 score). This score allowed for patients to be categorized per rising risk of mortality: from score 0, 0.7% to score 5, 57%. A systematic review and meta-analysis discovered that PSI and CURB-65 predict 30-day mortality in CAP with moderate to good accuracy. No significant differences in overall test performance existed between these scores (26).

Other scores also have been linked with an increased risk of short-term mortality in CAP. CURSI (confusion, urea >7 mmol/L, respiratory rate ≥30 times/min and shock index) (27), quick Sequential (sepsis-related) Organ Failure Assessment (qSOFA) (28), neutrophil-lymphocyte count ratio (29), APACHE II (30), severe CAP (SCAP) score (31), American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria (32), and predisposition, infection/insult, response, organ dysfunction (PIRO) score (33).

Biomarkers

Several humoral and cellular systems that mediate the host response against infection are activated during the acute episode of CAP, so investigators have suggested that such parameters could be of value in the prediction of prognosis in this disease. With such aim, the suitability of biomarkers has been assessed in various CAP studies. Studies have defined the relationship between short-term mortality in CAP and biomarkers of cardiovascular, coagulation, endocrine and immune pathways. However, studies vary significantly in design, setting, sample size and evaluation period. Furthermore, most studies did not control for factors that could affect the accuracy of the biomarkers predicting short-term mortality, such as age, medications and comorbidities (34).

Recently, a systematic review and meta-analysis were performed to investigate the prognostic value of different biomarkers and compare their accuracy as it relates to the established CAP-specific scores (PSI and CURB-65) used for predicting short-term mortality among patients with CAP (35). The authors found that the levels of studied biomarkers were associated with short-term mortality and had moderate to good accuracy in predicting this outcome in CAP. Pro-adrenomedullin, prohormone forms of atrial natriuretic peptide (ANP), cortisol, and procalcitonin had similar accuracy when predicting mortality. However, copeptin and C-reactive protein had the worst predictive performance compared with other biomarkers. However, none of the biomarkers demonstrated a clear advantage over the CAP-specific scores.

Other biomarkers related with increased risk of short-term mortality in CAP were albumin (36,37), cortisol (38), soluble RAGE (39), D-dimer (40), interleukins (41,42) 25-hydroxyvitamin D (43,44), YKL-40, CCL18, SP-D (45), presepsin (46), lactate (47,48) and endothelin-1 (49).

The utility of adding biomarkers to CAP-specific severity scores to predict mortality has also been assessed. Adding biomarkers to scores such as the PSI, CURB-65, APACHE II and SOFA did improve their predictive capability. However, studies are not consistent in relation to these findings. N-terminal pro-brain natriuretic peptide, D-dimer and mid-regional pro-adrenomedullin improved the predictive value for scores in some studies but not in others (50-54). By the same token, studies have assessed the predictive value of combining biomarkers from distinct biological pathways. One multicenter study assessed the prognostic accuracy of five prohormones (adrenomedullin, endothelin-1, ANP, antidiuretic hormone and procalcitonin) (52). Adding all these biomarkers instead of just one (pro-adrenomedullin) led to a significant improvement in the model for CURB-65 but not for PSI. In another study (51), C-reactive protein and IL-6 were independently associated with mortality. The addition of several biomarkers also was found to raise the predictive value of CAP-specific scores.

Causes of short-term mortality

Causes of death within 28 or 30-day after hospital admission or during hospitalization in CAP patients have not been systematically reported (*Table 3*). Mortensen *et al.* (55) performed a study to ascertain the causes of death for individuals with CAP. The investigators found pneumonia-

Table 3 Causes of early (28- or 30-day or in hospital mortality) mortality in CAP

First author	Year	Causes
Mortensen *et al.* (55)	2002	Pneumonia related deaths occur more frequently within 30-day of presentation: immediate causes of death (defined as the disease process, injury, or complication immediately preceding death) for pneumonia-related mortality were respiratory failure, pneumonia, multisystem organ failure and sepsis
Viasus *et al.* (56)	2011	Respiratory failure; shock/multiorgan failure; acute coronary syndrome; nosocomial infections; sudden death; stroke

CAP, community-acquired pneumonia.

related deaths occur more frequently within 30-day after onset. The most frequent immediate causes of death (defined as the disease process, injury, or complication immediately preceding death) for pneumonia-related mortality were respiratory failure, pneumonia, multisystem organ failure and sepsis.

Other studies have documented that the main causes of 30-day mortality in CAP individuals were respiratory failure and shock/multiorgan failure, followed by acute coronary syndrome, nosocomial infections, sudden death, and stroke (56,57).

Long-term mortality (months or years after hospital discharge)

There is evidence suggesting that hospitalized individuals with CAP have a higher frequency of long-term evidence mortality, even several years after the initial episode. Importantly, decreased long-term survival in CAP patients remained statistically significant even after adjusting for confounding factors (58). Studies have reported long-term mortality rates of 7.2% to 61.9% (59-64). Variability in long-term mortality rate found in the reports was dependent upon several factors such as demographic characteristics, comorbidities, ambulatory *vs.* hospitalized patient, severity of illness at presentation, and time to follow-up.

Underlying reasons of higher long-term mortality are not clear and there are no specific preventive treatments (65). Authors have hypothesized CAP could affect long-term outcomes via alterations in underlying biological processes (e.g., persistent systemic inflammatory activity), or because CAP could be a marker for physiological compromise or frailty (59). Therefore, it has been noted that additional research is in need in order to determine contributors to long-term mortality in CAP.

A study evaluated long-term survival of hospitalized individuals with CAP in comparison to those hospitalized in a medical ward without CAP. The investigators performed analysis adjusting for age and preexisting comorbidities. The survival resulted significantly lower among CAP patients in comparison with non-CAP patients (60). Similarly, Eurich *et al.* (59) performed a large, prospective cohort study that made an age, sex-matched comparison of long-term mortality between adult individuals with CAP and patients without pneumonia from the same settings and period. During a median follow-up of 9.8 years, of the 6,078 CAP patients, 2,858 (70 per 1,000 patient years) died during the follow-up period, in comparison to 9,399 (40 per 1,000 patient years) controls.

Another study used database and death certificates to ascertain mortality rates of up to 7 years after discharge (61). In individuals who had demonstrated recovery from CAP, cumulative 1-, 5- and 7-year mortality rates were 17%, 43% and 53%, respectively, in comparison to 4%, 19% and 24%, for an age-matched and sex-matched population reference cohort. Moreover, in the pneumonia patient outcomes research team (PORT) cohort study (mean follow-up duration, 5.9 years) (66), there existed a statistically significant higher mortality rate among patients with CAP across all age groups compared with that of an age-matched cohort for whom data was derived from US life tables. Similarly, in a population-based cohort study of elderly in Finland, patients that survived CAP from 1983 to 1994 were followed up for a median of 9.2 years later (67). The long-term survival rate was significantly lower in people who had survived CAP or pneumococcal CAP than in the rest of study population.

Moreover, a cohort study compared mortality after hospital discharge caused by CAP with mortality of hospitalized patients caused by several other acute and chronic conditions (68). Long-term mortality after hospitalization for CAP was similar to or higher than that associated with after an initial hospitalization for chronic heart failure, cerebrovascular accident, or fracture. One and

5-year mortality rates after an initial hospitalization for CAP were lower than that of subjects initially hospitalized for cancer. These risk estimates remained constant after adjusting for demographic characteristics, smoking status, functional status, nutritional markers, chronic health conditions and circulating concentrations of inflammatory markers.

Risk factors associated with long-term mortality

Demographic and clinical features

Studies have documented age, male sex, CAP severity and nursing home as risk factors related to long-term mortality. In addition, some clinical features upon admission have been related with long-term deaths, while others have been documented as protective factors. Furthermore, etiology of CAP does not seem to be related with long-term mortality.

A study investigated the relationship between clinical parameters and long-term mortality (18 months) in CAP patients. Male sex proved to be a demographic risk factor for long-term mortality. Conversely, initial presentation with temperature >38.7 ℃, chills and highest quartile of C-reactive protein were independent protective factors (69). Similarly, Mortensen *et al.* (66) found that the only "acute" pneumonia-related factors associated with long-term outcomes were feverishness upon presentation (related to reduced mortality) and the presence of pleural effusion (associated with higher mortality). The authors hypothesize that survival of a clinically and biochemically pronounced CAP may reflect a more vigorous host defense as well as a healthier general condition with less complications in the long run.

Another study found (61) that age >65 years, moderate to severe pneumonia CAP (PSI >90) and nursing home residence were independently associated with higher mortality during long-term follow-up. This data concurs with Adamuz *et al.* (62) results, who also found that nursing homes were independently associated with 1-year mortality, as well as Alan *et al.* (70), who documented that long-term mortality also was significantly elevated in individuals with higher PSI and CURB-65 scores. Likewise, in a large population-based cohort of patients with pneumonia and up to 5.4 years of follow-up; older age, male sex and higher calculated PSI scores were attributed with higher long-term mortality, with 92 (15%) of PSI class I–II patients dying in comparison to 616 (82%) PSI class V patients (63).

In the pneumonia PORT cohort study, (66) sociodemographic factors tied alongside with long-term mortality were age (stratified by decade), secondary education level or lower, male sex, and nursing home residence. Furthermore, steroid use was independently attributed with mortality. Similarly, Hedlund *et al.* (71) also found that chronic corticosteroid use was related to a higher risk of mortality in another study. The major reasons for steroid treatment were chronic obstructive pulmonary disease (COPD) as well as connective tissue or joint diseases.

Finally, it seems that etiology of CAP is not related with long-term morality. Ajayi *et al.* (72) performed a study in adults discharged after an episode of invasive pneumococcal disease. Patients were followed-up throughout three decades. No associations were found between any specific *Streptococcus pneumoniae* serotype and increased mortality. Similarly, microbial etiology was not able to predict mortality in a 5-year prospective follow-up study (64).

Comorbidities

The presence of comorbidities has been related with long-term mortality in CAP individuals. In the Pneumonia PORT cohort study (66), long-term mortality rate among CAP patients with underlying diseases represented by the Charlson comorbidity score was statistically, significantly more elevated. Similarly, the presence of comorbidity was independently related to higher mortality during long-term follow-up in another study (61), and Ajayi *et al.* (72) found that the number of comorbid diseases suffered by each adult released post an episode of invasive pneumococcal CAP was related with this outcome.

However, specific comorbid diseases have been evaluated in its influence on long-term mortality. Of the 13 comorbid diseases analyzed in a study (72), cancer and neurologic diseases were the significant variables associated with long-term mortality. Likewise, Guertler *et al.* (69) found that comorbidities independently associated with 18-month mortality in CAP patients were COPD and neoplastic disease. Similarly, after adjustment for confounders, COPD, diabetes mellitus, cancer, and dementia were independently associated with 1-year mortality in CAP individuals in another study (62). Koskela *et al.* (73) also saw that a previous diagnosis of diabetes and new postprandial hyperglycaemia among the non-diabetic population demonstrated independent associations with late mortality.

Holter *et al.* (64) found that underlying diseases related with late death were cardiovascular disease, COPD, and immunocompromising. Similarly, Saldías *et al.* (74) also found that chronic cardiovascular disease was related with

this outcome.

Biomarkers

There is growing literature on the utility of biomarkers in predicting long-term outcomes on CAP. There are several biomarkers that reflect different pathophysiological aspects of CAP that have been associated with long-term mortality.

Alan *et al.* (70) investigated the potential of varying blood biomarkers for long-term mortality prediction in a large and well-defined cohort of CAP individuals from a multicenter study over a 6-year follow-up period. Mortality was increased among patients in the highest pro-adrenomedullin, pro-ANP and urea quartiles. Observations of variations in mortality could not be made between patients in the varying quartiles of C-reactive protein and procalcitonin concentrations and leukocyte count. Similarly, after adjusting for comorbidity and pneumonia severity, Krüger *et al.* (75) found that mid-regional pro-ANP and copeptin were independent, as well as the strongest predictors of long-term mortality. In another study, N-terminal pro-B-type natriuretic peptide was an independent mortality predictor (76). Moreover, in patients with CAP who survived a 180-day follow-up, mid-regional pro-adrenomedullin, mid-regional pro-ANP, copeptin, and C-terminal proendothelin-1 levels upon admission were significantly lower in comparison to those in patients who passed away. It was also true for the inflammatory marker, procalcitonin, and the CURB-65 score; however, it was not the case for C-reactive protein and leukocytes (77). Vazquez *et al.* (78) also confirmed the high prognostic performance of mid-regional pro-ANP for long-term mortality.

Elevated high-sensitivity cardiac troponin during acute CAP episode was found to be a predictor of long-term (1–4.1 years) mortality (79). Furthermore, in a secondary follow-up analysis of data from a prospectively recruited well-defined cohort of 241 hospital survivors of CAP, Holter *et al.* (65) witnessed a statistically significant association between vitamin D deficiency upon hospital admission and long-term, all-cause mortality after discharge in these patients. The patterns of TNF, IL-6, IL-10, D-dimer, antithrombin-III, and factor IX witnessed among men could be associated with poorer long-term survival rates in another study (80).

Finally, elevations of thrombin-antithrombin III-complexes and D-dimer levels were documented as common at the moment of discharging individuals who gave the impression to have improved clinically from CAP. Thrombin-antithrombin III-complexes and D-dimer levels were related with increased risks of subsequent deaths, particularly as result of cardiovascular disease (81). In this study, patients who overcome the initial episode of CAP present with persistent inflammation or coagulation activation upon hospital discharge; this inflammation correlates with higher mortality post discharge. Investigators suggested that an acute infectious process, albeit resolved, creates tenacious alterations, accelerating the advancement of baseline comorbidities that induce earlier mortality.

However, care must be taken when interpreting cardiovascular biomarkers as risk factors associated for long-term mortality. The elevation of these biomarkers during an acute episode of CAP could be the result of underlying, pre-existing cardiac disease or septic cardiomyopathy. As a result, due to acute inflammatory activation, CAP may aggravate an underlying cardiovascular disease, which could or could not be known before admission.

Others

Another study evaluated whether the development of intra-hospital cardiac complications may impact mortality and cardiovascular events taking place throughout a long-term follow up of CAP patients post-hospital discharge (82). In the follow-up, 89 patients passed away (51% of whom had an intra-hospital cardiac complication and 26%, without). A Cox regression analysis illustrated that intra-hospital cardiac complications, age and PSI were significantly associated to general long-term mortality.

Moreover, Koskela *et al.* (73) evaluated 153 consecutive hospitalized individuals who remained alive at least 30 days post mild-to-moderate CAP. The surveillance status was recorded after a median of 5 years and 11 months. In that study, Karnofsky score ≤80% increases the risk of death for several years after CAP. Other studies have documented that low serum albumin levels upon hospital admission are associated with long-term mortality in CAP (64). *Table 4* shows the factors related to long-term mortality in CAP.

Causes of long-term mortality

Causes of long-term mortality in CAP individuals have been reported in some studies (*Table 5*). Holter *et al.* (64) documented that chronic diseases, including COPD, vascular diseases and malignancy were primary reasons for long-term mortality in CAP patients followed-up for 5 years after hospital discharge. The occurrence of vascular deaths was

Table 4 Risk factors associated with long-term (months or years after hospital discharge) mortality in CAP

First author	Year	Associated with higher mortality	Protective factor	Not related with mortality
Ajayi *et al.* (72)	2017	Cancer; neurologic disease; the number of comorbid diseases	–	*Streptococcus pneumoniae* serotype
Vestjens *et al.* (79)	2017	High-sensitivity cardiac troponin T	Smoking	–
Holter *et al.* (65)	2016	Serum 25-hydroxyvitamin D levels	–	–
Holter *et al.* (64)	2016	Age; cardiovascular disease; COPD; immunocompromising; low serum albumin	Smoking	Microbial etiology; CURB65
Cangemi *et al.* (82)	2015	Intra-hospital cardiac complications; age; PSI	–	–
Koskela *et al.* (73)	2014	Diabetes; new postprandial hyperglycaemia; Karnofsky equal or less than 80%; age; urea	–	–
Nowak *et al.* (76)	2012	NT-proBNP; PSI; age	–	–
Vazquez *et al.* (78)	2012	MR-proANP; PSI;	–	Procalcitonin; age; female gender; chronic heart failure; chronic renal failure
Guertler *et al.* (69)	2011	Male sex; COPD; neoplastic disease; pro-ADM	Temperature >38.7 ℃; chills; C-reactive-protein	Chronic heart failure; chronic renal failure;
Krüger *et al.* (77)	2010	MR-proANP; CT-proAVP; CRB-65; comorbidity	–	–
Johnstone *et al.* (63)	2008	Older age; male sex; PSI	–	–
Mortensen *et al.* (66)	2003	Age (stratified by decade); do-not-resuscitate; status; poor nutritional status; pleural effusion; glucocorticoid use; nursing home residence; high school graduation level or less; male sex; preexisting comorbid illnesses	Feeling feverish	–
Hedlund *et al.* (71)	1993	Corticosteroid treatment; non-lung malignancies; serum albumin <30 g/L; airway colonization with; gram negative enteric bacteria	–	Smoking; chronic pulmonary disease apart from obstructive; congestive heart failure
Saldías *et al.* (74)	2013	Age; chronic cardiovascular disease; chronic neurologic disease; PSI; lack of fever; C-reactive protein	–	–
Bruns *et al.* (61)	2011	Comorbidity; neoplasm; age >65 years; moderate to severe pneumonia (PSI >90); nursing home residence	–	–
Alan *et al.* (70)	2015	PSI; CURB-65; pro-ADM; pro-ANP; urea	–	C-reactive protein; procalcitonin ; leucocyte count
Adamuz *et al.* (62)	2014	COPD; diabetes mellitus; cancer; dementia; rehospitalization within 30 days of hospital discharge; nursing home	–	PSI; age; chronic heart disease; chronic renal disease; cerebrovascular disease; chronic steroid use; gastric acid suppressant; aspiration pneumonia

CAP, community-acquired pneumonia; PSI, pneumonia severity index; COPD, chronic obstructive pulmonary disease; NT-proBNP, N-terminal pro b-type natriuretic peptide; MR-proANP, midregional pro- atrial natriuretic peptide; pro-ADM, proadrenomedullin; CT-proAVP, copeptin.

Table 5 Causes of long-term (months or years after hospital discharge) mortality in CAP

First author	Year	Causes
Holter *et al.* (64)	2016	COPD (23.6%); vascular (22.2%); malignancy (16.7%); pneumonia (5.6%); other (31.9%)
Eurich *et al.* (59)	2015	Circulatory system (35%); neoplasm (24%); respiratory system (12%)
Koskela *et al.* (73)	2014	Cardiovascular (39%); obstructive lung disease (19%); cancer (17%); miscellaneous (25%); pneumonia (8%)
Hedlund *et al.* (71)	1993	Vascular diseases (47%); non-lung malignancies (19.6%); pneumonia (11.7%); lung cancer (3.9%); lower respiratory infection; other than pneumonia (3.9%); abdominal diseases (3.9%); Other causes (10%)
Bruns *et al.* (61)	2011	Pneumonia (5.9%); COPD (19.3%); vascular (16.7%); malignancy (26.7%); other causes (32.1%)
Adamuz *et al.* (62)	2014	Infectious diseases (48.4%); cardiovascular (20.4%); other (14%); unknown (17.2%)

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease.

at its peak within the first-year post CAP, while deaths from COPD and malignancies took place at a more constant level during follow-up. Similarly, Adamuz *et al.* (62) evaluated causes of mortality in CAP patients followed-up for 1 year following hospital discharge. They documented that the main reasons were infectious diseases, primarily pneumonia, succeeded by acute cardiovascular events. Mortality from infectious diseases was more elevated throughout the initial 6 months, while the number of deaths from cardiovascular causes remained constant during follow-up months. In another study, the primary underlying reasons for late death in CAP individuals were cardiovascular, obstructive lung disease and cancer. In this study, miscellaneous causes accounted for 25% of all cases (73).

Moreover, other studies have compared causes of long-term mortality occurring in CAP individuals with those in controls. Eurich *et al.* (59) documented that the three most common causes of death after hospital discharge in CAP patients were circulatory system, neoplasm, and respiratory system. Cause of death was alike for both CAP patients and controls, with the exception of respiratory causes which were significantly more frequent in CAP individual (24% *vs.* 9% for controls, P<0.001). Moreover, Bruns *et al.* (61) found that malignancy (27%), COPD (19%) and cardiovascular disease (16%) were the most frequent causes of death. Interestingly, only 6% passed away of pneumonia, in comparison to 3.2% within the general population. Patients who pulled through an episode of CAP had an approximately fourfold increased risk of having COPD recorded as their cause of death in comparison to the general population (19.3% *vs.* 4.4%). Inversely, general population controls presented a more elevated risk of death from cardiovascular diseases than the CAP population (30.2% *vs.* 16.0%). Also, 5.9% of patients who had experienced a prior episode of CAP died of recurrent pneumonia, in comparison to a 3.2% risk of death from pneumonia in the general population.

Conclusions

CAP continues to be related to high morbidity, mortality, and health costs. The associated risk factors and causes of mortality of individuals presenting with CAP vary according to the time in which mortality is evaluated. Information about the causes and factors related to mortality within the first 48 hours to 7 days of CAP is scarce. Studies suggest that early deaths depend on severity of the disease upon admission as well as antimicrobial efficacy. Moreover, short-term mortality in CAP has been widely evaluated. Age and the presence of coexisting diseases, abnormal physical findings and abnormal laboratory findings upon presentation have been associated with short-term mortality. Finally, although information regarding long-term mortality in CAP is growing, underlying reasons of higher long-term mortality are not clear and there are no specific preventive treatments. Multiple risk factors that include age, sex, comorbid conditions and persistence of inflammation upon hospital discharge are attributed with higher long-term mortality. However, most causes of death are related with newly diagnosed or underlying chronic diseases. Unlike short-term mortality, the severity of the physiologic abnormalities at initial presentation are not significantly

related with an elevated long-term mortality. What remains controversial is whether CAP is a causal risk factor or a risk marker for an underlying, and possibly unrecognized process that increases the risk for late death. Moreover, several biomarkers have shown to be independently related to short and long-term mortality.

In spite of progress made regarding the understanding of mortality among CAP patients, there remains an unacceptably elevated mortality rate. Due to the complexity factors that could impact CAP mortality, studies in the future would best set forth reliable strategies for improving outcomes in patients with CAP.

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Footnote

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