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Hospitalization with community-acquired pneumonia among type 2 diabetes patients: an observational population-based study in Spain from 2004 to 2013.

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ABSTRACT

Objectives: To describe trends in the incidence and outcomes of community-acquired pneumonia (CAP) hospitalizations among patients with or without diabetes in Spain (2004-2013).

Design: Retrospective, observational study using the Spanish National Hospital Discharge Database (CMBD, *Conjunto Mínimo Básico de Datos*).

Setting: Spain.

Participants: We used national hospital discharge data to select all hospital admissions for CAP.

Main outcome measures: Incidence was calculated overall and stratified by diabetes status: type 2 diabetes (T2DM) and no-diabetes.

Results: We identified 901,136 admissions for CAP (24.8% with T2DM). Incidence rates of CAP increased significantly in T2DM patients over time. The incidence was higher among people with T2DM for all time periods. T2DM patients were older and had higher comorbidity index than non-diabetic. *S. pneumoniae* decreased over time for both groups. Time trend analyses showed significant decreases in mortality during admission for CAP for patients with and without T2DM. Factor associated with higher mortality in both groups included: older age, higher comorbidity, mechanical ventilation, red cell transfusion, readmission and *S. aureus* detected. Diabetes was associated with a lower in-hospital mortality (OR: 0.92, 95%CI 0.91-0.94) after a CAP hospitalization.

Conclusions: CAP incidence rates were higher and increased over time at a higher rate among T2DM patients. Mortality decreased over time in all groups. The presence of diabetes is not a risk factor for death during admission for CAP.

Strengths and limitations of this study

- The strengths of our findings lie in the large sample size, the 10-year follow-up period, and the standardized methodology.
- Our findings are limited by the lack of data precluded adjustment for pneumococcal and influenza vaccinations, which have been associated with reduced mortality among patients hospitalized with pneumonia.
- We haven´t identified factors (specimen quality or antimicrobial treatments) that may influence in CAP outcomes because these variables were not collected in the Spanish Hospital Discharge Database.

- We did not classify diabetic patients into groups based on the therapy used to control blood glucose, with the result that we were unable to provide data on the control of blood glucose during the hospitalization.

INTRODUCTION

Prevalence of diabetes is steadily rising. In Spain the number of people with diabetes has more than doubled over the last decade due to an increasing obesity rate and an aging population.[1] This increase in diabetes prevalence is projected to lead a significant increase in patients with community-acquired pneumonia (CAP).[2]

CAP is a leading infectious cause of hospitalization worldwide, particularly among people with diabetes.[3-5] Previous studies have shown that diabetes is a risk factor for a pneumonia-related hospitalization.[6-8] A population-based cohort study found that the adjusted relative risk (RR) for pneumonia-related hospitalization among subjects with diabetes was 1.26 (95%CI 1.21-1.31) compared with non-diabetic patients.[4]

Advanced age and comorbidity are associated with increased mortality among adults hospitalized with CAP.[9] Diabetic patients may have increased susceptibility to pneumonia for several reasons. They are at increased risk of hyperglycemia, decreased immunity, impaired lung function and chronic complications such as heart disease, renal failure and pulmonary microangiopathy.[10] Kornum et al concluded that presence of type 2 diabetes (T2DM) predict increased pneumonia-related mortality.[5] However, Kaplan et al reported no association between in-hospital mortality (IHM) and diabetes.[11]

The incidence of pneumonia may be increasing.[3,9,12] Secular trends in incidence and outcomes of CAP among patients with and without T2DM have been examined.[4-6] However, to our knowledge, no previous studies have investigated national trends in the incidence, characteristics and outcomes of CAP in people with diabetes in Spain.

In this study, we used national hospital discharge data to examine trends in incidence and outcomes of CAP among patients with or without T2DM in Spain from 2004 to 2013. In particular, we analyzed patient comorbidities, diagnostic and therapeutic procedures, pneumonia pathogens and in-hospital outcomes, such as readmission, IHM and length of hospital stay (LOHS).

METHODS

We performed a retrospective, observational study using the Spanish National Hospital Discharge Database (CMBD, *Conjunto Mínimo Básico Datos*), which compiles all public and private hospital data, covering more than 98% of hospital admissions.[13] The CMBD includes patient variables (sex, date of birth), admission and discharge dates, up to 14 discharge diagnoses, and up to 20 procedures performed during the

hospital stay.[13] We analyzed data collected between January 1, 2004 and December 31, 2013 for subjects aged 40 and over.

The criteria for diseases and procedures were defined according to the ICD-9-CM, which is used in the Spanish CMBD.

We selected admissions for patients with a primary diagnosis of CAP (ICD-9-CM codes: 480-488, 507.0-507.8). We grouped admissions by diabetes status as follows: T2DM (ICD-9-CM codes: 250.x0 and 250.x2) or no-diabetes in any diagnostic position. We excluded people with type 1 diabetes mellitus (ICD-9-CM codes: 250.x1; 250.x3).

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson comorbidity index (CCI).[14] We divided patients into three categories: low index, which corresponds to patients with no previously recorded disease; medium index, patients with one disease category; and high index, patients with two or more disease categories.

Irrespectively of the position at the diagnoses coding list, we retrieved data about comorbidities as described by Kornum et al (2007).[5] Also, we specifically identified the following procedures: computerized axial tomography of thorax (ICD-9-CM code 87.41), bronchial fibroscopy (ICD-9-CM code 33.21-33.24), non-invasive mechanical ventilation (ICD-9-CM code 93.90), invasive mechanical ventilation (ICD-9-CM code 96.7, 96.70, 96.71, 96.72), thoracocentesis (ICD-9-CM code 34.91), and red cell transfusion (ICD-9-CM code 99.03, 99.04).

We analyzed pneumonia pathogens documented during hospitalizations for pneumonia using the following ICD-9-CM codes: 481 for *Streptococcus pneumonia*; 482.84 for *Legionella;* 482.41 and 482.42 for *Staphylococcus aureus;* 482.2 for *Haemophilus influenza;* and 482.1 for *Pseudomonas aeruginosa*. These were the five most frequently identified pathogens. All others represented under 0.30% of admissions.

We estimated the proportion of readmission (patients that had been discharged from the hospital within the previous 30 days), the median of LOHS and IHM. IHM is defined by the proportion of patients who died during admission for each year of study.

Statistical analysis

In order to assess time trends, the incidence rates of admissions for CAP in patients with T2DM and non-diabetic patients were calculated per 100,000 inhabitants, according to sex. We calculated yearly T2DM-specific incidence rates by dividing the number of admissions per year, sex, and age group by the corresponding number of people in that population group using the age-, sex-adjusted estimated prevalence of T2DM obtained

from National Health Surveys (NHS) conducted in 2003/04, 2006/07, 2009/10, and 2011/12 and based on data from the Di@bet.es Study, which estimated the prevalence of diabetes in the Spanish population.[1,15] From 2001 to 2010, Spanish NHS has been published every two or three years. So diabetic population for missing years (2005 and 2008) was estimated assuming that growth rate was the same thorough the period 2004-2010. We estimated rate fitting a linear regression model with population from years when NHS was available and we used this model to impute population for 2005 and 2008. We also calculated the yearly age-, sex-specific incidence rates for non-diabetic patients by dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group (excluding those with T2DM), according to the data from the Spanish National Institute of Statistics, as reported on December 31 of each year.[16]

To assess the effect of T2DM on the incidence we fitted two separate multivariate Poisson regression models for patients with and without T2DM adjusted by sex, age and year of discharge as independent variables. So that estimates correspond to Incidence Rate Ratio (IRR) with their 95% confidence intervals. A model adjusting by the same independent variables and including diabetes status was also conducted to assess the adjusted effect of diabetes in the incidence of the total population.

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for CAP according to diabetes status. Variables are expressed as proportions, as means with standard deviations or as medians with interquartile ranges (LOHS). A bivariate analysis of variables according to year was performed using the χ^2 test for linear trend (proportions), ANOVA (means) and Kruskall-Wallis (medians), as appropriate.

Lastly, we performed logistic regression analyses with mortality as a binary outcome using the independent variables and age, sex, CCI, readmission, diagnostic and therapeutic procedures, pathogens and year of admission for those with and without diabetes and for the entire population to assess the influence of diabetes on IHM. Estimates were Odds Ratios (OR) with their 95% confidence intervals. Statistical analyses were performed using Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p<0.05$ (2-tailed).

Ethical aspects

Data confidentiality was maintained at all times in accordance with Spanish legislation. Given the anonymous and mandatory nature of the dataset, it was not deemed necessary

to obtain informed consent. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.

RESULTS

From 2004 to 2013, we identified a total of 901,136 admissions for CAP as primary diagnosis in patients aged ≥40 years in Spain. Patients with T2DM accounted for 24.8% of total (134,534 men and 89,181 women).

Table 1 and Table 2 show the cumulative incidence and the clinical characteristics, comorbidities, diagnostic and therapeutic procedures and in-hospital outcomes of admissions for CAP in patients with T2DM and in patients without T2DM from 2004 to 2013, respectively.

Table 1. Incidence and characteristics of hospital admissions for pneumonia as primary diagnosis in patients with type 2 diabetes in Spain, 2004-2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
N	16161	19764	17267	20913	22002	24426	23377	25807	27655	26343	223715
Incidence*	812.64	948.39	792.36	959.67	974.43	1045.33	1000.43	962.56	1031.49	923.26	948.84
Women, n(%)*	6476(40.07)	8060(40.78)	6632(38.41)	8364(39.99)	8678(39.44)	9880(40.45)	9240(39.53)	10338(40.06)	11126(40.23)	10387(39.43)	89181(39.86)
Age, mean (SD)	75.97(10.24)	76.06(10.39)	76.18(10.47)	76.29(10.39)	76.91(10.47)	76.37(10.98)	77.53(10.28)	77.64(10.45)	78.41(10.15)	78.23(10.34)	77.08(10.46)
40-64 years n(%)*	2150(13.3)	2638(13.35)	2348(13.6)	2864(13.69)	2894(13.15)	3589(14.69)	2690(11.51)	3085(11.95)	2892(10.46)	2846(10.8)	27996(12.51)
65-74 years n(%)*	4329(26.79)	5096(25.78)	4302(24.91)	5017(23.99)	4780(21.73)	5262(21.54)	4880(20.88)	5178(20.06)	5030(18.19)	5027(19.08)	48901(21.86)
75-84 years n(%)*	6385(39.51)	7925(40.1)	6962(40.32)	8468(40.49)	8972(40.78)	9782(40.05)	9749(41.7)	10407(40.33)	11515(41.64)	10651(40.43)	90816(40.59)
≥85 years n (%)*	3297(20.4)	4105(20.77)	3655(21.17)	4564(21.82)	5356(24.34)	5793(23.72)	6058(25.91)	7137(27.66)	8218(29.72)	7819(29.68)	56002(25.03)
AMI, n(%)*	865(5.35)	1106(5.6)	991(5.74)	1180(5.64)	1167(5.3)	1141(4.67)	958(4.1)	1098(4.25)	1184(4.28)	1057(4.01)	10747(4.8)
CHF, n(%)*	2587(16.01)	3258(16.48)	2941(17.03)	3542(16.94)	3940(17.91)	4183(17.13)	4379(18.73)	5210(20.19)	5795(20.95)	5645(21.43)	41480(18.54)
PVD, n(%)*	950(5.88)	1205(6.1)	1041(6.03)	1249(5.97)	1239(5.63)	1391(5.69)	1371(5.86)	1681(6.51)	1728(6.25)	1874(7.11)	13729(6.14)
CEVD/HP/PAPL, n(%)*	1509(9.34)	1850(9.36)	1688(9.78)	1959(9.37)	2290(10.41)	2496(10.22)	2535(10.84)	2753(10.67)	3101(11.21)	2854(10.83)	23035(10.3)
Chronic pulmonary disease, n(%)*	5618(34.76)	6693(33.86)	5730(33.18)	6927(33.12)	7244(32.92)	7986(32.69)	7762(33.2)	8511(32.98)	9006(32.57)	8822(33.49)	74299(33.21)
Dementia n(%)*	1676(10.37)	1973(9.98)	1881(10.89)	2062(9.86)	2404(10.93)	2672(10.94)	2762(11.82)	3182(12.33)	3403(12.31)	3062(11.62)	25077(11.21)
Renal disease n(%)*	1893(11.71)	2260(11.43)	2187(12.67)	2659(12.71)	3082(14.01)	3640(14.9)	3878(16.59)	4504(17.45)	5160(18.66)	5261(19.97)	34524(15.43)
Any type of malignancy n(%)*	1154(7.14)	1335(6.75)	1323(7.66)	1594(7.62)	1634(7.43)	1906(7.8)	1953(8.35)	2181(8.45)	2350(8.5)	2338(8.88)	17768(7.94)
Any liver disease n(%)	793(4.91)	1001(5.06)	879(5.09)	1059(5.06)	1058(4.81)	1248(5.11)	1156(4.95)	1220(4.73)	1359(4.91)	1407(5.34)	11180(5)
Obesity n(%)*	1240(7.67)	1593(8.06)	1400(8.11)	1766(8.44)	1754(7.97)	2339(9.58)	2167(9.27)	2599(10.07)	2671(9.66)	2822(10.71)	20351(9.1)
Pleuritis, n(%)*	913(5.65)	1263(6.39)	1107(6.41)	1299(6.21)	1391(6.32)	1393(5.7)	1326(5.67)	1511(5.86)	1611(5.83)	1481(5.62)	13295(5.94)
CCI 0 n(%)*	4646(28.75)	5726(28.97)	4905(28.41)	6175(29.53)	6162(28.01)	6782(27.77)	6064(25.94)	6429(24.91)	6835(24.72)	6237(23.68)	59961(26.8)
CCI 1 n(%)*	8140(50.37)	9870(49.94)	8663(50.17)	10253(49.03)	10951(49.77)	12304(50.37)	11865(50.76)	13141(50.92)	13929(50.37)	13368(50.75)	112484(50.28)
CCI ≥2 n (%)*	3375(20.88)	4168(21.09)	3699(21.42)	4485(21.45)	4889(22.22)	5340(21.86)	5448(23.3)	6237(24.17)	6891(24.92)	6738(25.58)	51270(22.92)
CAT, n(%)*	1441(8.92)	1759(8.9)	1701(9.85)	2229(10.66)	2447(11.12)	2656(10.87)	2725(11.66)	2929(11.35)	3100(11.21)	3071(11.66)	24058(10.75)
Bronchial fibroscopy, n(%)*	424(2.62)	516(2.61)	418(2.42)	521(2.49)	540(2.45)	583(2.39)	537(2.3)	564(2.19)	581(2.1)	642(2.44)	5326(2.38)
Non-invasive MV, n (%)*	135(0.84)	170(0.86)	160(0.93)	255(1.22)	308(1.4)	387(1.58)	558(2.39)	791(3.07)	946(3.42)	918(3.48)	4628(2.07)
Invasive MV, n (%)*	354(2.19)	462(2.34)	316(1.83)	343(1.64)	346(1.57)	411(1.68)	319(1.36)	388(1.5)	331(1.2)	340(1.29)	3610(1.61)
Thoracocentesis , n (%)*	268(1.66)	401(2.03)	311(1.8)	345(1.65)	446(2.03)	439(1.8)	383(1.64)	474(1.84)	452(1.63)	449(1.7)	3968(1.77)
Red cell transfusion n(%)*	512(3.17)	584(2.95)	572(3.31)	718(3.43)	771(3.5)	899(3.68)	899(3.85)	1054(4.08)	1219(4.41)	1051(3.99)	8279(3.7)
Readmission, n(%)*	2031(12.57)	2619(13.25)	2267(13.13)	2728(13.04)	2948(13.4)	3375(13.82)	3274(14.01)	3692(14.31)	3971(14.36)	3860(14.65)	30765(13.75)
LOHS, median (IQR)	8(8)	8(8)	8(8)	8(7)	8(7)	8(7)	8(7)	7(6)	7(6)	7(7)	8(7)
IHM n(%)*	2232(13.81)	2728(13.8)	2345(13.58)	2619(12.52)	2797(12.71)	3167(12.97)	2987(12.78)	3415(13.23)	3728(13.48)	3256(12.36)	29274(13.09)
S. pneumonia, n(%)*	2504(15.49)	3411(17.26)	2977(17.24)	3873(18.52)	3783(17.19)	3992(16.34)	3501(14.98)	2380(9.22)	2027(7.33)	2095(7.95)	30543(13.65)
Legionella, n(%)*	154(0.95)	197(1)	207(1.2)	189(0.9)	217(0.99)	213(0.87)	197(0.84)	158(0.61)	170(0.61)	159(0.6)	1861(0.83)
S. aureus, n(%)*	69(0.43)	91(0.46)	104(0.6)	104(0.5)	127(0.58)	157(0.64)	131(0.56)	133(0.52)	171(0.62)	187(0.71)	1274(0.57)
H. influenza, n(%)	58(0.36)	63(0.32)	57(0.33)	85(0.41)	77(0.35)	76(0.31)	94(0.4)	81(0.31)	92(0.33)	109(0.41)	792(0.35)
P. aeruginosa, n(%)	139(0.86)	159(0.8)	146(0.85)	160(0.77)	160(0.73)	154(0.63)	169(0.72)	184(0.71)	206(0.74)	193(0.73)	1670(0.75)

AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay; IQR: Interquartile range; IHM: In-hospital mortality.
*P<0.05 to assess time trend form 2004 to 2013.

Table 2. Characteristics of hospital admissions for pneumonia as primary diagnosis in patients without type 2 diabetes in Spain, 2004-2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
N	56991	66996	58233	66504	67123	74338	67643	72762	74816	72015	677421
Incidence*	316.24	355.18	295.55	337.53	333.66	362.07	329.46	348.43	358.27	341.98	338.21
Women, n(%)*	20375(35.75)	24955(37.25)	21500(36.92)	25263(37.99)	26195(39.03)	29742(40.01)	26715(39.49)	29407(40.42)	30912(41.32)	29455(40.9)	264519(39.05)
Age, mean (SD)	73.96(13.25)	74.26(13.36)	74.24(13.64)	74.33(13.78)	74.79(13.78)	73.77(14.61)	75.67(13.72)	75.65(13.86)	77.02(13.28)	76.36(13.73)	75.06(13.76)
40-64 years n(%)*	12471(21.88)	14327(21.38)	13036(22.39)	15012(22.57)	14768(22)	18992(25.55)	13930(20.59)	15392(21.15)	13497(18.04)	14306(19.87)	145731(21.51)
65-74 years n(%)*	12578(22.07)	14150(21.12)	11555(19.84)	12535(18.85)	12153(18.11)	12409(16.69)	11068(16.36)	11581(15.92)	11321(15.13)	10965(15.23)	120315(17.76)
75-84 years n(%)*	19395(34.03)	23171(34.59)	19755(33.92)	22482(33.81)	22213(33.09)	23189(31.19)	22555(33.34)	23706(32.58)	24640(32.93)	23151(32.15)	224257(33.1)
≥85 years n (%)*	12547(22.02)	15348(22.91)	13887(23.85)	16475(24.77)	17989(26.8)	19748(26.57)	20090(29.7)	22083(30.35)	25358(33.89)	23593(32.76)	187118(27.62)
AMI, n(%)*	1932(3.39)	2309(3.45)	1917(3.29)	2279(3.43)	2123(3.16)	2207(2.97)	1884(2.79)	1955(2.69)	1952(2.61)	1802(2.5)	20360(3.01)
CHF, n(%)*	6649(11.67)	7929(11.84)	6761(11.61)	8228(12.37)	8673(12.92)	9310(12.52)	9516(14.07)	10896(14.97)	12004(16.04)	11680(16.22)	91646(13.53)
PVD, n(%)*	1857(3.26)	2345(3.5)	2121(3.64)	2239(3.37)	2237(3.33)	2445(3.29)	2496(3.69)	2753(3.78)	2923(3.91)	3074(4.27)	24490(3.62)
CEVD/HP/PAPL, n(%)*	3993(7.01)	4543(6.78)	4020(6.9)	4505(6.77)	4969(7.4)	5487(7.38)	5561(8.22)	6088(8.37)	6508(8.7)	6322(8.78)	51996(7.68)
Chronic pulmonary disease, n(%)*	20012(35.11)	23065(34.43)	19416(33.34)	21961(33.02)	21810(32.49)	24120(32.45)	22753(33.64)	24112(33.14)	24376(32.58)	23789(33.03)	225414(33.28)
Dementia n(%)*	5402(9.48)	6295(9.4)	5833(10.02)	6224(9.36)	6904(10.29)	7599(10.22)	7793(11.52)	8536(11.73)	9300(12.43)	8742(12.14)	72628(10.72)
Renal disease n(%)*	4363(7.66)	5327(7.95)	4609(7.91)	5760(8.66)	6328(9.43)	7189(9.67)	7312(10.81)	8278(11.38)	9609(12.84)	9572(13.29)	68347(10.09)
Any type of malignancy n(%)*	5696(9.99)	6420(9.58)	6006(10.31)	6671(10.03)	6929(10.32)	7642(10.28)	7504(11.09)	8234(11.32)	8289(11.08)	8407(11.67)	71798(10.6)
Any liver disease n(%)	2825(4.96)	3362(5.02)	2942(5.05)	3436(5.17)	3409(5.08)	3852(5.18)	3457(5.11)	3689(5.07)	3733(4.99)	3754(5.21)	34459(5.09)
Obesity n(%)*	1940(3.4)	2352(3.51)	2044(3.51)	2304(3.46)	2489(3.71)	3188(4.29)	2839(4.2)	3367(4.63)	3393(4.54)	3529(4.9)	27445(4.05)
Pleuritis, n(%)*	3992(7)	4898(7.31)	4240(7.28)	4936(7.42)	4760(7.09)	4892(6.58)	4782(7.07)	4954(6.81)	5054(6.76)	5101(7.08)	47609(7.03)
CCI 0 n(%)*	18620(32.67)	22311(33.3)	19452(33.4)	22643(34.05)	21991(32.76)	24786(33.34)	20436(30.21)	21691(29.81)	21653(28.94)	20550(28.54)	214133(31.61)
CCI 1 n(%)*	28219(49.51)	32726(48.85)	28327(48.64)	31765(47.76)	32752(48.79)	35890(48.28)	33399(49.38)	36155(49.69)	37205(49.73)	35850(49.78)	332288(49.05)
CCI ≥2 n (%)*	10152(17.81)	11959(17.85)	10454(17.95)	12096(18.19)	12380(18.44)	13662(18.38)	13808(20.41)	14916(20.5)	15958(21.33)	15615(21.68)	131000(19.34)
CAT, n(%)*	5936(10.42)	6931(10.35)	6565(11.27)	8042(12.09)	8487(12.64)	9356(12.59)	9191(13.59)	9690(13.32)	9627(12.87)	10028(13.92)	83853(12.38)
Bronchial fibroscopy, n(%)*	2165(3.8)	2256(3.37)	2068(3.55)	2245(3.38)	2220(3.31)	2258(3.04)	2135(3.16)	2207(3.03)	2195(2.93)	2351(3.26)	22100(3.26)
Non-invasive MV, n (%)*	442(0.78)	584(0.87)	531(0.91)	718(1.08)	945(1.41)	1188(1.6)	1616(2.39)	1934(2.66)	2307(3.08)	2286(3.17)	12551(1.85)
Invasive MV, n (%)*	1426(2.5)	1700(2.54)	1140(1.96)	1338(2.01)	1405(2.09)	1520(2.04)	1279(1.89)	1516(2.08)	1336(1.79)	1287(1.79)	13947(2.06)
Thoracocentesis , n (%)*	1271(2.23)	1476(2.2)	1308(2.25)	1527(2.3)	1549(2.31)	1655(2.23)	1502(2.22)	1508(2.07)	1518(2.03)	1636(2.27)	14950(2.21)
Red cell transfusion n(%)*	1830(3.21)	2125(3.17)	2034(3.49)	2189(3.29)	2498(3.72)	2642(3.55)	2709(4)	2830(3.89)	3073(4.11)	3009(4.18)	24939(3.68)
Readmission, n(%)*	6633(11.64)	7830(11.69)	7063(12.13)	7889(11.86)	8121(12.1)	8947(12.04)	8794(13)	9515(13.08)	10427(13.94)	9716(13.49)	84935(12.54)
LOHS, median (IQR)	8(8)	8(8)	8(7)	8(7)	8(7)	7(8)	7(7)	7(7)	7(7)	7(7)	7(7)
IHM n(%)*	8036(14.1)	9900(14.78)	8121(13.95)	8758(13.17)	9105(13.56)	9727(13.08)	9087(13.43)	10209(14.03)	10777(14.4)	9803(13.61)	93523(13.81)
S. pneumonia, n(%)*	9736(17.08)	11685(17.44)	10295(17.68)	12295(18.49)	11899(17.73)	12099(16.28)	10081(14.9)	7147(9.82)	5918(7.91)	6101(8.47)	97256(14.36)
Legionella, n(%)*	667(1.17)	808(1.21)	727(1.25)	667(1)	678(1.01)	729(0.98)	668(0.99)	544(0.75)	546(0.73)	449(0.62)	6483(0.96)
S. aureus, n(%)*	253(0.44)	350(0.52)	286(0.49)	366(0.55)	368(0.55)	378(0.51)	400(0.59)	438(0.6)	503(0.67)	470(0.65)	3812(0.56)
H. influenza, n(%)	267(0.47)	272(0.41)	257(0.44)	264(0.4)	263(0.39)	293(0.39)	295(0.44)	289(0.4)	300(0.4)	333(0.46)	2833(0.42)
P. aeruginosa, n(%)	509(0.89)	597(0.89)	514(0.88)	574(0.86)	617(0.92)	622(0.84)	632(0.93)	632(0.87)	638(0.85)	685(0.95)	6020(0.89)

AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay; IQR: Interquartile range; IHM: In-hospital mortality.
*P<0.05 to assess time trend form 2004 to 2013.

Among patients with T2DM, crude incidence of admissions for CAP increased significantly from 812.64 cases per 100,000 T2DM population in 2004 to 923.26 cases in 2013 (Table 1). In patients without T2DM the cumulative incidence of admissions increased significantly from 316.24 cases per 100,000 population without diabetes in 2004 to 341.98 in 2013 (Table 2). Incidence was significantly higher in T2DM people than in non-diabetic people for all years analysed. From 2004 to 2013, the adjusted IRR of having CAP admission diagnosis in patients with type 2 diabetes was significant and higher than in those without diabetes (1.27 95%CI 1.23-1.31 vs. 1.05 95% CI 1.03-1.07).

Taking people without diabetes admitted with CAP as the reference category and using the Poisson regression models constructed to compare the adjusted incidence of admissions for CAP from 2004 to 2013, we obtained an adjusted IRR of 1.66 (95%CI 1.65-1.67) for patients with T2DM. In other words, the incidence of admissions for CAP over the entire period was 1.66-times higher among patients with T2DM than those without diabetes.

In patients who have an admission for CAP, there was a significant male predominance (60.14% for T2DM and 60.95% for no diabetes). Overall, patients with T2DM were significantly older (77.08±10.46 years) than patients without diabetes (75.06±13.76 years) and had more coexisting medical conditions. Specifically, had higher prevalence of acute myocardial infarction (4.8% vs. 3.1%), congestive heart failure (18.54% vs. 13.53%), cerebrovascular disease/hemiplegia/paraplegia (10.3% vs. 7.68%), dementia (11.21% vs. 10.72%), renal disease (15.43% vs. 10.09%), peripheral vascular disease (6.14% vs. 3.62%) and prevalence of obesity is two times higher (all P values<0.05). On the other hand, any type of malignancy and pleuritis were more prevalent in non-diabetic patients (10.6% and 7.03%, respectively) than in those with T2DM (7.94% and 5.94%). Age and all these comorbidities increased significantly over time in both people with T2DM and without diabetes (Table 1 and Table 2).

As can been seen in Table 1 and Table 2, acute myocardial infarction and chronic pulmonary disease decreased significantly in both groups over the study period. Male sex increased significantly in people with T2DM only.

A significant decrease in the use of bronchial fibroscopy was found reducing from 2.62% in 2004 to 2.44% in 2013 among T2DM subjects and from 3.8% to 3.26% in those without diabetes. We detected a significant increase in use of thorax CAT in both groups over the study period as can been seen in Table 1 and Table 2.

The use of all therapeutics procedures (except invasive mechanical ventilation which showed a significant decrease) have significantly increased in the last ten years in diabetic and non-diabetic patients (Table 1 and Table 2). The use of non invasive mechanical ventilation has shown an over three fold increase in both groups of patients over the study period.

Of the pathogens analysed the most commonly found was *S. pneumoniae*, followed by *Legionella*, *P. aeruginosa*, *S. aureus* and *H. influenza*.

In year 2013 *S. pneumonia* was detected in 7.95% of diabetic patients and 8.47% in those without the disease. All other pathogens were found in under 1% of patients.

S. pneumoniae and *Legionella* decreased over time in both people with T2DM and without diabetes. However, we detected a significant increase of *S. aureus* in both groups over the study period (Table 1 and Table 2). The prevalence of pathogens analysed was similar in patients with and without the disease.

Readmissions increased in both groups during the study (Table 1 and Table 2). Among diabetic patients, the increase was from 12.57% in 2004 to 14.65% in 2013. Equivalent figures for subjects without diabetes were significantly lower (11.64% and 13.49%).

Overall median LOHS was significantly higher in patients with T2DM (8 vs.7 days). Over time, LOHS following CAP fell significantly in both patients with T2DM and without diabetes.

IHM was 13.81% for T2DM patients and 13.09% for non-diabetic people ($p<0.05$). Crude IHM decreased significantly over time in both people with T2DM and without diabetes (from 13.81% and 14.1%, respectively in 2004 to 12.36% and 13.61% in 2013), as can been seen in Table 1 and Table 2.

Table 3 shows the characteristics of hospital admissions for CAP in patients with and without T2DM according to IHM during the study period.

Table 3. Characteristics of hospital admissions for pneumonia as primary diagnosis in patients with and without type 2 diabetes in Spain, 2001-2013 according to in hospital mortality.

	Diabetes		No Diabetes	
	LIVE	**DIED**	**LIVE**	**DIED**
Women, n(%)*†	76301(39,24)	12880(44)	225626(38,64)	38893(41,59)
Age, mean (SD)* †	76.42(10.51)	81.48(8.94)	74.11(13.87)	80.97(11.43)
40-64 years n(%)*†	26507(13.63)	1489(5.09)	136594(23.39)	9137(9.77)
65-74 years n(%)*†	45070(23.18)	3831(13.09)	109241(18.71)	11074(11.84)
75-84 years n(%)*†	78684(40.47)	12132(41.44)	192709(33)	31548(33.73)
≥85 years n (%)*†	44180(22.72)	11822(40.38)	145354(24.89)	41764(44.66)
AMI, n(%)*†	9163(4.71)	1584(5.41)	17000(2.91)	3360(3.59)
CHF, n(%)*†	35096(18.05)	6384(21.81)	74122(12.69)	17524(18.74)
PVD, n(%)*†	11802(6.07)	1927(6.58)	20931(3.58)	3559(3.81)
CEVD/HP/PAPL, n(%)*†	18199(9.36)	4836(16.52)	40554(6.95)	11442(12.23)
Chronic pulmonary disease, n(%)*†	67498(34.71)	6801(23.23)	203108(34.78)	22306(23.85)
Dementia n(%)*†	18657(9.6)	6420(21.93)	53446(9.15)	19182(20.51)
Renal disease n(%)*†	29173(15)	5351(18.28)	55766(9.55)	12581(13.45)
Any type of malignancy n(%)*†	14089(7.25)	3679(12.57)	56195(9.62)	15603(16.68)
Any liver disease n(%)	9730(5)	1450(4.95)	29671(5.08)	4788(5.12)
Obesity n(%)*†	19076(9.81)	1275(4.36)	25570(4.38)	1875(2)
Pleuritis, n(%)*†	11774(6.06)	1521(5.2)	42000(7.19)	5609(6)
CCI 0 n(%)*†	54116(27.83)	5845(19.97)	191839(32.85)	22294(23.84)
CCI 1 n(%)*†	97047(49.91)	15437(52.73)	283688(48.59)	48600(51.97)
CCI ≥2 n (%)*†	43278(22.26)	7992(27.3)	108371(18.56)	22629(24.2)
CAT, n(%)*†	22383(11.51)	1675(5.72)	77695(13.31)	6158(6.58)
Bronchial fibroscopy, n(%)*†	4859(2.5)	467(1.6)	20039(3.43)	2061(2.2)
Non-invasive MV, n (%)*†	3563(1.83)	1065(3.64)	9250(1.58)	3301(3.53)
Invasive MV, n (%)*†	1937(1)	1673(5.71)	7248(1.24)	6699(7.16)
Thoracocentesis , n (%)*†	3610(1.86)	358(1.22)	13535(2.32)	1415(1.51)
Red cell transfusion n(%)*†	6866(3.53)	1413(4.83)	19626(3.36)	5313(5.68)
Readmission, n(%)*†	24306(12.5)	6459(22.06)	66353(11.36)	18582(19.87)
LOHS, median (IQR) *†	8(7)	6(10)	8(7)	6(11)
S. pneumonia, n(%)*†	28086(14.44)	2457(8.39)	89171(15.27)	8085(8.64)
Legionella, n(%)*†	1766(0.91)	95(0.32)	6134(1.05)	349(0.37)
S. aureus, n(%)*†	1042(0.54)	232(0.79)	3017(0.52)	795(0.85)
H. influenza, n(%)*†	763(0.39)	29(0.1)	2704(0.46)	129(0.14)
P. aeruginosa, n(%)*†	1400(0.72)	270(0.92)	4934(0.85)	1086(1.16)

AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay.

*Without diabetes † With diabetes

For the entire time period IHM was slightly but significantly higher among those without diabetes (13.81%vs. 13.09%).

Overall, patients with T2DM who died during their hospitalization were significantly older (81.48±8.94 years) than those that survived (76.42±10.51 years) and had more coexisting medical conditions. Including higher prevalence of acute myocardial infarction (5.41% vs 4.71%), congestive heart failure (21.81% vs. 18.05%), vascular disease (6.58% vs, 6.07%), cerebrovascular disease/hemiplegia/paraplegia (16.52% vs. 9.36%), dementia (21.93% vs. 9.6%), renal disease (18.28% vs. 15%), any type of malignancy (12.57% vs. 7.25%). On the other hand chronic obstructive pulmonary disease, obesity and pleuritis were more prevalent in diabetic patients that didn't die during their hospital stay.

Invasive and non-invasive mechanical ventilation and red cell transfusion procedures were significantly more used in diabetic patients who died than in those that survived (5.71%, 3.64% and 4.83% vs. 1%, 1.83% and 3.53%, respectively). However, CAT of thorax, thoracocentesis, bronchial fibroscopy were more frequent in T2DM and non-diabetic patients that survived than in those who died.

As can been seen in Table 3, non-diabetic patients who died were significantly older, had more coexisting conditions like acute myocardial infarction, congestive heart failure, vascular disease, cerebrovascular disease/hemiplegia/paraplegia, dementia, renal disease and any type of malignancy and were underwent invasive and non-invasive mechanical ventilation and red cell transfusion procedures than those non-diabetic patients that survived.

We found that 22.06% of diabetic patients that died and 12.5%% of diabetic patients that survived were readmission (P< 0.01). LOHS was 6 days in those diabetic and non-diabetic patients who died vs. 8 days in those diabetic and non-diabetic patients that survived.

S. pneumoniae was more frequently detected in patients who lived than in those who died in both T2DM and non-diabetic patients (14.44% vs. 8.39% and 15.27% vs. 8.64%), as can been seen in Table 3.

In Table 4 we can see the results of the multivariate analysis of the factors independently associated with in hospital mortality in diabetic and non-diabetic patients. during hospital admission for CAP in Spain, 2004-2013.

Table 4. Multivariate analysis of the factors potentially associated with in-hospital mortality for patients with and without type 2 diabetes in Spain, 2001-2013 with pneumonia as primary diagnosis.

		Diabetes OR(CI 95%)	No diabetes OR(CI 95%)	Total OR(CI 95%)
Age, years	40-64	1	1	1
	65-74	1.47(1.38-1.57)	1.47(1.42-1.51)	1.46(1.42-1.50)
	75-84	2.70(2.55-2.87)	2.49(2.42-2.55)	2.53(2.47-2.59)
	≥85	4.75(4.47-5.05)	4.52(4.40-4.64)	4.55(4.44-4.66)
CCI	0	1	1	1
	1	1.35(1.30-1.39)	1.28(1.26-1.31)	1.30(1.28-1.32)
	≥2	1.50(1.44-1.56)	1.44(1.411.47)	1.46(1.43-1.48)
Obesity		0.51(0.48-0.54)	0.50(0.47-0.52)	0.50(0.48-0.52)
Non-invasive MV		2.04(1.89-2.21)	2.01(1.92-2.11)	2.02(1.94-2.10)
Invasive MV		11.53(10.68-12.45)	12.55(12.06-13.06)	12.34(11.91-12.78)
Red cell transfusion		1.14(1.07-1.21)	1.35(1.31-1.40)	1.30(1.26-1.34)
Readmission		1.91(1.85-1.97)	1.85(1.82-1.89)	1.87(1.84-1.90)
CAT		0.54(0.51-0.57)	0.53(0.51-0.55)	0.53(0.52-0.55)
Thoracocentesis		0.82(0.73-0.93)	0.86(0.80-0.91)	0.85(0.80-0.90)
Bronchial fibroscopy		0.75(0.67-0.83)	0.71(0.67-0.75)	0.72(0.68-0.75)
S. pneumonia		0.54(0.52-0.57)	0.52(0.51-0.53)	0.52(0.51-0.54)
Legionella,		0.43(0.34-0.53)	0.38(0.34-0.42)	0.39(0.35-0.43)
S. aureus		1.22(1.04-1.42)	1.26(1.16-1.37)	1.25(1.16-1.35)
H. influenza,		0.22(0.15-0.32)	0.26(0.21-0.31)	0.25(0.21-0.29)
Year		0.97(0.96-0.99)	0.97(0.96-0.98)	0.97(0.96-0.98)
Diabetes			-	0.92(0.91-0.94)

CCI Charlson comorbidity index. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax.

Among diabetic patients, IHM was significantly higher in older subjects (vs.<40-64 years old, OR: 4.75, 95%CI 4.47-5.05 for ≥ 85 years old) and in those with more comorbidities according to the CCI (vs. no comorbidities, OR: 1.35, 95%CI 1.30-1.39, for one comorbidity; OR: 1.50, 95%CI 1.44-1.56, for two or more comorbidities).

For diabetic patients, IHM was significantly lower in obese persons (OR: 0.51, 95%CI 0.48-0.54) than in those with normal body mass index.

Over the entire study period, a diabetic patient with readmission was 1.14 (95%CI, 1.07-1.21) times more likely to die than a diabetic patient without readmission.

T2DM patients having an in-hospital infection during admission for CAP (*S. pneumoniae or Legionella or H. influenza* were identified) had lower probability of dying than patients without these pathogens. However diabetic patients with *S. aureus* had 1.22-fold higher probability of dying during their stay than those without that pathogen. IHM was significantly higher in patients who underwent invasive and non-invasive mechanical ventilation (OR: 11.53, 95%CI 10.68-12.45 and OR: 2.04, 95%CI 1.89-2.21) and red cell transfusion (OR: 1.14, 95%CI 1.07-1.21).

Diabetic patients who underwent CAT of thorax, bronchial fibroscopy and thoracocentesis procedures had a 0.54-fold, 0.75-fold and 0.82-fold, respectively, lower probability of dying during their stay than those who did not undergo these procedures.

Time trend analysis showed a minor but significant decrease in IHM from 2004 to 2013 in T2DM patients (OR: 0.97, 95%CI 0.96-0.99).

As can been seen in Table 4, for non-diabetic patients, IHM was significantly higher in older persons, in those with more comorbidities, in those with readmissions, in those with infections for *S. aureus* and in those who underwent invasive and non-invasive mechanical ventilation and red cell transfusion procedures. As for diabetic patients we found a significant decrease in mortality over time.

In our study, suffering diabetes was associated with a lower IHM (OR: 0.92, 95%CI 0.91-0.94).

Finally, for the entire population time trend analyses showed a significant decrease in mortality from 2004 to 2013 in patients admitted for CAP in Spain (OR: 0.97, 95%CI 0.96-0.98).

DISCUSSION

Using data from the Spanish National Hospital Database, we found that rates of hospitalization for CAP in patients with and without T2DM increased significantly from

2004 to 2013. These results are consistent with a report from Denmark, which pointed that total pneumonia hospitalization increased by 63%, from 4.96 per 1000 population in 1997 to 8.09 in 2011.[12] Recently, Quan et al concluded that hospital admission for CAP are increasing by ≈9% per year between 2009 and 2014.[9] Possible explanations for the CAP increase are that more low-severity cases are presenting to hospital and ageing population.[3,9,17]

We found that readmissions for CAP increased over time in patients with and without T2DM and LOHS decreased in both groups of patients. These data are consistent with other published study, suggesting that the fact that readmissions for pneumonia increased over time supports another plausible explanation for the shortening LOHS, namely an increased pressure for early discharge.[9,18]

After adjusting for age and sex, we found that the incidence of CAP among T2DM patients was 1.66-times higher than among non-diabetic patients. Our results agree with the Fremantle Diabetes Study data, in this study Hamilton et al compared patients with T2DM in Australia to matched nondiabetic subjects and indicated that IRR for pneumonia was 1.86 (95%CI 1.55-2.21).[6] In US, Jackson et al, also reported that the adjusted RR for hospitalizations for CAP was 1.52 (95%CI 1.29-1.78) among patients with diabetes compared with patients without diabetes, based on 46,237 subjects aged >65 years.[19] In a Canadian study, the authors indicated that patients with diabetes had an increased risk of pneumonia-related hospitalization than those without diabetes (RR 1.46 [95%CI 1.42-1.49]).[8] In a case-control study in Denmark, Kornum et al found that T2DM was associated with a 1.2-fold increased risk of a pneumonia-related hospitalization.[4] They concluded that longer duration of diabetes and poor glycemic control increase the risk of CAP-related hospitalization.

Like other authors, we found that patients admitted for CAP were increasing older.[9,17] In UK, using linked electronic health records of patients with diabetes, McDonald et al observed that pneumonia incidence was 6-8 times higher among patients aged ≥85 years than patients aged 65-69 years.[20] Possible explanations include a general improvement in clinical management, especially changes in immunosuppressive regimens and handling of comorbidities.[12]

In our study, T2DM patients had a higher number of simultaneous comorbidities and were more frequently obese, but obesity was not associated with a higher mortality risk during admission for CAP. Obesity is known to have adverse effects on immune function and to increase susceptibility to infections such as pneumonia,[21] however

Hamilton et al concluded that a high body mass index was independently associated with any infection in their cohort of diabetic patients.[6] A recent meta-analysis concluded that overweight and obesity were significantly associated with reduced risk of pneumonia mortality (RR: 0.83, 95% CI 0.77 to 0.91, P < 0.01) and suggests that an 'obexity survival paradox' exists for pneumonia.[22]

The use of non invasive mechanical ventilation has shown an over three fold increase in patients with and without T2DM over the study period. In a study about CAP in elderly, the authors found that mechanical ventilation was provided commonly and that almost half of the patients older than 90 years who received such care were discharged alive, supporting the belief that such care for the critically ill elderly patient is often justified.[11]

As expected, *S. pneumoniae* was the most frequent etiological agent among patients with and without diabetes, however, its dominance is decreasing. Smith et al concluded that declines in cases of pneumonia due to *S. pneumoniae* (from 7.1% in 1993 to 2.3% 2011) may be related to more frequent and effective vaccination, which reduces the risk of invasive pneumococcal disease and bacteriemia.[23] Also this reduced risk may have resulted in less-frequent coding because more thorough diagnostic evaluations accompany a higher severity of disease. In Spain *S. pneumoniae* vaccine is recommended for high-risk groups, including people with diabetes, and for all persons aged 65 years or over.[24]

We found that other organism's particularly *S aureus* was more prevalent in dead patients than in survivors in both T2DM and non-diabetic patients. Like other authors despite the trends observed,[23,25] the low incidence of *S aureus* (0.57% in patients with T2DM and 0.56% in those without T2DM), may be suggests that *S aureus* is not routinely search for and detected for patients with CAP.[23,26] It has been reported that pneumonia is the leading infectious cause of death in Spain, however the mortality rate for pneumonia has decreased between 1980 and 2011.[27] In our study, we found that crude IHM decreased over among diabetic and non-diabetic patients with a diagnosis of CAP. Simonetti AF et al found a progressive downward trend of thirty-day mortality in hospitalized patients with CAP (-0.2% death/year; P for trend=.003]) and concluded that the decreased in mortality rates suggest general improvement in the management of CAP.[28]

We detected that patients with T2DM who died during their stay were older, had more coexisting comorbid conditions and had significantly more readmissions than those

patients with T2DM that survived. In diabetic patients who died mechanical ventilation and red cell transfusion were significantly more used than in those that survived. An alternative explanation is that there is a trend to hospitalizing a higher proportion of fragil or terminal patients who previously may have been treated at home.[12]

In our population, the presence of T2DM was not a risk factor of death during admission for CAP. The results add important evidence to previous information. An observational cohort study of all Medicare recipients, aged 65 years or older, hospitalized in nonfederal U.S. hospitals Kaplan et al reported no association between IHM and diabetes.[11] In a Canadian study of 2,471 patients with CAP, the authors concluded that hyperglycemia, but not the presence of diabetes, was the only factor having a significant negative effect on patient survival.[29] However, Kornum et al, indicated that high glucose levels were associated with increased mortality in both patients with and without T2DM.[5] Perhaps the fact that patients with diabetes are more likely to be hospitalized with less severity. In fact, in our study, we observed a lower frequency of pleuritis and any type of malignancy in diabetics than in non-diabetics, which could justify the lower mortality in the first group.

In our study mechanical ventilation (invasive and non-invasive) and red cell transfusion were significantly associated with mortality during admission for CAP in both groups of patients with and without diabetes.

A recent study, reported that noninvasive pressure ventilation is frequently used in CAP but is associated with high failure rates, indicated that patients who failed non invasive mechanical ventilation had an increased odds of death when compared with patients who were treated with invasive ventilation (OR, 2.2; 95% CI, 1.0-4.8; P = .03).[30]

The strengths of our findings lie in the large sample size, the 10-year follow-up period, and the standardized methodology, which has been used to investigate diabetes and its complications in Spain and elsewhere.[31]

Limitations of the study

Nevertheless, our study is subject to several limitations. Our data source was the CMBD, an administrative database that contains discharge data for hospitalizations in Spain and uses information the physician has included in the discharge report. Therefore, our findings are limited by the lack of data precluded adjustment for pneumococcal and influenza vaccinations, which have been associated with reduced mortality among patients hospitalized with pneumonia.[5]

Other studies have identified factors that may influence in CAP outcomes and that were

not included in our investigation because these variables were not collected in the Spanish Hospital Discharge Database. These factors include, among others, specimen quality or antimicrobial treatments.[9] Additionally, we also cannot identify whether gradual changes were made in referral practice during the study period.

Another significant limitation is the fact that we did not classify diabetic patients into groups based on the therapy used to control blood glucose, with the result that we were unable to provide data on the control of blood glucose during the hospitalization.

CONCLUSIONS

In conclusion, Spanish national data show that rates of hospitalization for CAP in patients with and without T2DM increased significantly from 2004 to 2013 and incidence rates were higher in T2DM patients than in those without diabetes in all time periods studied. CAP incidence seems to be increasing at a higher rate among T2DM patients than among non-diabetic patients. IHM after CAP shows downward trends over time in all groups analyzed. Remarkably, the presence of T2DM is not a risk factor of death after CAP in our cohort.

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CONTRIBUTIONS

AL and RJG researched data, contributed to the discussion, wrote the manuscript, and reviewed/edited the manuscript. VHB researched data and reviewed/edited the manuscript. JMD, IJT, JMMY, MMB, NPF and MASF contributed to the discussion and reviewed/edited the manuscript.

All authors reviewed and gave their final approval of the version to be submitted.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	6,7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6,7
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Hospitalization with community-acquired pneumonia among type 2 diabetes patients: an observational population-based study in Spain from 2004 to 2013.

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Keywords:	type 2 diabetes, community-acquired pneumonia, hospitalization, in-hospitall mortality

Hospitalization with community-acquired pneumonia among type 2 diabetes patients: an observational population-based study in Spain from 2004 to 2013.

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Keywords: type 2 diabetes; community-acquired pneumonia; hospitalization; in-hospital mortality

Wordcount: 4,000

ABSTRACT

Objectives: To describe trends in the incidence and outcomes of community-acquired pneumonia (CAP) hospitalizations among patients with or without diabetes in Spain (2004-2013).

Design: Retrospective, observational study using the Spanish National Hospital Discharge Database (CMBD, *Conjunto Mínimo Básico de Datos*).

Setting: Spain.

Participants: We used national hospital discharge data to select all hospital admissions for CAP.

Main outcome measures: Incidence was calculated overall and stratified by diabetes status: type 2 diabetes (T2DM) and no-diabetes.

Results: We identified 901,136 admissions for CAP (24.8% with T2DM). Incidence rates of CAP increased significantly in T2DM patients over time. The incidence was higher among people with T2DM for all time periods. T2DM patients were older and had higher comorbidity index than non-diabetic. *S. pneumoniae* decreased over time for both groups. Time trend analyses showed significant decreases in mortality during admission for CAP for patients with and without T2DM. Factor associated with higher mortality in both groups included: older age, higher comorbidity, mechanical ventilation, red cell transfusion, readmission and *S. aureus* detected. Diabetes was associated with a lower in-hospital mortality (OR: 0.92, 95%CI 0.91-0.94) after a CAP hospitalization.

Conclusions: CAP incidence rates were higher and increased over time at a higher rate among T2DM patients. Mortality decreased over time in all groups. The presence of diabetes is not a risk factor for death during admission for CAP.

Strengths and limitations of this study

- The strengths of our findings lie in the large sample size, the 10-year follow-up period, and the standardized methodology.
- Our findings are limited by the lack of data precluded adjustment for pneumococcal and influenza vaccinations, which have been associated with reduced mortality among patients hospitalized with pneumonia.
- We haven´t identified factors (specimen quality or antimicrobial treatments) that may influence in CAP outcomes because these variables were not collected in the Spanish Hospital Discharge Database.

- We did not classify diabetic patients into groups based on the therapy used to control blood glucose, with the result that we were unable to provide data on the control of blood glucose during the hospitalization.

INTRODUCTION

Prevalence of diabetes is steadily rising. In Spain the number of people with diabetes has more than doubled over the last decade due to an increasing obesity rate and an aging population.[1] This increase in diabetes prevalence is projected to lead a significant increase in patients with community-acquired pneumonia (CAP).[2]

CAP is a leading infectious cause of hospitalization worldwide, particularly among people with diabetes.[3-5] Previous studies have shown that diabetes is a risk factor for a pneumonia-related hospitalization.[6-8] A population-based cohort study found that the adjusted relative risk (RR) for pneumonia-related hospitalization among subjects with diabetes was 1.26 (95%CI 1.21-1.31) compared with non-diabetic patients.[4]

Advanced age and comorbidity are associated with increased mortality among adults hospitalized with CAP.[9] Diabetic patients may have increased susceptibility to pneumonia for several reasons. They are at increased risk of hyperglycemia, decreased immunity, impaired lung function and chronic complications such as heart disease, renal failure and pulmonary microangiopathy.[10] Kornum et al concluded that presence of type 2 diabetes (T2DM) predict increased pneumonia-related mortality.[5] However, Kaplan et al reported no association between in-hospital mortality (IHM) and diabetes.[11]

The incidence of pneumonia may be increasing.[3,9,12] Secular trends in incidence and outcomes of CAP among patients with and without T2DM have been examined.[4-6] However, to our knowledge, no previous studies have investigated national trends in the incidence, characteristics and outcomes of CAP in people with diabetes in Spain.

In this study, we used national hospital discharge data to examine trends in incidence and outcomes of CAP among patients with or without T2DM in Spain from 2004 to 2013. In particular, we analyzed patient comorbidities, diagnostic and therapeutic procedures, pneumonia pathogens and in-hospital outcomes, such as readmission, IHM and length of hospital stay (LOHS).

METHODS

We performed a retrospective, observational study using the Spanish National Hospital Discharge Database (CMBD, *Conjunto Mínimo Básico Datos*), which compiles all public and private hospital data, covering more than 98% of hospital admissions.[13] The CMBD includes patient variables (sex, date of birth), admission and discharge dates, up to 14 discharge diagnoses, and up to 20 procedures performed during the

hospital stay.[13] We analyzed data collected between January 1, 2004 and December 31, 2013 for subjects aged 40 and over.

The criteria for diseases and procedures were defined according to the ICD-9-CM, which is used in the Spanish CMBD.

We selected admissions for patients with a primary diagnosis of CAP (ICD-9-CM codes: 480-488, 507.0-507.8). We grouped admissions by diabetes status as follows: T2DM (ICD-9-CM codes: 250.x0 and 250.x2) or no-diabetes in any diagnostic position. We excluded people with type 1 diabetes mellitus (ICD-9-CM codes: 250.x1; 250.x3).

Clinical characteristics included information on overall comorbidity at the time of diagnosis, which was assessed by calculating the Charlson comorbidity index (CCI).[14] We divided patients into three categories: low index, which corresponds to patients with no previously recorded disease; medium index, patients with one disease category; and high index, patients with two or more disease categories.

Irrespectively of the position at the diagnoses coding list, we retrieved data about comorbidities as described by Kornum et al (2007).[5] Also, we specifically identified the following procedures: computerized axial tomography of thorax (ICD-9-CM code 87.41), bronchial fibroscopy (ICD-9-CM code 33.21-33.24), non-invasive mechanical ventilation (ICD-9-CM code 93.90), invasive mechanical ventilation (ICD-9-CM code 96.7, 96.70, 96.71, 96.72), thoracocentesis (ICD-9-CM code 34.91), and red cell transfusion (ICD-9-CM code 99.03, 99.04).

We analyzed pneumonia pathogens documented during hospitalizations for pneumonia using the following ICD-9-CM codes: 481 for *Streptococcus pneumonia*; 482.84 for *Legionella;* 482.41 and 482.42 for *Staphylococcus aureus;* 482.2 for *Haemophilus influenza;* and 482.1 for *Pseudomonas aeruginosa*. These were the five most frequently identified pathogens. All others represented under 0.30% of admissions.

We estimated the proportion of readmission (patients that had been discharged from the hospital within the previous 30 days), the median of LOHS and IHM. IHM is defined by the proportion of patients who died during admission for each year of study.

Statistical analysis

In order to assess time trends, the age and sex incidence rates of admissions for CAP in patients with T2DM and non-diabetic patients were calculated per 100,000 inhabitants,. We calculated yearly T2DM-specific incidence rates by dividing the number of admissions per year, sex, and age group by the corresponding number of people in that population group using the age-, sex-adjusted estimated prevalence of T2DM obtained

from National Health Surveys (NHS) conducted in 2003/04, 2006/07, 2009/10, and 2011/12 and based on data from the Di@bet.es Study, which estimated the prevalence of diabetes in the Spanish population.[1,15] From 2001 to 2010, Spanish NHS has been published every two or three years. So diabetic population for missing years (2005 and 2008) was estimated assuming that growth rate was the same thorough the period 2004-2010. We estimated rates by fitting a linear regression model with population from years when NHS was available and we used this model to impute population for 2005 and 2008. We also calculated the yearly age-, age and sex adjusted-specific incidence rates for non-diabetic patients by dividing the number of cases per year, sex, and age group by the corresponding number of people in that population group (excluding those with T2DM), according to the data from the Spanish National Institute of Statistics, as reported on December 31 of each year.[16]

To assess the effect of T2DM on the incidence we fitted two separate multivariate Poisson regression models for patients with and without T2DM adjusted by sex, age and year of discharge as independent variables. The results of these models are shown as adjusted Incidence Rate Ratio (IRR) with their 95% confidence intervals. A model adjusting by the same independent variables and including diabetes status was also conducted to assess the adjusted effect of diabetes in the incidence of the total population.

To assess whether there was any over-inflation we tried also with models of negative binomial regression, obtaining very similar results so we decided to use conventional poison regression models.

A descriptive statistical analysis was performed for all continuous variables and categories by stratifying admissions for CAP according to diabetes status. Variables are expressed as proportions, as means with standard deviations or as medians with interquartile ranges (LOHS). A bivariate analysis of variables according to year was performed using the χ^2 test for linear trend (proportions), ANOVA (means) and Kruskall-Wallis (medians), as appropriate.

To assess differences between those patients with and without T2DM, for each year and for the total sample, the statistical tests conducted for continuous variables were the T test for normal distributions and the Mann–Whitney test for non-normal distributions; categorical variables were compared using the Chi-square test and adjusted incidences were compared using Poisson regression. These same tests were used to compare the characteristics of those diabetic patients who died with those who survived to the

hospital admission and equally for non diabetic subjects. Lastly, we performed logistic regression analyses with mortality as a binary outcome using the independent variables and age, sex, CCI, readmission, diagnostic and therapeutic procedures, pathogens and year of admission for those with and without diabetes and for the entire population to assess the influence of diabetes on IHM. Estimates were Odds Ratios (OR) with their 95% confidence intervals. Statistical analyses were performed using Stata version 10.1 (Stata, College Station, Texas, USA). Statistical significance was set at $p<0.05$ (2-tailed).

Ethical aspects

Data confidentiality was maintained at all times in accordance with Spanish legislation. Given the anonymous and mandatory nature of the dataset, it was not deemed necessary to obtain informed consent. The study protocol was approved by the ethics committee of the Universidad Rey Juan Carlos.

RESULTS

From 2004 to 2013, we identified a total of 901,136 admissions for CAP as primary diagnosis in patients aged ≥40 years in Spain. Patients with T2DM accounted for 24.8% of total (134,534 men and 89,181 women).

Table 1 and Table 2 show the incidence and the clinical characteristics, comorbidities, diagnostic and therapeutic procedures and in-hospital outcomes of admissions for CAP in patients with T2DM and in patients without T2DM from 2004 to 2013, respectively.

Table 1. Incidence and characteristics of hospital admissions for pneumonia as primary diagnosis in patients with type 2 diabetes in Spain, 2004-2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
N	16161	19764	17267	20913	22002	24426	23377	25807	27655	26343	223715
Incidence* (per 100,000 inhabitants)	812.64	948.39	792.36	959.67	974.43	1045.33	1000.43	962.56	1031.49	923.26	948.84
Women, n(%)*	6476(40.07)	8060(40.78)	6632(38.41)	8364(39.99)	8678(39.44)	9880(40.45)	9240(39.53)	10338(40.06)	11126(40.23)	10387(39.43)	89181(39.86)
Age, mean (SD)	75.97(10.24)	76.06(10.39)	76.18(10.47)	76.29(10.39)	76.91(10.47)	76.37(10.98)	77.53(10.28)	77.64(10.45)	78.41(10.15)	78.23(10.34)	77.08(10.46)
40-64 years n(%)†	2150(13.3)	2638(13.35)	2348(13.6)	2864(13.69)	2894(13.15)	3589(14.69)	2690(11.51)	3085(11.95)	2892(10.46)	2846(10.8)	27996(12.51)
65-74 years n(%)†	4329(26.79)	5096(25.78)	4302(24.91)	5017(23.99)	4780(21.73)	5262(21.54)	4880(20.88)	5178(20.06)	5030(18.19)	5027(19.08)	48901(21.86)
75-84 years n(%)*	6385(39.51)	7925(40.1)	6962(40.32)	8468(40.49)	8972(40.78)	9782(40.05)	9749(41.7)	10407(40.33)	11515(41.64)	10651(40.43)	90816(40.59)
≥85 years n (%)*	3297(20.4)	4105(20.77)	3655(21.17)	4564(21.82)	5356(24.34)	5793(23.72)	6058(25.91)	7137(27.66)	8218(29.72)	7819(29.68)	56002(25.03)
AMI, n(%)†	865(5.35)	1106(5.6)	991(5.74)	1180(5.64)	1167(5.3)	1141(4.67)	958(4.1)	1098(4.25)	1184(4.28)	1057(4.01)	10747(4.8)
CHF, n(%)*	2587(16.01)	3258(16.48)	2941(17.03)	3542(16.94)	3940(17.91)	4183(17.13)	4379(18.73)	5210(20.19)	5795(20.95)	5645(21.43)	41480(18.54)
PVD, n(%)*	950(5.88)	1205(6.1)	1041(6.03)	1249(5.97)	1239(5.63)	1391(5.69)	1371(5.86)	1681(6.51)	1728(6.25)	1874(7.11)	13729(6.14)
CEVD/HP/PAPL, n(%)*	1509(9.34)	1850(9.36)	1688(9.78)	1959(9.37)	2290(10.41)	2496(10.22)	2535(10.84)	2753(10.67)	3101(11.21)	2854(10.83)	23035(10.3)
Chronic pulmonary disease, n(%)†	5618(34.76)	6693(33.86)	5730(33.18)	6927(33.12)	7244(32.92)	7986(32.69)	7762(33.2)	8511(32.98)	9006(32.57)	8822(33.49)	74299(33.21)
Dementia n(%)*	1676(10.37)	1973(9.98)	1881(10.89)	2062(9.86)	2404(10.93)	2672(10.94)	2762(11.82)	3182(12.33)	3403(12.31)	3062(11.62)	25077(11.21)
Renal disease n(%)*	1893(11.71)	2260(11.43)	2187(12.67)	2659(12.71)	3082(14.01)	3640(14.9)	3878(16.59)	4504(17.45)	5160(18.66)	5261(19.97)	34524(15.43)
Any type of malignancy n(%)*	1154(7.14)	1335(6.75)	1323(7.66)	1594(7.62)	1634(7.43)	1906(7.8)	1953(8.35)	2181(8.45)	2350(8.5)	2338(8.88)	17768(7.94)
Any liver disease n(%)	793(4.91)	1001(5.06)	879(5.09)	1059(5.06)	1058(4.81)	1248(5.11)	1156(4.95)	1220(4.73)	1359(4.91)	1407(5.34)	11180(5)
Obesity n(%)*	1240(7.67)	1593(8.06)	1400(8.11)	1766(8.44)	1754(7.97)	2339(9.58)	2167(9.27)	2599(10.07)	2671(9.66)	2822(10.71)	20351(9.1)
Pleuritis, n(%)†	913(5.65)	1263(6.39)	1107(6.41)	1299(6.21)	1391(6.32)	1393(5.7)	1326(5.67)	1511(5.86)	1611(5.83)	1481(5.62)	13295(5.94)
CCI 0 n(%)†	4646(28.75)	5726(28.97)	4905(28.41)	6175(29.53)	6162(28.01)	6782(27.77)	6064(25.94)	6429(24.91)	6835(24.72)	6237(23.68)	59961(26.8)
CCI 1 n(%)*	8140(50.37)	9870(49.94)	8663(50.17)	10253(49.03)	10951(49.77)	12304(50.37)	11865(50.76)	13141(50.92)	13929(50.37)	13368(50.75)	112484(50.28)
CCI ≥2 n (%)*	3375(20.88)	4168(21.09)	3699(21.42)	4485(21.45)	4889(22.22)	5340(21.86)	5448(23.3)	6237(24.17)	6891(24.92)	6738(25.58)	51270(22.92)
CAT, n(%)*	1441(8.92)	1759(8.9)	1701(9.85)	2229(10.66)	2447(11.12)	2656(10.87)	2725(11.66)	2929(11.35)	3100(11.21)	3071(11.66)	24058(10.75)
Bronchial fibroscopy, n(%)†	424(2.62)	516(2.61)	418(2.42)	521(2.49)	540(2.45)	583(2.39)	537(2.3)	564(2.19)	581(2.1)	642(2.44)	5326(2.38)
Non-invasive MV, n (%)*	135(0.84)	170(0.86)	160(0.93)	255(1.22)	308(1.4)	387(1.58)	558(2.39)	791(3.07)	946(3.42)	918(3.48)	4628(2.07)
Invasive MV, n (%)†	354(2.19)	462(2.34)	316(1.83)	343(1.64)	346(1.57)	411(1.68)	319(1.36)	388(1.5)	331(1.2)	340(1.29)	3610(1.61)
Thoracocentesis , n (%)*	268(1.66)	401(2.03)	311(1.8)	345(1.65)	446(2.03)	439(1.8)	383(1.64)	474(1.84)	452(1.63)	449(1.7)	3968(1.77)
Red cell transfusion n(%)*	512(3.17)	584(2.95)	572(3.31)	718(3.43)	771(3.5)	899(3.68)	899(3.85)	1054(4.08)	1219(4.41)	1051(3.99)	8279(3.7)
Readmission, n(%)*	2031(12.57)	2619(13.25)	2267(13.13)	2728(13.04)	2948(13.4)	3375(13.82)	3274(14.01)	3692(14.31)	3971(14.36)	3860(14.65)	30765(13.75)
LOHS, median (IQR)	8(5-13)	8(5-13)	8(5-13)	8(5-12)	8(5-12)	8(5-12)	8(5-12)	7(5-11)	7(5-11)	7(4-11)	8(5-12)
IHM n(%)†	2232(13.81)	2728(13.8)	2345(13.58)	2619(12.52)	2797(12.71)	3167(12.97)	2987(12.78)	3415(13.23)	3728(13.48)	3256(12.36)	29274(13.09)
S. pneumonia, n(%)†	2504(15.49)	3411(17.26)	2977(17.24)	3873(18.52)	3783(17.19)	3992(16.34)	3501(14.98)	2380(9.22)	2027(7.33)	2095(7.95)	30543(13.65)
Legionella, n(%)†	154(0.95)	197(1)	207(1.2)	189(0.9)	217(0.99)	213(0.87)	197(0.84)	158(0.61)	170(0.61)	159(0.6)	1861(0.83)
S. aureus, n(%)*	69(0.43)	91(0.46)	104(0.6)	104(0.5)	127(0.58)	157(0.64)	131(0.56)	133(0.52)	171(0.62)	187(0.71)	1274(0.57)
H. influenza, n(%)	58(0.36)	63(0.32)	57(0.33)	85(0.41)	77(0.35)	76(0.31)	94(0.4)	81(0.31)	92(0.33)	109(0.41)	792(0.35)
P. aeruginosa, n(%)	139(0.86)	159(0.8)	146(0.85)	160(0.77)	160(0.73)	154(0.63)	169(0.72)	184(0.71)	206(0.74)	193(0.73)	1670(0.75)

Incidence was adjusted by age and sex. AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay; IQR: Interquartile range; IHM: In-hospital mortality.
*P<0.05 to assess increased time trend from 2004 to 2013. †P<0.05 to assess decreased time trend from 2004 to 2013.

Table 2. Characteristics of hospital admissions for pneumonia as primary diagnosis in patients without type 2 diabetes in Spain, 2004-2013.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	Total
N	56991	66996	58233	66504	67123	74338	67643	72762	74816	72015	677421
Incidence* (per 100,000 inhabitants)	316.24	355.18	295.55	337.53	333.66	362.07	329.46	348.43	358.27	341.98	338.21
Women, n(%)*	20375(35.75)	24955(37.25)	21500(36.92)	25263(37.99)	26195(39.03)	29742(40.01)	26715(39.49)	29407(40.42)	30912(41.32)	29455(40.9)	264519(39.05)
Age, mean (SD)	73.96(13.25)	74.26(13.36)	74.24(13.64)	74.33(13.78)	74.79(13.78)	73.77(14.61)	75.67(13.72)	75.65(13.86)	77.02(13.28)	76.36(13.73)	75.06(13.76)
40-64 years n(%)†	12471(21.88)	14327(21.38)	13036(22.39)	15012(22.57)	14768(22)	18992(25.55)	13930(20.59)	15392(21.15)	13497(18.04)	14306(19.87)	145731(21.51)
65-74 years n(%)†	12578(22.07)	14150(21.12)	11555(19.84)	12535(18.85)	12153(18.11)	12409(16.69)	11068(16.36)	11581(15.92)	11321(15.13)	10965(15.23)	120315(17.76)
75-84 years n(%)†	19395(34.03)	23171(34.59)	19755(33.92)	22482(33.81)	22213(33.09)	23189(31.19)	22555(33.34)	23706(32.58)	24640(32.93)	23151(32.15)	224257(33.1)
≥85 years n (%)*	12547(22.02)	15348(22.91)	13887(23.85)	16475(24.77)	17989(26.8)	19748(26.57)	20090(29.7)	22083(30.35)	25358(33.89)	23593(32.76)	187118(27.62)
AMI, n(%)*	1932(3.39)	2309(3.45)	1917(3.29)	2279(3.43)	2123(3.16)	2207(2.97)	1884(2.79)	1955(2.69)	1952(2.61)	1802(2.5)	20360(3.01)
CHF, n(%)*	6649(11.67)	7929(11.84)	6761(11.61)	8228(12.37)	8673(12.92)	9310(12.52)	9516(14.07)	10896(14.97)	12004(16.04)	11680(16.22)	91646(13.53)
PVD, n(%)*	1857(3.26)	2345(3.5)	2121(3.64)	2239(3.37)	2237(3.33)	2445(3.29)	2496(3.69)	2753(3.78)	2923(3.91)	3074(4.27)	24490(3.62)
CEVD/HP/PAPL, n(%)*	3993(7.01)	4543(6.78)	4020(6.9)	4505(6.77)	4969(7.4)	5487(7.38)	5561(8.22)	6088(8.37)	6508(8.7)	6322(8.78)	51996(7.68)
Chronic pulmonary disease, n(%)†	20012(35.11)	23065(34.43)	19416(33.34)	21961(33.02)	21810(32.49)	24120(32.45)	22753(33.64)	24112(33.14)	24376(32.58)	23789(33.03)	225414(33.28)
Dementia n(%)*	5402(9.48)	6295(9.4)	5833(10.02)	6224(9.36)	6904(10.29)	7599(10.22)	7793(11.52)	8536(11.73)	9300(12.43)	8742(12.14)	72628(10.72)
Renal disease n(%)*	4363(7.66)	5327(7.95)	4609(7.91)	5760(8.66)	6328(9.43)	7189(9.67)	7312(10.81)	8278(11.38)	9609(12.84)	9572(13.29)	68347(10.09)
Any type of malignancy n(%)*	5696(9.99)	6420(9.58)	6006(10.31)	6671(10.03)	6929(10.32)	7642(10.28)	7504(11.09)	8234(11.32)	8289(11.08)	8407(11.67)	71798(10.6)
Any liver disease n(%)	2825(4.96)	3362(5.02)	2942(5.05)	3436(5.17)	3409(5.08)	3852(5.18)	3457(5.11)	3689(5.07)	3733(4.99)	3754(5.21)	34459(5.09)
Obesity n(%)*	1940(3.4)	2352(3.51)	2044(3.51)	2304(3.46)	2489(3.71)	3188(4.29)	2839(4.2)	3367(4.63)	3393(4.54)	3529(4.9)	27445(4.05)
Pleuritis, n(%)*	3992(7)	4898(7.31)	4240(7.28)	4936(7.42)	4760(7.09)	4892(6.58)	4782(7.07)	4954(6.81)	5054(6.76)	5101(7.08)	47609(7.03)
CCI 0 n(%)†	18620(32.67)	22311(33.3)	19452(33.4)	22643(34.05)	21991(32.76)	24786(33.34)	20436(30.21)	21691(29.81)	21653(28.94)	20550(28.54)	214133(31.61)
CCI 1 n(%)*	28219(49.51)	32726(48.85)	28327(48.64)	31765(47.76)	32752(48.79)	35890(48.28)	33399(49.38)	36155(49.69)	37205(49.73)	35850(49.78)	332288(49.05)
CCI ≥2 n (%)*	10152(17.81)	11959(17.85)	10454(17.95)	12096(18.19)	12380(18.44)	13662(18.38)	13808(20.41)	14916(20.5)	15958(21.33)	15615(21.68)	131000(19.34)
CAT, n(%)*	5936(10.42)	6931(10.35)	6565(11.27)	8042(12.09)	8487(12.64)	9356(12.59)	9191(13.59)	9690(13.32)	9627(12.87)	10028(13.92)	83853(12.38)
Bronchial fibroscopy, n(%)†	2165(3.8)	2256(3.37)	2068(3.55)	2245(3.38)	2220(3.31)	2258(3.04)	2135(3.16)	2207(3.03)	2195(2.93)	2351(3.26)	22100(3.26)
Non-invasive MV, n (%)*	442(0.78)	584(0.87)	531(0.91)	718(1.08)	945(1.41)	1188(1.6)	1616(2.39)	1934(2.66)	2307(3.08)	2286(3.17)	12551(1.85)
Invasive MV, n (%)†	1426(2.5)	1700(2.54)	1140(1.96)	1338(2.01)	1405(2.09)	1520(2.04)	1279(1.89)	1516(2.08)	1336(1.79)	1287(1.79)	13947(2.06)
Thoracocentesis , n (%)*	1271(2.23)	1476(2.2)	1308(2.25)	1527(2.3)	1549(2.31)	1655(2.23)	1502(2.22)	1508(2.07)	1518(2.03)	1636(2.27)	14950(2.21)
Red cell transfusion n(%)*	1830(3.21)	2125(3.17)	2034(3.49)	2189(3.29)	2498(3.72)	2642(3.55)	2709(4)	2830(3.89)	3073(4.11)	3009(4.18)	24939(3.68)
Readmission, n(%)*	6633(11.64)	7830(11.69)	7063(12.13)	7889(11.86)	8121(12.1)	8947(12.04)	8794(13)	9515(13.08)	10427(13.94)	9716(13.49)	84935(12.54)
LOHS, median (IQR)	8(5-13)	8(5-13)	8(5-12)	8(5-12)	8(5-12)	7(4-12)	7(5-12)	7(4-11)	7(4-11)	7(4-11)	7(5-12)
IHM n(%)†	8036(14.1)	9900(14.78)	8121(13.95)	8758(13.17)	9105(13.56)	9727(13.08)	9087(13.43)	10209(14.03)	10777(14.4)	9803(13.61)	93523(13.81)
S. pneumonia, n(%)†	9736(17.08)	11685(17.44)	10295(17.68)	12295(18.49)	11899(17.73)	12099(16.28)	10081(14.9)	7147(9.82)	5918(7.91)	6101(8.47)	97256(14.36)
Legionella, n(%)†	667(1.17)	808(1.21)	727(1.25)	667(1)	678(1.01)	729(0.98)	668(0.99)	544(0.75)	546(0.73)	449(0.62)	6483(0.96)
S. aureus, n(%)*	253(0.44)	350(0.52)	286(0.49)	366(0.55)	368(0.55)	378(0.51)	400(0.59)	438(0.6)	503(0.67)	470(0.65)	3812(0.56)
H. influenza, n(%)	267(0.47)	272(0.41)	257(0.44)	264(0.4)	263(0.39)	293(0.39)	295(0.44)	289(0.4)	300(0.4)	333(0.46)	2833(0.42)
P. aeruginosa, n(%)	509(0.89)	597(0.89)	514(0.88)	574(0.86)	617(0.92)	622(0.84)	632(0.93)	632(0.87)	638(0.85)	685(0.95)	6020(0.89)

Incidence was adjusted by age and sex.. AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay; IQR: Interquartile range; IHM: In-hospital mortality.
*P<0.05 to assess increased time trend from 2004 to 2013. †P<0.05 to assess decreased time trend from 2004 to 2013

Among patients with T2DM, adjusted incidence of admissions for CAP increased significantly from 812.64 cases per 100,000 T2DM population in 2004 to 923.26 cases in 2013 (Table 1). In patients without T2DM the adjusted incidence of admissions increased significantly from 316.24 cases per 100,000 population without diabetes in 2004 to 341.98 in 2013 (Table 2). Incidence was significantly higher in T2DM people than in non-diabetic people for all years analysed. From 2004 to 2013, the adjusted IRR of having CAP admission diagnosis in patients with type 2 diabetes was significant and higher than in those without diabetes (1.27 95%CI 1.23-1.31 vs. 1.05 95% CI 1.03-1.07).

Using the Poisson regression model, including the total population and diabetes status as an independent variable, we obtained an adjusted IRR per year of 1.66 (95%CI 1.65-1.67) for patients with T2DM using those without diabetes as the reference category. In other words, the incidence of admissions for CAP over the entire period was 1.66-times higher among patients with T2DM than those without diabetes.

In patients who have an admission for CAP, there was a significant male predominance (60.14% for T2DM and 60.95% for no diabetes). Overall, patients with T2DM were significantly older (77.08; SD=10.46 years) than patients without diabetes (75.06; SD=13.76 years) and had more coexisting medical conditions. Specifically, had higher prevalence of acute myocardial infarction (4.8% vs. 3.1%), congestive heart failure (18.54% vs. 13.53%), cerebrovascular disease/hemiplegia/paraplegia (10.3% vs. 7.68%), dementia (11.21% vs. 10.72%), renal disease (15.43% vs. 10.09%), peripheral vascular disease (6.14% vs. 3.62%) and prevalence of obesity is two times higher (all P values<0.05). On the other hand, any type of malignancy and pleuritis were more prevalent in non-diabetic patients (10.6% and 7.03%, respectively) than in those with T2DM (7.94% and 5.94%). Age and all these comorbidities increased significantly over time in both people with T2DM and without diabetes (Table 1 and Table 2).

As can been seen in Table 1 and Table 2, acute myocardial infarction and chronic pulmonary disease decreased significantly in both groups over the study period. Male sex percentage increased significantly in people with T2DM and female percentage showed a much larger change over time in patients without T2DM.

We detected a significant increase in use of thorax CAT in both groups over the study period as can been seen in Table 1 and Table 2.

The use of all therapeutics procedures (except invasive mechanical ventilation which showed a significant decrease) have significantly increased in the last ten years in

diabetic and non-diabetic patients (Table 1 and Table 2). The use of non invasive mechanical ventilation has shown an over three fold increase in both groups of patients over the study period.

Of the pathogens analysed the most commonly found was *S. pneumoniae*, followed by *Legionella*, *P. aeruginosa*, *S. aureus* and *H. influenza*.

In year 2013 *S. pneumonia* was detected in 7.95% of diabetic patients and 8.47% in those without the disease. All other pathogens were found in under 1% of patients.

S. pneumoniae and *Legionella* decreased over time in both people with T2DM and without diabetes. However, we detected a significant increase of *S. aureus* in both groups over the study period (Table 1 and Table 2). The prevalence of pathogens analysed was similar in patients with and without the disease.

Readmissions increased in both groups during the study (Table 1 and Table 2). Among diabetic patients, the increase was from 12.57% in 2004 to 14.65% in 2013. Equivalent figures for subjects without diabetes were significantly lower (11.64% and 13.49%).

Overall median LOHS was significantly higher in patients with T2DM (8 vs.7 days). Over time, LOHS following CAP fell significantly in both patients with T2DM and without diabetes.

IHM was 13.81% for T2DM patients and 13.09% for non-diabetic people ($p<0.05$). Crude IHM decreased significantly over time in both people with T2DM and without diabetes (from 13.81% and 14.1%, respectively in 2004 to 12.36% and 13.61% in 2013), as can been seen in Table 1 and Table 2.

Table 3 shows the characteristics of hospital admissions for CAP in patients with and without T2DM according to IHM during the study period.

Table 3. Characteristics of hospital admissions for pneumonia as primary diagnosis in patients with and without type 2 diabetes in Spain, 2001-2013 according to in hospital mortality.

	Diabetes		No Diabetes	
	ALIVE	**DIED**	**ALIVE**	**DIED**
Women, n(%)*†	76301(39,24)	12880(44)	225626(38,64)	38893(41,59)
Age, mean (SD)* †	76.42(10.51)	81.48(8.94)	74.11(13.87)	80.97(11.43)
40-64 years n(%)*†	26507(13.63)	1489(5.09)	136594(23.39)	9137(9.77)
65-74 years n(%)*†	45070(23.18)	3831(13.09)	109241(18.71)	11074(11.84)
75-84 years n(%)*†	78684(40.47)	12132(41.44)	192709(33)	31548(33.73)
≥85 years n (%)*†	44180(22.72)	11822(40.38)	145354(24.89)	41764(44.66)
AMI, n(%)*†	9163(4.71)	1584(5.41)	17000(2.91)	3360(3.59)
CHF, n(%)*†	35096(18.05)	6384(21.81)	74122(12.69)	17524(18.74)
PVD, n(%)*†	11802(6.07)	1927(6.58)	20931(3.58)	3559(3.81)
CEVD/HP/PAPL, n(%)*†	18199(9.36)	4836(16.52)	40554(6.95)	11442(12.23)
Chronic pulmonary disease, n(%)*†	67498(34.71)	6801(23.23)	203108(34.78)	22306(23.85)
Dementia n(%)*†	18657(9.6)	6420(21.93)	53446(9.15)	19182(20.51)
Renal disease n(%)*†	29173(15)	5351(18.28)	55766(9.55)	12581(13.45)
Any type of malignancy n(%)*†	14089(7.25)	3679(12.57)	56195(9.62)	15603(16.68)
Any liver disease n(%)	9730(5)	1450(4.95)	29671(5.08)	4788(5.12)
Obesity n(%)*†	19076(9.81)	1275(4.36)	25570(4.38)	1875(2)
Pleuritis, n(%)*†	11774(6.06)	1521(5.2)	42000(7.19)	5609(6)
CCI 0 n(%)*†	54116(27.83)	5845(19.97)	191839(32.85)	22294(23.84)
CCI 1 n(%)*†	97047(49.91)	15437(52.73)	283688(48.59)	48600(51.97)
CCI ≥2 n (%)*†	43278(22.26)	7992(27.3)	108371(18.56)	22629(24.2)
CAT, n(%)*†	22383(11.51)	1675(5.72)	77695(13.31)	6158(6.58)
Bronchial fibroscopy, n(%)*†	4859(2.5)	467(1.6)	20039(3.43)	2061(2.2)
Non-invasive MV, n (%)*†	3563(1.83)	1065(3.64)	9250(1.58)	3301(3.53)
Invasive MV, n (%)*†	1937(1)	1673(5.71)	7248(1.24)	6699(7.16)
Thoracocentesis , n (%)*†	3610(1.86)	358(1.22)	13535(2.32)	1415(1.51)
Red cell transfusion n(%)*†	6866(3.53)	1413(4.83)	19626(3.36)	5313(5.68)
Readmission, n(%)*†	24306(12.5)	6459(22.06)	66353(11.36)	18582(19.87)
LOHS, median (IQR) *†	8(5-12)	6(2-12)	8(5-12)	6(2-13)
S. pneumonia, n(%)*†	28086(14.44)	2457(8.39)	89171(15.27)	8085(8.64)
Legionella, n(%)*†	1766(0.91)	95(0.32)	6134(1.05)	349(0.37)
S. aureus, n(%)*†	1042(0.54)	232(0.79)	3017(0.52)	795(0.85)
H. influenza, n(%)*†	763(0.39)	29(0.1)	2704(0.46)	129(0.14)
P. aeruginosa, n(%)*†	1400(0.72)	270(0.92)	4934(0.85)	1086(1.16)

AMI: acute myocardial infarction. CHF: congestive heart failure. PVD: pheripheral vascular disease. CEVD/HP/PAPL: cerebrovascular disease/hemiplegia/paraplegia. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax. CCI: Charlson comorbidity index. LOHS: length of hospital stay.

* Significant differences (P<0.05) when comparing "alive" vs. "died" subjects without diabetes.

† Significant differences (P<0.05) when comparing "alive" vs. "died" subjects with diabetes

For the entire time period IHM was slightly but significantly higher among those without diabetes (13.81%vs. 13.09%).

Overall, patients with T2DM who died during their hospitalization were significantly older (81.48; SD=8.94 years) than those that survived (76.42; SD=10.51 years) and had more coexisting medical conditions. Including higher prevalence of acute myocardial infarction (5.41% vs 4.71%), congestive heart failure (21.81% vs. 18.05%), vascular disease (6.58% vs, 6.07%), cerebrovascular disease/hemiplegia/paraplegia (16.52% vs. 9.36%), dementia (21.93% vs. 9.6%), renal disease (18.28% vs. 15%), any type of malignancy (12.57% vs. 7.25%). On the other hand chronic obstructive pulmonary disease, obesity and pleuritis were more prevalent in diabetic patients that didn't die during their hospital stay.

Invasive and non-invasive mechanical ventilation and red cell transfusion procedures were significantly more used in diabetic patients who died than in those that survived (5.71%, 3.64% and 4.83% vs. 1%, 1.83% and 3.53%, respectively). However, CAT of thorax, thoracocentesis, bronchial fibroscopy were more frequent in T2DM and non-diabetic patients that survived than in those who died.

As can been seen in Table 3, non-diabetic patients who died were significantly older, had more coexisting conditions like acute myocardial infarction, congestive heart failure, vascular disease, cerebrovascular disease/hemiplegia/paraplegia, dementia, renal disease and any type of malignancy and were underwent invasive and non-invasive mechanical ventilation and red cell transfusion procedures than those non-diabetic patients that survived.

We found that 22.06% of diabetic patients that died and 12.5%% of diabetic patients that survived were readmission (P< 0.01). LOHS was 6 days in those diabetic and non-diabetic patients who died vs. 8 days in those diabetic and non-diabetic patients that survived.

S. pneumoniae was more frequently detected in patients who lived than in those who died in both T2DM and non-diabetic patients (14.44% vs. 8.39% and 15.27% vs. 8.64%), as can been seen in Table 3.

In Table 4 we can see the results of the multivariate analysis of the factors independently associated with in hospital mortality in diabetic and non-diabetic patients. during hospital admission for CAP in Spain, 2004-2013.

Table 4. Multivariate analysis of the factors potentially associated with in-hospital mortality for patients with and without type 2 diabetes in Spain, 2001-2013 with pneumonia as primary diagnosis.

		Diabetes OR(CI 95%)	No diabetes OR(CI 95%)	Total OR(CI 95%)
Age, years	40-64	1	1	1
	65-74	1.47(1.38-1.57)	1.47(1.42-1.51)	1.46(1.42-1.50)
	75-84	2.70(2.55-2.87)	2.49(2.42-2.55)	2.53(2.47-2.59)
	≥85	4.75(4.47-5.05)	4.52(4.40-4.64)	4.55(4.44-4.66)
CCI	0	1	1	1
	1	1.35(1.30-1.39)	1.28(1.26-1.31)	1.30(1.28-1.32)
	≥2	1.50(1.44-1.56)	1.44(1.411.47)	1.46(1.43-1.48)
Obesity		0.51(0.48-0.54)	0.50(0.47-0.52)	0.50(0.48-0.52)
Non-invasive MV		2.04(1.89-2.21)	2.01(1.92-2.11)	2.02(1.94-2.10)
Invasive MV		11.53(10.68-12.45)	12.55(12.06-13.06)	12.34(11.91-12.78)
Red cell transfusion		1.14(1.07-1.21)	1.35(1.31-1.40)	1.30(1.26-1.34)
Readmission		1.91(1.85-1.97)	1.85(1.82-1.89)	1.87(1.84-1.90)
CAT		0.54(0.51-0.57)	0.53(0.51-0.55)	0.53(0.52-0.55)
Thoracocentesis		0.82(0.73-0.93)	0.86(0.80-0.91)	0.85(0.80-0.90)
Bronchial fibroscopy		0.75(0.67-0.83)	0.71(0.67-0.75)	0.72(0.68-0.75)
*S. pneumonia**		0.54(0.52-0.57)	0.52(0.51-0.53)	0.52(0.51-0.54)
*Legionella**		0.43(0.34-0.53)	0.38(0.34-0.42)	0.39(0.35-0.43)
*S. aureus**		1.22(1.04-1.42)	1.26(1.16-1.37)	1.25(1.16-1.35)
H. influenza *		0.22(0.15-0.32)	0.26(0.21-0.31)	0.25(0.21-0.29)
Year		0.97(0.96-0.99)	0.97(0.96-0.98)	0.97(0.96-0.98)
Diabetes			-	0.92(0.91-0.94)

CCI Charlson comorbidity index. MV: Mechanical ventilation. CAT: computerized axial tomography of thorax.
*The pathogen ORs are all relative to the baseline of "no pathogen identified".

Among diabetic patients, IHM was significantly higher in older subjects (vs.<40-64 years old, OR: 4.75, 95%CI 4.47-5.05 for ≥ 85 years old) and in those with more comorbidities according to the CCI (vs. no comorbidities, OR: 1.35, 95%CI 1.30-1.39, for one comorbidity; OR: 1.50, 95%CI 1.44-1.56, for two or more comorbidities).

For diabetic patients, IHM was significantly lower in obese persons (OR: 0.51, 95%CI 0.48-0.54) than in those with normal body mass index.

Over the entire study period, a diabetic patient with readmission was 1.14 (95%CI, 1.07-1.21) times more likely to die than a diabetic patient without readmission.

T2DM patients having an in-hospital infection during admission for CAP (*S. pneumoniae or Legionella or H. influenza* were identified) had lower probability of dying than patients without these pathogens. However diabetic patients with *S. aureus* had 1.22-fold higher probability of dying during their stay than those without that pathogen. IHM was significantly higher in patients who underwent invasive and non-invasive mechanical ventilation (OR: 11.53, 95%CI 10.68-12.45 and OR: 2.04, 95%CI 1.89-2.21) and red cell transfusion (OR: 1.14, 95%CI 1.07-1.21).

Diabetic patients who underwent CAT of thorax, bronchial fibroscopy and thoracocentesis procedures had a 0.54-fold, 0.75-fold and 0.82-fold, respectively, lower probability of dying during their stay than those who did not undergo these procedures.

Time trend analysis showed a minor but significant decrease in IHM from 2004 to 2013 in T2DM patients (OR: 0.97, 95%CI 0.96-0.99).

As can been seen in Table 4, for non-diabetic patients, IHM was significantly higher in older persons, in those with more comorbidities, in those with readmissions, in those with infections for *S. aureus* and in those who underwent invasive and non-invasive mechanical ventilation and red cell transfusion procedures. As for diabetic patients we found a significant decrease in mortality over time.

In our study, suffering diabetes was associated with a lower IHM (OR: 0.92, 95%CI 0.91-0.94).

Finally, for the entire population time trend analyses showed a significant decrease in mortality from 2004 to 2013 in patients admitted for CAP in Spain (OR: 0.97, 95%CI 0.96-0.98).

DISCUSSION

Using data from the Spanish National Hospital Database, we found that rates of hospitalization for CAP in patients with and without T2DM increased significantly from

2004 to 2013. These results are consistent with a report from Denmark, which pointed that total pneumonia hospitalization increased by 63%, from 4.96 per 1000 population in 1997 to 8.09 in 2011.[12] Recently, Quan et al in Osfordshire, UK, concluded that hospital admission for CAP are increasing by ≈9% per year between 2009 and 2014.[9] The authors concluded that there was no evidence that the increase was caused by more low-severity cases presenting to hospital [9], and that the ageing population only explains part of the increase [3,9,17]

We found that readmissions for CAP increased over time in patients with and without T2DM and LOHS decreased in both groups of patients. These data are consistent with other published study, suggesting that the fact that readmissions for pneumonia increased over time supports another plausible explanation for the shortening LOHS, namely an increased pressure for early discharge.[9,18]

After adjusting for age and sex, we found that the incidence of CAP among T2DM patients was 1.66-times higher than among non-diabetic patients. Our results agree with the Fremantle Diabetes Study data, in this study Hamilton et al compared patients with T2DM in Australia to matched nondiabetic subjects and indicated that IRR for pneumonia was 1.86 (95%CI 1.55-2.21).[6] In US, Jackson et al, also reported that the adjusted RR for hospitalizations for CAP was 1.52 (95%CI 1.29-1.78) among patients with diabetes compared with patients without diabetes, based on 46,237 subjects aged >65 years.[19] In a Canadian study, the authors indicated that patients with diabetes had an increased risk of pneumonia-related hospitalization than those without diabetes (RR 1.46 [95%CI 1.42-1.49]).[8] In a case-control study in Denmark, Kornum et al found that T2DM was associated with a 1.2-fold increased risk of a pneumonia-related hospitalization.[4] They concluded that longer duration of diabetes and poor glycemic control increase the risk of CAP-related hospitalization.

Like other authors, we found that patients admitted for CAP were increasing older over time.[9,17] In UK, using linked electronic health records of patients with diabetes, McDonald et al observed that pneumonia incidence was 6-8 times higher among patients aged ≥85 years than patients aged 65-69 years.[20] Possible explanations include a general improvement in clinical management, especially changes in immunosuppressive regimens and handling of comorbidities.[12]

In our study, T2DM patients had a higher number of simultaneous comorbidities and were more frequently obese, but obesity was not associated with a higher mortality risk during admission for CAP. Obesity is known to have adverse effects on immune

function and to increase susceptibility to infections such as pneumonia,[21] however Hamilton et al concluded that a high body mass index was independently associated with any infection in their cohort of diabetic patients.[6] A recent meta-analysis concluded that overweight and obesity were significantly associated with reduced risk of pneumonia mortality (RR: 0.83, 95% CI 0.77 to 0.91, P < 0.01) and suggests that an 'obexity survival paradox' exists for pneumonia.[22]

The use of non invasive mechanical ventilation has shown an over three fold increase in patients with and without T2DM over the study period. In a study about CAP in elderly, the authors found that mechanical ventilation was provided to 31.8% of patients and that almost half of the patients older than 90 years who received such care were discharged alive, supporting the belief that such care for the critically ill elderly patient is often justified.[11] Our investigation showed that mechanical ventilation was a strong risk factor for IHM in both groups studied. However, given our study design it is not possible, with our data, to determine if mechanical ventilation is effective for critically ill elderly patient with CAP.

As expected, *S. pneumoniae* was the most frequent etiological agent among patients with and without diabetes, however, its dominance is decreasing. Smith et al concluded that declines in cases of pneumonia due to *S. pneumoniae* (from 7.1% in 1993 to 2.3% 2011) may be related to more frequent and effective vaccination, which reduces the risk of invasive pneumococcal disease and bacteriemia.[23] Also this reduced risk may have resulted in less-frequent coding because more thorough diagnostic evaluations accompany a higher severity of disease. In Spain *S. pneumoniae* vaccine is recommended for high-risk groups, including people with diabetes, and for all persons aged 65 years or over.[24]

We found that other organism's particularly *S aureus* was more prevalent in dead patients than in survivors in both T2DM and non-diabetic patients. Like other authors despite the trends observed,[23,25] the low incidence of *S aureus* (0.57% in patients with T2DM and 0.56% in those without T2DM), perhaps suggests that *S aureus* is not routinely search for and detected for patients with CAP.[23,26] It has been reported that pneumonia is the leading infectious cause of death in Spain, however the mortality rate for pneumonia has decreased between 1980 and 2011.[27] In our study, we found that crude IHM decreased over among diabetic and non-diabetic patients with a diagnosis of CAP. Simonetti AF et al found a progressive downward trend of thirty-day mortality in hospitalized patients with CAP (-0.2% death/year; P for trend=.003]) and concluded that

the decreases in mortality rates suggest general improvement in the management of CAP.[28]

We detected that patients with T2DM who died during their stay were older, had more coexisting comorbid conditions and had significantly more readmissions than those patients with T2DM that survived. In diabetic patients who died mechanical ventilation and red cell transfusion were significantly more used than in those that survived. One possible explanation is that there is a trend to hospitalizing a higher proportion of fragil or terminal patients who previously may have been treated at home.[12]

In our population, the presence of T2DM was not a risk factor of death during admission for CAP. The results add important evidence to previous information. An observational cohort study of all Medicare recipients, aged 65 years or older, hospitalized in nonfederal U.S. hospitals Kaplan et al reported no association between IHM and diabetes.[11] In a Canadian study of 2,471 patients with CAP, the authors concluded that hyperglycemia, but not the presence of diabetes, was the only factor having a significant negative effect on patient survival.[29] However, Kornum et al, indicated that high glucose levels were associated with increased mortality in both patients with and without T2DM.[5] Perhaps the fact that patients with diabetes are more likely to be hospitalized with less severity. In fact, in our study, we observed a lower frequency of pleuritis and any type of malignancy in diabetics than in non-diabetics, which could justify the lower mortality in the first group. Finally we think that this T2DM result is part of the obesity paradox [22].

In our study mechanical ventilation (invasive and non-invasive) and red cell transfusion were significantly associated with mortality during admission for CAP in both groups of patients with and without diabetes.

A recent study, reported that noninvasive pressure ventilation is frequently used in CAP but is associated with high failure rates, indicated that patients who failed non invasive mechanical ventilation had an increased odds of death when compared with patients who were treated with invasive ventilation (OR, 2.2; 95% CI, 1.0-4.8; P = .03).[30]

The strengths of our findings lie in the large sample size, the 10-year follow-up period, and the standardized methodology, which has been used to investigate diabetes and its complications in Spain and elsewhere.[31]

Limitations of the study

Nevertheless, our study is subject to several limitations. Our data source was the CMBD, an administrative database that contains discharge data for hospitalizations in

Spain and uses information the physician has included in the discharge report. Therefore, our findings are limited by the lack of data precluded adjustment for pneumococcal and influenza vaccinations, which have been associated with reduced mortality among patients hospitalized with pneumonia.[5] A further limitation is the use of IHM which misses patients who may have died soon after discharge.

Other studies have identified factors that may influence in CAP outcomes and that were not included in our investigation because these variables were not collected in the Spanish Hospital Discharge Database. These factors include, among others, illness-severity or antimicrobial treatments.[9-32] Additionally, we also cannot identify whether gradual changes were made in referral practice during the study period.

Another significant limitation is the fact that we did not classify diabetic patients into groups based on the therapy used to control blood glucose, with the result that we were unable to provide data on the control of blood glucose during the hospitalization.

The ICD-9-CM used in the Spanish National Hospital Database (CMBD) does not contain any codes specifically for CAP but only has more general codes for pneumonia. Therefore, the ICD-9-CM cannot differentiate a CAP from a Hospital Acquired Pneumonia (HAP). In the CMBD database the first diagnosis in the main reason why a patient is admitted to the hospital. By definition a patient with HAP has to acquire this infection after admission to the hospital. Therefore according to this methodology is very improbable that a HAP could appear as a first diagnosis. The only possible situation for this would be that a patient previously hospitalized, and discharged from the hospital, would return in the first days with a pneumonia that acquired in the previous hospitalization. As commented before we belief this is an extremely improbable situation that would only have a very small impact in the results. Furthermore, the use of cases with a primary diagnosis of pneumonia ICD-9-CM codes (480-488, 507.0-507.8) in the hospital discharge report has been used by other authors, such as Kaplan et al and Hamilton et al, considering those as community-acquired pneumonia admissions [6,11].

Beside the limitations of administrative databases for clinical investigation on CAP, many studies have used this data sources for relevant epidemiological studies on respiratory diseases. [6, 11, 33,34]. The CMBD is periodically audited and the validity of the "diabetes diagnosis" in hospital discharge reports has been demonstrated in the past. [35-38]. However, as a result of this audits it is possible and desirable that accuracy of coding may have improved over time so this would affect the results of our

investigation and must be taken in consideration.

CONCLUSIONS

In conclusion, Spanish national data show that rates of hospitalization for CAP in patients with and without T2DM increased significantly from 2004 to 2013 and incidence rates were higher in T2DM patients than in those without diabetes in all time periods studied. CAP incidence seems to be increasing at a higher rate among T2DM patients than among non-diabetic patients. IHM after CAP shows downward trends over time in all groups analyzed. Remarkably, the presence of T2DM is not a risk factor of death after CAP in our cohort.

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CONTRIBUTIONS

AL and RJG researched data, contributed to the discussion, wrote the manuscript, and reviewed/edited the manuscript. VHB researched data and reviewed/edited the manuscript. JMD, IJT, JMMY, MMB, NPF and MASF contributed to the discussion and reviewed/edited the manuscript.

All authors reviewed and gave their final approval of the version to be submitted.

COMPETING INTERESTS

The authors declare that they have no competing interests.

DATA SHARING STATEMENT

"No additional data available"

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38. Chen G, Khan N, Walker R, Quan H. Validating ICD coding algorithms for diabetes mellitus from administrative data. *Diabetes Res Clin Pract.* 2010;89:189-195.

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,6
Bias	9	Describe any efforts to address potential sources of bias	5,6
Study size	10	Explain how the study size was arrived at	5,6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	6,7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	6,7
		(*e*) Describe any sensitivity analyses	

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-11
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-11
		(*b*) Report category boundaries when continuous variables were categorized	7-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.