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# Hospitalization for Pneumonia is Associated With Decreased 1-Year Survival in Patients With Type 2 Diabetes

## Results From a Prospective Cohort Study

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**Abstract:** Diabetes mellitus is a frequent comorbid conditions among patients with pneumonia living in the community.

The aim of our study is to evaluate the impact of hospitalization for pneumonia on early (30 day) and late mortality (1 year) in patients with type 2 diabetes mellitus.

Prospective comparative cohort study of 203 patients with type 2 diabetes hospitalized for pneumonia versus 206 patients with diabetes hospitalized for other noninfectious causes from January 2012 to December 2013 at Policlinico Umberto I (Rome). Enrolled patients were followed up to discharge and up to 1 year after initial hospital admission or death.

Overall, 203 patients with type 2 diabetes admitted to hospital for pneumonia were compared to 206 patients with type 2 diabetes admitted for other causes (39.3% decompensated diabetes, 21.4% cerebrovascular diseases, 9.2% renal failure, 8.3% acute myocardial infarction, and 21.8% other causes). Compared to control patients, those admitted for pneumonia showed a higher 30-day (10.8% vs 1%,  $P < 0.001$ ) and 1-year mortality rate (30.3% vs 16.8%,  $P < 0.001$ ). Compared to survivors, nonsurvivor patients with pneumonia had a higher incidence of moderate to severe chronic kidney disease, hemodialysis, and malnutrition were more likely to present with a mental status deterioration, and had a higher number of cardiovascular events during the follow-up period. Cox regression analysis found age, Charlson comorbidity index, pH  $< 7.35$  at admission, hemodialysis, and hospitalization for pneumonia as variables independently associated with mortality.

Hospitalization for pneumonia is associated with decreased 1-year survival in patients with type 2 diabetes, and appears to be a major determinant of long-term outcome in these patients.

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**Abbreviations:** AKI = acute kidney injury, AMI = acute myocardial infarction, CAP = community acquired pneumonia, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary diseases, CVD = cardiovascular disease, DM = diabetes mellitus, ED = Emergency Department, eGFR = estimated glomerular filtration rate, PSI = pneumonia severity index, US = United States.

## INTRODUCTION

Type 2 diabetes mellitus (DM) is a major public health issue because of its high and rising prevalence worldwide. According to International Diabetes Federation data, 382 million people worldwide have diabetes and this number is expected to rise to 592 million by 2035.<sup>1</sup> The latest statistics for the United States (US) indicates that 29.1 million people or 9.3% of the population have DM,<sup>2</sup> and DM remains the 7th leading cause of death in the US.<sup>2</sup>

Among individuals with DM, cardiovascular disease (CVD) is the major cause of morbidity and mortality and the largest contributor to the direct and indirect costs of DM. The presence of DM significantly increases the risk (2- to 4-fold) for developing CVD and of dying when CVD is present.<sup>3</sup> Despite multiple efforts and secondary prevention programs, patients with DM remain a population at high risk of mortality.<sup>4,5</sup>

Infections are relatively frequent among patients with DM and may range from rare forms such as malignant external otitis, rhino-cerebral mucormycosis, or emphysematous infections of the gallbladder, kidney, and urinary bladder, to more common ones such as respiratory infections.<sup>6</sup> DM is one of the most common underlying diseases in patients with pneumonia, with a reported prevalence of 6% to 25% among those with community acquired pneumonia (CAP).<sup>7,8</sup> Several studies have evaluated outcomes and factors associated with early mortality in patients with DM affected by pneumonia.<sup>9-13</sup> However, it is not well known whether the hospitalization for pneumonia affects the long-term survival in patients with type 2 diabetes.

The aim of this prospective cohort study is to evaluate the early (30-day) and late (1-year) mortality rates in patients with type 2 diabetes hospitalized for pneumonia compared to patients with DM hospitalized for other causes, and to assess the factors independently associated with mortality in this cohort of patients.

## METHODS

### Study Design and Patient Selection

The study was conducted at the University-Hospital Policlinico Umberto I, a large 1100-bed teaching hospital in Rome.

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Patients with DM admitted to medical wards with diagnosis of community-onset pneumonia (case group) or with diagnosis other than pneumonia (control group) through the Emergency Department (ED) from January 2012 to December 2013 were consecutively recruited and prospectively followed up. Patients fulfilling the following criteria were enrolled in the study after giving written informed consent: age 18 years or over; previous diagnosis of type 2 DM defined as fasting plasma glucose levels  $\geq 126$  mg/dL (7.0 mmol/L) or HbA1C  $\geq 6.5\%$  or 2-hour plasma glucose levels  $\geq 200$  mg/dL (11.1 mmol/L) after a 75-g oral glucose tolerance test or random plasma glucose  $\geq 200$  mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis or antidiabetic ongoing therapy.<sup>14</sup> Diagnosis of pneumonia was performed if the following criteria were satisfied: signs or symptoms suggesting pneumonia: presence of rales, rhonchi, bronchial breath sounds, fever ( $>38.0^\circ\text{C}$ ), tachycardia, chills, dyspnea, coughing (with or without sputum), or chest pain; and presence of new consolidation(s) on chest X-ray.

The study included patients having CAP, defined as pneumonia diagnosed upon hospitalization in patients who had not been discharged from an acute care facility within 14 days preceding the clinical presentation, and patients having health care associated pneumonia, defined as pneumonia occurring in patients coming from the community who had attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the past 30 days, had been admitted to an acute-care hospital for at least 2 days or had surgery in the past 90 days, or resided in a nursing home or long-term care facility.<sup>15,16</sup>

Patients were excluded from the study if one of the following criteria was applied: radiographic evidence of a preexisting infiltrates, criteria for hospital-acquired pneumonia, pregnancy or breastfeeding, documented severe allergy to antibiotics, type 1 DM diagnosis, diagnosis of rapidly fatal disease according to McCabe classification,<sup>17</sup> or refusal to sign informed consent. The control group was represented by patients with DM consecutively admitted in our hospital through the ED for causes other than infection during the same period of admission of the cases (January 2012–December 2013). The present study was conducted according to the principles stated in the Declaration of Helsinki and was approved by the local research ethics committee.

## Baseline Assessment and Follow-Up

Data on demographic characteristics, comorbidities, antibiotic, and concomitant therapies were collected; for patients with pneumonia, severity of illness at presentation was quantified by the pneumonia severity index (PSI) and CURB-65 (confusion, urea  $>7$  mmol/L, respiratory rate  $\geq 30$  breaths per minute, and blood pressure  $\leq 90/60$  mmHg) score.<sup>18</sup> Charlson comorbidity index, a recognized method for classifying comorbid conditions which might alter the risk of mortality, was calculated for all patients when they were admitted to ED, using the same criteria.<sup>19</sup> Hypertension, history of coronary heart disease, dyslipidemia, and chronic obstructive pulmonary diseases (COPD) were defined as previously described.<sup>20,21</sup> Baseline treatments were defined according to the patients' pharmacological history. At hospital admission all patients with pneumonia underwent physical examination, laboratory investigations, arterial blood gases analysis, and chest X-ray.

According to Kidney Disease Outcomes Quality Initiative guidelines, chronic kidney disease (CKD) was defined as the presence of one of the following criteria:

- (i) kidney damage for  $\geq 3$  months, evaluated as structural or functional abnormalities of the kidney with or without decreased estimated glomerular filtration rate (eGFR), manifest by either pathological abnormalities or markers of kidney damage, including abnormalities of the composition of the blood or the urine or abnormalities in the imaging tests;
- (ii) eGFR  $<60$  mL/min/1.73 m<sup>2</sup> for  $\geq 3$  months, with or without kidney damage.

CKD stage has been defined as: stage 1 in presence of kidney damage with normal or increased eGFR (eGFR  $\geq 90$  mL/min/1.73 m<sup>2</sup>); stage 2 in presence of kidney damage with mild decrease of eGFR (eGFR 60–89 mL/min/1.73 m<sup>2</sup>); stage 3 in presence of moderate decrease of eGFR (eGFR 30–59 mL/min/1.73 m<sup>2</sup>); stage 4 in presence of severe decrease of eGFR (eGFR 15–29 mL/min/1.73 m<sup>2</sup>); and stage 5 in presence of kidney failure (eGFR  $<15$  mL/min/1.73 m<sup>2</sup> or dialysis).<sup>22</sup> Septic shock was defined according to the Surviving Sepsis Campaign criteria as sepsis-induced hypotension persisting despite adequate fluid resuscitation.<sup>23</sup> Diagnosis of malnutrition was based on the presence of one or more of the following criteria: weight loss  $\geq 5\%$  in 1 month or  $\geq 10\%$  in 6 months; body mass index  $<21$  kg/m<sup>2</sup>; serum albumin concentrations  $<35$  g/L; and mini nutritional assessment score  $<17$ .<sup>24</sup>

Microbiological examinations performed on sputum, urine, and blood during the first 24 hours after admission and according to standards of practice were evaluated for assessment of microbial etiology. Clinical isolates obtained from patients were identified in the Microbiology Laboratory of our hospital using the automatic system VITEK 2 (bioMérieux Inc., Hazelwood, MO). Microbiological determinations were performed as previously described.<sup>25</sup> Antibiotic therapy was initiated in the ED following the hospital guidelines and/or the advice of an infectious diseases specialist. Patients included in study or control groups were followed up to the end of hospitalization and for 1 year after discharge or until death. Follow-up assessment was performed in all patients by means of telephone interviews, evaluation during a new hospitalization, or ambulatory visit when possible. A fatal or nonfatal ischemic cardiovascular event during follow-up was defined as the occurrence of an acute myocardial infarction (AMI) or ischemic stroke.<sup>20</sup>

## Study Endpoint and Statistical Analysis

The study endpoint was to compare the occurrence of death during the first 30 days and 1 year after hospital admission discharge between cases (patients with DM admitted for pneumonia) and controls (patients with DM admitted for other causes). The results obtained were analyzed using commercially available statistical software packages (SPSS, version 20.0; SPSS, Inc., Chicago, IL and R, version 3.0.2; R development core team, Vienna, Austria).

The sample size was planned using a log-rank test for comparing mortality rate in patients with DM hospitalized or not for pneumonia. Assuming equal allocation between groups, a hazard ratio equal to 2, an incidence rate of 22% at 1 year,<sup>26</sup> we evaluated that a total sample size of 397 would yield a power of at least 90% at a fixed a type I error rate of 5%. Estimation of drop-out rate was not established a priori. To detect significant differences between groups, we used the Chi-square test or Fisher exact test for categorical variables and the 2-tailed *t*-test or Mann–Whitney test for continuous variables, when appropriate. Survival curves for time-to-event variables were constructed with the use of Kaplan–Meier estimates based on all

available data and were compared with the use of the log-rank test. In a multivariate analysis of survival, the Cox regression model was used to determine the effects of different variables on overall survival. All variables were considered for the multivariate Cox model analysis. At multivariate analysis the predictors were selected via a stepwise selection procedure optimizing the Akaike Information Criterion. The proportionality of hazards assumption for the Cox model has been checked using plots of Schoenfeld residuals. Statistical significance was established at  $\leq 0.05$ . All reported *P* values are 2-tailed.

### RESULTS

A total of 409 patients with DM were included in the study. Out of these, 203 were patients with DM admitted to hospital for

pneumonia, while 206 were patients with DM admitted for other causes (39.3% decompensated diabetes, 21.4% cerebrovascular diseases, 9.2% renal failure, 8.3% AMI, and 21.8% other non-infectious causes). Comparison between cases and controls is summarized in Table 1. The median duration of DM diagnosis was 13 (interquartile range [IQR] 11–15) years among patients with DM with pneumonia and 12 (IQR 10–15) years among patients with DM without pneumonia; this difference was not statistically significant. No differences in demographic characteristics were recorded between the study groups, but patients with DM admitted for pneumonia showed a higher frequency of chronic heart failure, CKD, and COPD compared to patients with DM admitted for other causes. Table S1, <http://links.lww.com/MD/A676> shows a comparison of cases and controls with a 3rd group of patients without diabetes admitted for pneumonia: as

**TABLE 1.** Characteristics of Diabetic Patients by Study Groups

Variable	Diabetic Patients Admitted for Pneumonia N = 203, %	Diabetic Patients Without Pneumonia N = 206, %	<i>P</i> Value
Demographic data			
Males	130 (64)	127 (61.7)	0.617
Age, median (IQR), year	75 (67–82)	74 (66–80.25)	0.697
Duration of diabetes, median (IQR) year	13 (11–15)	12 (10–15)	0.250
Comorbid conditions			
Chronic heart failure	58 (28.6)	23 (11.2)	<b>&lt;0.001</b>
Chronic hepatitis	12 (5.9)	11 (5.3)	0.802
Chronic kidney failure	66 (32.5)	48 (23.3)	<b>0.038</b>
Hemodialysis	8 (3.9)	5 (2.4)	0.383
Dyslipidemia	85 (41.9)	69 (33.5)	0.080
COPD	68 (33.5)	23 (11.2)	<b>&lt;0.001</b>
Previous cardiovascular events	94 (46.3)	88 (42.7)	0.465
History of atrial fibrillation	36 (17.7)	31 (15.1)	0.476
Charlson comorbidity index, median (IQR)	3 (2–4)	3 (3–4)	<b>0.033</b>
Reasons for hospitalization			
Pneumonia	203 (100)	–	
Decompensated diabetes	–	81 (39.3)	
Acute myocardial infarction	–	17 (8.3)	
Cerebrovascular diseases	–	44 (21.4)	
Renal failure	–	19 (9.2)	
Others	–	45 (21.8)	
Clinical features at admission			
pH < 7.35	12 (8.9)	12 (8.7)	0.956
PSI II to III class	26 (12.8)	–	
PSI IV class	129 (63.5)	–	
PSI V class	48 (23.6)	–	
CURB-65 I class	43 (21.2)	–	
CURB-65 II class	86 (42.4)	–	
CURB-65 III class	74 (36.5)	–	
Therapy			
Metformin therapy	89 (43.8)	98 (50.4)	0.449
Insulin therapy	64 (31.5)	84 (40.8)	0.052
Statin therapy	84 (41.4)	68 (33)	0.080
30-day mortality	22 (10.8)	2 (1)	<b>&lt;0.001</b>
90-day mortality	35 (17.2)	15 (7.3)	<b>0.001</b>
180-day mortality	49 (24.1)	18 (8.7)	<b>&lt;0.001</b>
1-year mortality*	60 (33.3)	32 (16.8)	<b>&lt;0.001</b>

*P* < 0.05 is considered statistically significant, *P* < 0.001 is considered statistically highly significant. COPD = chronic obstructive pulmonary disease, CURB-65 = confusion, urea >7 mmol/L, respiratory rate  $\geq 30$  breaths per minute, and blood pressure  $\leq 90/60$  mmHg, IQR = interquartile range, PSI = pneumonia severity index, SD = standard deviation.

\* 1 year mortality rate was calculated on 180 patients admitted for pneumonia and 190 control patients.

expected, patients with DM admitted for pneumonia had a higher incidence of chronic kidney failure, dyslipidemia, and previous cardiovascular events compared to patients without DM admitted for pneumonia.

Among patients with DM admitted for pneumonia, the etiologic microorganism was identified in 65 (32%) patients. The most frequent causative microorganisms were *Staphylococcus aureus* (24.6%), *Streptococcus pneumoniae* (23%), *Pseudomonas aeruginosa* (10.8%), *Klebsiella pneumoniae* (9.2%), *Mycoplasma pneumoniae* (6.2%), *Haemophilus influenzae* (4.6%), *Escherichia coli* (4.6%), and others (17%). Antibiotic therapy of patients with DM admitted for pneumonia was the following: 34 (16.7%) patients were treated with  $\beta$  lactam/ $\beta$  lactamase inhibitor plus macrolides or fluoroquinolone, 57 (28.1%) patients with cephalosporin plus macrolides or fluoroquinolone, 29 (14.3%) patients with  $\beta$  lactam/ $\beta$  lactamase inhibitor alone, 27 (13.3%) patients with fluoroquinolone alone, 24 (11.8%) patients with cephalosporin alone, 6 (3%) patients with macrolides alone, 6 (3%) patients with carbapenem plus glycopeptide, and 20 (9.8%) patients with other therapies.

Twenty-three (11.3%) patients with DM admitted for pneumonia and 16 (7.8%) control patients were lost to 1-year follow-up. Patients with DM admitted for pneumonia showed a higher 30-day (10.8% vs 1%,  $P < 0.001$ ), 90-day (17.2% vs 7.3%,  $P = 0.001$ ), 180-day (24.1% vs 8.7%,  $P < 0.001$ ), and 1-year mortality rate (30.3% vs 16.8%,  $P < 0.001$ ) compared to those admitted for other causes. Figure 1 shows Kaplan–Meier analysis on estimated survival within 1 year after admission of patients with DM admitted for pneumonia compared to controls.

Clinical features and outcomes of survivors and nonsurvivors patients with DM within 30 days and 1 year after hospitalization for pneumonia are reported in Tables 2 and 3, respectively. Patients who died at 30 days showed a higher incidence of hospitalization in the previous 3 months, intravascular devices, COPD, malnutrition, and previous cardiovascular events; furthermore, nonsurvivors within 30 days had a higher incidence of health care associated pneumonia, PSI class V, multilobar pneumonia, metabolic acidosis (pH < 7.35) at admission, and septic shock. Interestingly, metformin therapy was more frequent in patients who survived. Patients who died

at 1-year follow-up had a higher incidence of moderate to severe CKD, hemodialysis, malnutrition, and were more likely to present with a mental status deterioration and a PSI V class and CURB-65 class III. Patients who died during the follow-up period had a higher incidence of cardiovascular events compared to survivors (31.7% vs 10%,  $P < 0.001$ ).

To evaluate the predictors independently associated with 1-year mortality, a Cox regression analysis was performed. Table 4 shows univariate and multivariate Cox regression analyses about effect of different variables on overall survival during follow-up period. Age, Charlson comorbidity index, pH < 7.35 at admission, hemodialysis, and hospitalization for pneumonia resulted factors independently associated with 1-year mortality.

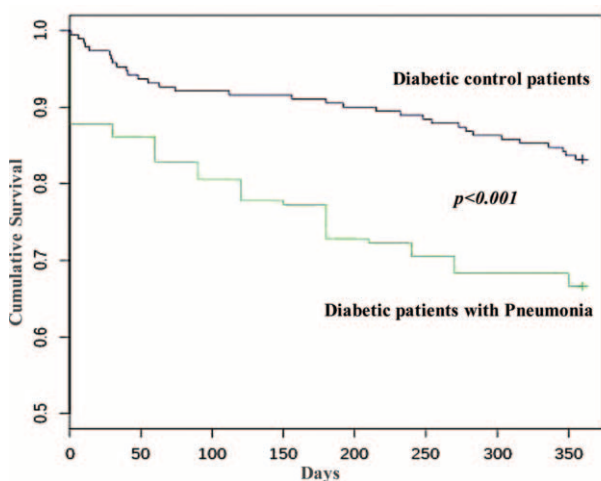
## DISCUSSION

The relevant finding of our prospective study is that among patients with type 2 DM hospital admission for pneumonia is associated with higher mortality compared to hospitalization for other noninfectious illnesses. Diabetic subjects admitted for pneumonia had higher mortality within the first 30 days, and one third died at 1 year.

The 30-day mortality rate (10.9%) observed in our population is similar to that previously reported. In a retrospective observational study, Hirata et al<sup>9</sup> studied 185 patients with DM hospitalized for the first time for pneumonia and the 30-day mortality was 7.6%. Similarly, Di Yacovo et al<sup>10</sup> in a prospective study reported an in-hospital mortality of 7.2% among 526 patients with DM hospitalized for CAP, while mortality was as high as 17% in a further study on 106 patients with DM.<sup>7</sup> Conversely, very few data are available about the long-term mortality. Lepper et al<sup>8</sup> found a 90-day mortality of 14.5% among 1114 patients with type 2 diabetes with CAP, significantly higher than mortality observed in patients without diabetes. A retrospective study by Yende et al<sup>27</sup> demonstrated that preexisting DM is associated with a higher risk of death following hospitalization for CAP. More recently, a prospective study recorded the causes of death of 153 patients hospitalized for CAP after a median of 5 years and 11 months and the mortality rates at the end of follow-up were 54% among patients with DM and 10% among patients without DM (however, diabetic population was represented only by 22 patients, without distinction between type-1 and type-2 DM).<sup>28</sup>

The strength of our study is that we designed a prospective cohort study to investigate whether pneumonia is an event that increases short and long-term mortality in a well-defined population of patients with DM, following the subjects overtime up to 1 year after hospital admission. According to our findings, hospitalization for pneumonia increases the risk of death in patients with type 2 diabetes, and the Cox regression analysis confirmed that pneumonia is a factor independently associated with 1-year mortality. This is an important finding because a change in causes of death was observed in patients with DM in recent years. According to data of National Health Interview Survey, 3-year CVD death rates declined by 9.5 deaths per 1000 person-years during the period 1997 to 1998 to 5.6 per 1000 person-years during the period 2003 to 2004<sup>4</sup> in US, with a 40% decrease in CVD mortality. Another recent study showed that the rate of 5 major complications, including AMI, stroke, amputation, end renal stage disease, and death from hyperglycemic crisis, significantly decline between 1990 and 2010.<sup>5</sup>

The exact underlying pathophysiological mechanisms responsible for the higher long-term mortality in patients with



**FIGURE 1.** Kaplan–Meier plot showing long-term survival after discharge among patients with diabetes admitted for pneumonia (N=203, the green line) and diabetic control patients (N=206, the blue line);  $P < 0.001$  between the study groups.



**TABLE 2.** Comparison of Diabetic Patients With Pneumonia Survived or Not Survived at 30-day of Hospitalization

Variable	Nonsurvivors n = 22, %	Survivors n = 181, %	P Value
Demographic data			
Males	13 (59.1)	117 (64.6)	0.608
Hospitalization in the previous 3 months	12 (54.5)	32 (17.7)	<0.001
Prior antibiotic therapy (last 30 days)	3 (13.6)	24 (13.3)	0.961
Intravascular devices	6 (27.3)	10 (5.5)	<0.001
Comorbid conditions			
Chronic heart failure	6 (27.3)	52 (28.7)	0.886
Chronic hepatitis	1 (4.5)	11 (6.1)	0.774
Moderate to severe renal disease	10 (45.5)	56 (30.9)	0.170
Dyslipidemia	6 (27.3)	79 (43.6)	0.142
COPD	1 (4.5)	67 (37)	0.002
Malnutrition	5 (22.7)	7 (3.9)	<0.001
Previous cardiovascular events	16 (72.7)	78 (43.1)	0.008
History of atrial fibrillation	2 (9.1)	34 (18.8)	0.261
Characteristics of pneumonia			
CAP	8 (36.4)	126 (69.6)	0.002
HCAP	14 (63.6)	55 (30.6)	0.002
Pleural effusion	11 (50)	67 (37)	0.237
Bilateral pneumonia	11 (50)	60 (33.1)	0.118
Multilobar pneumonia	13 (59.1)	55 (30.4)	0.007
Clinical and laboratory findings at admission			
Dyspnea	15 (68.2)	94 (52.5)	0.149
Tachypnea ( $\geq 30$ breaths/min)	8 (36.4)	50 (27.6)	0.392
Chest pain	1 (4.5)	4 (2.2)	0.511
Mental status deterioration	6 (27.3)	7 (3.9)	<0.001
Leukocytosis (leukocytes $\geq 10,000/\mu\text{L}$ )	15 (68.2)	117 (64.6)	0.742
pH < 7.35	9 (40.9)	9 (5)	<0.001
Increased troponin	18 (81.8)	135 (74.6)	0.457
Hyperglycemia at admission ( $\geq 11$ mmol/L)	8 (36.4)	82 (45.3)	0.500
PSI classes			
Class II to III	1 (4.5)	25 (13.8)	
Class IV	11 (50)	118 (65.2)	
Class V	10 (45.5)	38 (21)	
CURB-65 classes			
Class I	2 (9.1)	41 (22.7)	0.127
Class II	8 (36.4)	78 (43.1)	
Class III	12 (54.5)	62 (34.2)	
Therapy			
Metformin therapy	3 (13.6)	86 (47.5)	0.002
Insulin therapy	6 (27.3)	58 (32)	0.649
Statin therapy	6 (27.3)	78 (43.1)	0.155
Septic shock	9 (40.9)	3 (1.7)	<0.001

*P* < 0.05 is considered statistically significant, *P* < 0.001 is considered statistically highly significant. CAP = community acquired pneumonia, COPD = chronic obstructive pulmonary disease, CURB-65 = confusion, urea > 7 mmol/L, respiratory rate  $\geq 30$  breaths per minute, and blood pressure  $\leq 90/60$  mmHg, HCAP = health care associated pneumonia, PSI = pneumonia severity index.

DM admitted to hospital for pneumonia are not well known, but the following explanations could be proposed: pneumonia may be a trigger which accelerates preexisting chronic diseases, through the activation of a persisting proinflammatory status and the precipitation of fatal cardiovascular events; and pneumonia itself and/or antibiotic therapies could determine a worsening of renal function increasing the risk of morbidity and medium long-term mortality.

It is known that, in patients with CAP, cytokine concentrations (TNF $\alpha$ , IL-6, and IL-10) are high at hospital admission, decline rapidly over the 1st few days, but persist elevated for several weeks after resolution of clinical signs of

inflammation.<sup>29</sup> Hemostasis markers, in particular thrombin-antithrombin complexes, continue to be elevated at hospital discharge;<sup>30</sup> of interest, these alterations have been observed even in subjects who experienced less severe illness during the hospital course or to those that appeared to have recovered clinically.<sup>30</sup> Both higher cytokines concentration and high hemostasis markers at hospital discharge are associated with higher risk of death over 1 year, particularly due to acute deterioration of CVD.<sup>30,31</sup> Platelets activation, vasoconstriction, systemic inflammation, and increased metabolic demand strongly support a role for acute infections in triggering acute cardiovascular events.<sup>32</sup> As a matter of fact, in our study

**TABLE 3.** Comparison of Diabetic Patients With Pneumonia Survived or Not Survived at 1 year After Hospitalization

Variable	1 year Nonsurvivors n = 60, %	1 year Survivors n = 120, %	P Value
Demographic data			
Males	37 (61.7)	80 (66.7)	0.507
Hospitalization in the previous 3 months	23 (38.3)	20 (16.7)	<b>0.001</b>
Prior antibiotic therapy (last 30 days)	6 (10)	16 (13.3)	0.520
Intravascular devices	8 (13.3)	8 (6.7)	0.138
Comorbid conditions			
Chronic heart failure	18 (30)	37 (30.8)	0.909
Chronic hepatitis	4 (6.7)	8 (6.7)	1.000
Moderate to severe renal disease*	27 (45)	31 (25.8)	<b>0.009</b>
Dyslipidemia	22 (36.7)	55 (45.8)	0.241
COPD	15 (25)	44 (36.7)	0.116
Malnutrition	10 (16.7)	2 (1.7)	<b>&lt;0.001</b>
Previous cardiovascular events	32 (53.3)	53 (44.2)	0.246
History of atrial fibrillation	8 (13.3)	25 (20.8)	0.220
Characteristics of pneumonia			
CAP	27 (45)	88 (73.3)	<b>&lt;0.001</b>
HCAP	33 (55)	32 (26.7)	<b>&lt;0.001</b>
Pleural effusion	28 (46.7)	44 (36.7)	0.197
Bilateral pneumonia	31 (51.7)	35 (29.2)	<b>0.003</b>
Multilobar pneumonia	28 (46.7)	34 (28.6)	<b>0.015</b>
Clinical and laboratory findings at admission			
Mental status deterioration	9 (15)	3 (2.5)	<b>0.002</b>
pH < 7.35	10 (16.7)	7 (5.8)	<b>0.019</b>
Increased troponin	51 (85)	85 (70.8)	<b>0.037</b>
Hyperglycemia at admission ( $\geq 11$ mmol/L)	25 (41.7)	54 (45)	0.671
PSI classes			<b>&lt;0.001</b>
Class II to III	4 (6.7)	20 (16.7)	
Class IV	29 (48.3)	82 (68.3)	<b>0.017</b>
Class V	27 (45)	18 (15)	
CURB-65 classes			
Class I	8 (13.3)	34 (28.3)	
Class II	23 (38.3)	51 (42.5)	
Class III	29 (48.3)	35 (29.2)	
Therapy			
Metformin therapy	22 (36.7)	57 (47.5)	0.167
Insulin therapy	20 (33.3)	37 (30.8)	0.734
Statin therapy	22 (36.7)	53 (44.2)	0.336
Cardiovascular events during follow-up period	19 (31.7)	12 (10)	<b>&lt;0.001</b>

$P < 0.05$  is considered statistically significant,  $P < 0.001$  is considered statistically highly significant. CAP = community acquired pneumonia, COPD = chronic obstructive pulmonary disease, CURB-65 = confusion, urea  $> 7$  mmol/L, respiratory rate  $\geq 30$  breaths per minute, and blood pressure  $\leq 90/60$  mmHg, HCAP = health care associated pneumonia, PSI = pneumonia severity index.

\* Including patients undergoing hemodialysis.

cardiovascular events during the follow-up period were more frequent in patients who died. Respiratory tract infections have been directly associated with an increased risk for vascular disease, including AMI,<sup>33,34</sup> and we found a significant association between platelet activation, thromboxane A2 production, and AMI in patients with pneumonia.<sup>20</sup> Furthermore, we recently showed that chronic aspirin use, probably reducing the occurrence of cardiovascular complications, is associated with lower mortality rate in this setting of patients.<sup>21</sup>

Another deleterious effect of pneumonia in patients with DM may be related to the worsening of renal function. Association between CKD and acute community acquired infections has been reported. In the retrospective study by McDonald et al,<sup>35</sup> a high incidence of CAP and sepsis was observed among patients with DM with CKD (manifested as reduced glomerular

filtrate and/or history of proteinuria). Murugan et al<sup>36</sup> found an incidence of acute kidney injury (AKI) of 34% in patients with CAP, even among those without severe sepsis or severe CAP. Moreover, a further study revealed that, compared with patients with normal kidney function, older patients with DM with eGFR  $< 30$  mL/min/1.73 m<sup>2</sup> have a higher 28- and 90-day mortality following CAP.<sup>37</sup> A retrospective analysis of 2 multicenter cohorts confirmed that DM increases the risk of AKI in patients with CAP (30.2% vs 22.9% for subjects with and without diabetes,  $P = 0.007$ ) and this association remained significant when adjusted for age, sex, and race ( $P = 0.02$ ).<sup>27</sup> Furthermore, AKI may also be related to toxicity of antibiotic therapies. This aspect is of particular importance in patients with pneumonia due to MDR pathogens who need potentially toxic antibiotics like glycopeptides, aminoglycosides, colistin, or others. In this

**TABLE 4.** Univariate and Multivariate Cox Regression Analysis About Effects of Different Variables on Overall Survival During Follow-Up

	Univariate Analysis Unadjusted Effects of Variables				Multivariate Analysis Adjusted Effects of Variables			
	HR	95.0% CI for HR		P-Value	HR	95.0% CI for HR		P-Value
		Lower	Upper			Lower	Upper	
Hospitalization for pneumonia	2.275	1.481	3.494	<0.001	1.805	1.134	2.874	0.012
Age	1.051	1.029	1.074	<0.001	1.057	1.032	1.082	<0.001
pH < 7.35	1.918	1.043	3.529	0.036	3.385	1.768	6.482	<0.001
Hemodialysis	4.359	2.105	9.023	<0.001	3.701	1.678	8.164	0.001
Charlson comorbidity index	1.360	1.204	1.538	<0.001	1.225	1.059	1.418	0.006
Gender (male)	1.110	0.730	1.687	0.626				
Renal insufficiency	2.390	1.583	3.606	<0.001				
Chronic hepatitis	1.339	0.619	2.893	0.458				
Dementia	1.191	0.377	3.763	0.766				
Pleural effusion	2.140	1.372	3.338	0.001				
Malnutrition	4.626	2.333	9.171	<0.001				

CI = confidence interval, HR = hazard ratio.

view, we also found the hemodialysis as an independent factor for mortality in patients with DM. Hemodialysis may affect clearance of medications, including antibiotics, and in critically ill patients with pneumonia and kidney failure drug disposition are likely to be altered from that observed in healthy volunteers,<sup>38</sup> with possible antibiotic underdosing on the site of infection.

Although it was not an endpoint of our study, we observed that hyperglycemia at admission was not associated with increased mortality in patients with pneumonia. This result may be explained by the fact that we analyzed a population of patients with type 2 diabetes requiring hospitalization, and the presence of hyperglycemia was very common. Data about the role of hyperglycemia are contrasting: Kornum et al<sup>12</sup> reported that a high serum glucose level at admission was a predictor of death among patients with DM but the impact of hyperglycemia on mortality was lower in patients with DM than in nondiabetic individuals. On the same hand, Hirata et al<sup>9</sup> found that serum glucose levels on admission were not independently associated with mortality. A further study did not find correlation between mortality and the degree of hyperglycemia on admission.<sup>39</sup> As consequence, hyperglycemia does not appear a determinant of unfavorable outcome in patients with DM admitted for pneumonia.

Our study has some limitations. First, our analysis included elderly patients requiring hospitalization, and therefore our data cannot be extrapolated to a younger population of patients with DM affected by pneumonia. Second, our study is a cohort study conducted in a single center, and study groups are not very large. Consequently, the results need to be confirmed in multi-center studies with a higher number of patients. Third, a percentage of patients (9.5% of all patient population) were lost to follow-up and the estimation of drop out was not calculated a priori. Although the above-mentioned limitations, the strength of the study is its prospective design and the consecutively recruitment of the patients, which reduce potential bias in the interpretation of data, and the fact that the characteristics of our patients are representative of the population of patients with hospitalized patients with DM observed

in clinical practice. On this hand, we believe that our observations may be generalized to elderly patients with DM needing hospitalization. Nevertheless, larger studies may be necessary to validate our findings.

In conclusion, we have shown that hospitalization for pneumonia is associated with poor 1-year survival in patients with type 2 diabetes, and it appears to be a major determinant of long-term outcome in these patients. The mechanism is likely to be due to worsening of preexisting CVD and higher risk of kidney injury. These findings suggest to physicians and general practitioners a diligent clinical control of patients with type 2 diabetes discharged after hospitalization for pneumonia, including frequent ambulatory visits, monitoring of renal function, and prompt hospitalization in presence of any sign or symptom of CVD at least up to 1 year after the episode of pneumonia. Further studies are necessary to better elucidate the underlying mechanisms responsible for the excess of mortality correlated to pneumonia in patients with type 2 diabetes.

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