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Original Article

Hospitalizations from pandemic Influenza [A(H1N1)pdm09] infections among type 1 and 2 diabetes patients in Spain

Rodrigo Jiménez-García,[a] Valentín Hernández-Barrera,[a] Cristina Rodríguez-Rieiro,[a] Ana L. de Andres,[a] Javier de Miguel-Diez,[b] Isabel Jimenez-Trujillo,[a] Angel Gil de Miguel,[a] Pilar Carrasco-Garrido[a]

[a]Preventive Medicine Unit, Rey Juan Carlos University, Madrid, Spain. [b]Pneumology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain.
Correspondence: Rodrigo Jiménez-García, Unidad Medicina Preventiva, Facultad de Ciencias de la Salud, Avda de Atenas s/n, 28922 Alcorcón, Madrid, Spain. E-mail: rodrigo.jimenez@urjc.es

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Objectives To describe and analyze the clinical characteristics and outcomes for all patients with diabetes who were hospitalized with laboratory-confirmed A(H1N1)pdm09 infections in Spain during 2009.

Methods Observational retrospective study using data collected by the Spanish National Hospital Discharge Database. We selected all admissions with diagnosis ICD-9-CM code 488·1 [A(H1N1)pdm09]. Discharges were grouped as follows: no diabetes, Type1 and Type 2 diabetes. Underlying medical conditions and risk factors included all those that constitute an indication for annual influenza vaccination, pregnancy, and obesity. The outcome variables analyzed were in-hospital case fatality risk, length of hospital stay, and costs.

Results The total number of persons hospitalized with A(H1N1)pdm09 was 11 499. Of those, 97 suffered Type 1 and 936 Type 2, giving an overall prevalence of diabetes of 9%. The most common underlying medical condition among Type 2 subjects was obesity (26·8%), and for Type 1 renal disease (10·3%). In-hospital mortality was 2·1% among Type 1 patients, 3·8% among Type 2 patients, and 2·3% among non-diabetics; after multivariate analysis, diabetes was not a factor independently associated with dying during hospitalization for A(H1N1)pdm09. Independent factors increasing the risk of death among diabetic patients included age (OR 1·03; 95% CI1·01–1·05), hematological disorders (OR 3·49; 95% CI, 1·46–8·37), and obesity (OR 1·88; 95% CI1·07–3·92).

Conclusions Among individuals hospitalized in Spain with A(H1N1)pdm09 infections, the age-specific prevalence of diabetes was higher than the general population in most age groups. The results of multivariate analysis suggest that possibly concomitant conditions such as obesity increase the risk of dying from the infection, but not diabetes itself.

Keywords Diabetes, H1N1, hospitalizations, Influenza A, obesity, pandemic.

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Introduction

In June 2009, the World Health Organization declared the most recent influenza pandemic, which was caused by a new influenza A type H1N1 [A(H1N1)pdm09] virus.[1] In Spain, as in other European countries, the first sporadic cases were detected in April, and the epidemic wave started in October and decreased by December 2009.[2,3]

Patients with diabetes have been found to have higher mortality, morbidity, medical consultations, and hospitalizations attributable to seasonal influenza-related infections when compared to non-diabetic subjects.[4,5]

However, available information on the clinical course and outcomes of A(H1N1)pdm09 infections in patients with diabetes is still scare and with non-conclusive results.[6–14] Recently, a pooled data analysis from nineteen countries or administrative regions showed that the median prevalence of diabetes was 9·0% among hospitalized patients, 13·6% among those admitted to an intensive care unit (ICU), and 14·4% among fatal cases.[6] The pooled unadjusted risk of death among A(H1N1)pdm09 patients with diabetes compared to the risk of death among A(H1N1)pdm09 patients without this risk factor was 4 (95% CI 3·1–6·9).[6]

Allard *et al.*[7] reached a similar conclusion, finding that among hospitalized patients with PCR-confirmed A(H1N1)pdm09, the odds ratio for ICU admission was 4·29 (95% CI 1·29–14·3) among patients with diabetes compared to those without.

In Spain, a case–control study using severe laboratory-confirmed cases reported to the Spanish Surveillance System found that worse outcomes among patients with diabetes could be a consequence of the higher prevalence of comorbid underlying medical conditions, such as cardiovascular disease and morbid obesity, but not diabetes itself.[8]

In this report, we use a hospital discharge database to describe and analyze the clinical characteristics and outcomes for all persons suffering diabetes, type 1 and 2, who were hospitalized with laboratory-confirmed A(H1N1)pdm09 in Spain during 2009. We also compare their characteristics with non-diabetic patients from the same hospital discharge database.

Patients and methods

The investigation design is an observational retrospective study using hospitalization data collected by the Spanish National Hospital Discharge Database, namely Conjunto Minimo Basico de Datos (CMBD), which compiles all the public and private hospital data covering more than 95% of hospital discharges.[15] This national hospital database is managed by the Spanish Ministry of Health, which sets standards for registration and performs periodic audits.[15] The CMBD database includes patients' variables (sex, date of birth), date of admittance, date of discharge, discharge destination (home, death, or other health/social institution), up to 14 discharge diagnoses, and up to 20 procedures performed during admission.[15] We used the database entries where admission had occurred between January 1, 2009 and December 31, 2009.

The new ICD-9-CM code 488·1, which corresponds to persons infected with the novel A(H1N1)pdm09 that had to be confirmed with PCR, was introduced in Spain on July 17, 2009.[16] For study purposes, we selected all admissions with diagnosis code 488·1 in any position of the 14 discharge diagnoses. Discharges were grouped by diabetes status as follows: no diabetes, type 1 diabetes (T1DM) (ICD-9-CM codes: 250.X1; 250.X3), and type 2 diabetes (T2DM) (ICD-9-CM codes: 250.X0; 250.X2) in any diagnosis position.[17]

Demographic data analyzed included age and sex. Underlying medical conditions and risk factors included all those chronic diseases that constitute an indication for annual influenza vaccination in Spain, in addition to pregnancy and obesity.[18] The chronic conditions analyzed are shown in Table 1.

The outcome variables analyzed included the proportion of patients who died during hospital admission [in-hospital case fatality risk (CFR)], length of hospital stay (LOHS), and costs of hospitalization. Costs were calculated using diagnosis-related groups (DRG) for the disease. DRG represents a medical-economic entity concerning a set of diseases requiring analogous management resources.[19]

Statistical analysis

We calculated descriptive statistics for all study variables. We reported data for continuous variables as means (with interquartile ranges) and for categorical variables as percentages.

We compared the characteristics of those with T1DM, T2DM, and without diabetes using the chi-square test, Student's *t*-tests, anova, Fisher's exact test, or Wilcoxon rank-sum test, as appropriate. To compare those subjects with diabetes (grouped T1DM and T2DM) and without the disease who died, we estimated the CFR with 95% CIs for each subgroup and incidence rate ratios (IRR) with their 95% CIs using Poisson regression

Also, we described and compared the characteristics of those patients suffering diabetes who died in the hospital with those who survived. We performed multivariate logistic regression analysis to identify factors independently associated with dying for the whole sample in order to assess the effect of diabetes (grouped as T1DM and T2DM) on A(H1N1)pdm09 mortality. Finally, another logistic regression model was conducted to identify factors independently associated with dying among only those patients suffering from diabetes. We analyzed type 1 and type 2 patients together to increase numbers because there were only 2 deaths among patients with type 1 diabetes.

The multivariate analyses were performed using those statistically significant variables in the bivariate analysis. We have also included cardiovascular disease and other chronic conditions in the multivariate model because previous studies have found that these diseases are associated with a worse outcome among A(H1N1)pdm09 infection patients.[6–14] Furthermore, epidemiological evidence shows that the presence of cardiovascular disease and diabetes is significantly associated.[6,7]

Estimations were made using the stata program, and statistical significance was set at two-tailed $\alpha < 0{\cdot}05$. Data confidentiality was maintained at all times according to Spanish legislation. Patient identifiers were deleted before the database was provided to the authors to maintain patient anonymity. It is not possible to identify patients at individual levels, either in this paper or in the database. Given the anonymous and mandatory nature of the data set, the requirement for informed consent was not necessary.

Results

The total number of persons hospitalized with A(H1N1)pdm09 infection was 11 499, and the overall

Table 1. Age- and sex-specific prevalences of diabetes among patients hospitalized with A(H1N1)pdm09 infections versus the general population in Spain

	Persons hospitalized with A(H1N1)pdm09 infections in Spain during 2009						Spanish general population di@bet.es Study[20]	
	T1DM (*n* = 97)		T2DM (*n* = 937)		T1DM+T2DM		Prevalence of Known diabetes T1DM + T2DM	Prevalence of known and unknown diabetes T1DM + T2DM
	n	%	*n*	%	*n*	%	%	%
Male (years)								
<18	15	0·8	0	0	15	0·8	NA	NA
18–30[a,b]	12	1·6	7	0·8	19	2·4	0·3	0·3
31–45[a]	13	1·0	65	5·2	78	6·2	2·1	6·7
46–60[a,b]	5	0·4	189	16·8	194	17·2	11·9	23·8
61–75[b]	1	0·2	169	28·2	170	28·4	24·8	42·4
76 and over[a,b]	1	0·4	59	26·3	60	26·7	20·7	37·4
Female (years)								
<18	22	1·6	0	0·0	22	1·6	NA	NA
18–30	12	1·1	9	0·8	21	1·9	0·3	0·6
31–45[a,b]	10	0·7	49	3·6	59	4·3	0·9	2·2
46–60[a,b]	3	0·3	154	14·5	157	14·8	6·6	10·9
61–75[a]	2	0·4	165	31·4	167	31·8	18·7	29·8
76 and over[a]	1	0·5	71	33·8	72	34·3	23·2	41·3

[a]Significant difference ($P < 0·05$) when comparing prevalence of diabetes among persons hospitalized with A(H1N1)pdm09 infections and Prevalence of ''Known diabetes'' according to the di@bet.es Study.[20]
[b]Significant difference ($P < 0·05$) when comparing prevalence of diabetes among persons hospitalized with A(H1N1)pdm09 infections and prevalence of ''Known and unknown diabetes'' according to the di@bet.es Study.[20]

prevalence of diabetes was 9% (1033/11 499). Of these, 97 suffered T1DM and 936 T2DM. The mean age was significantly higher for patients with T2DM (60·2 years) followed by non-diabetic subjects (31·7 years) and patients with T1DM (26·9). Overall, women represent 49·9% of the sample with similar distribution in all subgroups studied.

Table 1 shows the age- and sex-specific prevalences of diabetes among patients hospitalized with A(H1N1)pdm09 infections versus the general population in Spain.[20] The overall estimated age- and sex-adjusted prevalence of diabetes, according to the Spanish population in 2010 and using the direct standardization method, for those aged ≥18 years was 13·6% (14·3% for women and 12·9% for men).[21] The demographic characteristics, underlying medical conditions, CFR, LOHS, and costs of patients hospitalized in 2009 with confirmed A(H1N1)pdm09 are summarized in Table 2 according to diabetes status.

Among those suffering T2DM, only 28·1% did not report any other underlying medical condition. This proportion reached 71·1% among patients with T1DM and 48·7% among those without diabetes, with the differences between all groups being significant. The most common underlying medical conditions among T2DM subjects included obesity (26·8%), chronic respiratory diseases other than asthma (21·1%), and chronic renal disease (10·4%). For patients with T1DM, renal disease (10·3%) was the most prevalent comorbidity.

Only four pregnant women suffering diabetes (2 with T2DM and 2 with T1DM) were hospitalized with A(H1N1)pdm09 infection during the study period. The mean overall LOHS was highest for T2DM subjects (8·0 days), followed by non-diabetic subjects (6·7 days) and then patients with T1DM (5·6 days). When the analysis was stratified by age groups, no significant differences were found. The mean costs per patient were also highest among patients with T2DM when compared to patients with T1DM and non-diabetic subjects (3754, 3039, and 3032 Euros, respectively).

There were two deaths during hospitalization among patients with T1DM (aged 41 and 49 years) resulting in a CFR of 2·1% and 36 among patients with T2DM (CFR 3·8%). For non-diabetics, CFR was 2·3% with no significant

Table 2. Demographic characteristics, underlying medical conditions, in-hospital case fatality risk (CFR), length of hospital stay (LOHS), and costs of patients hospitalized with confirmed 2009 A(H1N1)pdm09 according to diabetes status

	T1DM		T2DM		Non-diabetics (*n* = 10416)	
	n	**% (IC 95%)**	***n* (Mean)**	**% (CI 95%)**	***n* (Mean)**	**% (CI 95%)**
Age[a,b,c]	(26·92)	(23·3–30·5)	60·19	(59·3–61·1)	31·7	(31·3–32·1)
Age groups[a,b,c] (years)						
<18	37	38·1	0	0	3184	30·6
18–30	24	24·7	16	1·7	1842	17·7
31–45	23	23·7	114	12·2	2464	23·7
46–60	8	8·2	343	36·6	1835	17·6
61–75	3	3·1	334	35·6	789	7·6
76 and over	2	2·1	130	13·9	302	2·9
Sex						
Women	50	51·5	448	47·8	5195	49·9
Pregnancy[b,c]	2	7·7	2	4·0	709	28·4
No chronic disease[*,a,b,c]	69	71·1	263	28·1	5074	48·7
Chronic Cardiovascular disease[b,c]	5	5·1	79	8·4	151	1·4
Asthma[b]	5	5·1	107	11·4	1648	15·8
Chronic respiratory disease (Asthma not included)[a]	0	0	215	22·9	969	9·3
Obesity[a,c]	4	4·1	251	26·8	716	6·9
Endocrine disease	7	7·2	67	7·1	410	3·9
Cancer[c]	0	0	46	4·9	466	4·5
Hematological disease[c]	2	2·1	65	6·9	825	7·9
Epilepsy	2	2·1	12	1·3	243	2·3
Diseases of the CNS	0	0	25	2·7	94	0·9
Chronic liver disease	0	0	7	0·7	30	0·3
Chronic renal disease[a,b,c]	10	10·3	97	10·3	280	2·7
HIV[c]	0	0	9	1·0	245	2·3
CFR	2	2·1	36	3·8	244	2·3
LOHS in days [Median; IQR] (years)						
<18	[4; 3–6]		NA		[3; 2–6]	
18–30	[4; 3–6]		[5; 4–9]		[4;2–6]	
31–45	[5; 3–8]		[7; 4–11]		[6;3–7]	
46–60	[6; 4–9]		[6; 4–9]		[5; 2·5–11·5]	
61–75	[6; 4–9]		[6; 4–9]		[6;2–12]	
76 and over	[6; 4–9]		[7; 5–10]		[6·5; 4–9]	
Total[a,c]	[5·6; 4·5–6·7]		[8·0; 7·6–8·5]		[6·7; 6·6–6·9]	
Cost per patient (Mean; 95%CI)	(3039; 1837–4241)		(3754; 3426–4083)		(3032; (2929–3135)	

T1DM Type 1 diabetes mellitus. T2DM Type 2 diabetes mellitus.
[*]No chronic disease excludes all listed diseases.
[a]*P*-value < 0·05 Comparing patients with T1DM versus patients with T2DM.
[b]*P*-value < 0·05 Comparing T1DM versus non-diabetic patients.
[c]*P*-value < 0·05 Comparing T2DM versus non-diabetic patients.

difference found between any subgroups. In-hospital CFR among diabetic (grouped type 1 and type 2) and non-diabetic patients hospitalized with confirmed 2009 A(H1N1)pdm09 in Spain according to study variables is shown in Table 3. The results show no significant difference in CFR in any age group between those with and without diabetes.

The multivariate analysis results showed that, as found in the bivariate comparisons, suffering diabetes (grouped as T1DM and T2DM) was not a factor independently associated with dying during hospitalization for A(H1N1)pdm09 (OR = 0·76 95% CI 0·52–1·11). Suffering cardiovascular diseases (OR 1·85), obesity (OR 2·54), cancer (OR 3·71,) chronic renal disease (OR 1·84), or hematological disease (3·78) increased the risk of CFR in subjects admitted to Spanish hospitals because of A(H1N1)pdm09 in 2009 after adjusting for other covariates. Age, as a continuous variable, also showed a significant OR (1·02)

Table 3. In-hospital case fatality risk (CFR) among diabetic (grouped type 1 and type 2) and non-diabetic patients hospitalized with confirmed 2009 A(H1N1)pdm09 in Spain according to study variables

	Patients with diabetes		Non-diabetics patients		
	n	CFR % 95% CI	*n*	CFR % 95% CI	IRR (95%CI)*
Age groups (years)					
<18	0	0 (–)	26	0·8 (0·5–1·13)	NA
18–30	0	0 (–)	33	1·8 (1·1–2·4)	NA
31–45	6	4·4 (0·9–7·8)	56	2·3 (1·6–2·8)	1·96 (0·83–4·65)
46–60	11	3·1 (1·3–4·9)	63	3·4 (2·6–4·2)	0·90 (0·47–1·74)
61–75	15	4·4 (2·2–6·6)	38	4·82 (3·3–6·3)	0·92 (0·50–1·70)
76 and over	6	4·5 (0·9–8·1)	28	9·3 (6–12·5)	0·46 (0·18–1·15)
Sex					
Men	20	3·7 (2·1–5·3)	141	2·7 (2·2–3·1)	1·39 (0·87–2·24)
Women	18	3·6 (1·9–5·2)	103	2·0 (1·6–2·3)	1·85 (1·11–3·09)
Pregnancy	0	0 (0–0)	7	1·0 (0·26–1·7)	NA
No chronic disease*	9	2·7 (0·9–4·4)	50	0·9 (0·6–1·13)	3·08 (1·50–6·33)
Chronic cardiovascular disease	4	4·76 (0·2–9·3)	14	9·3 (4·6–13·9)	0·48 (0·15–1·53)
Chronic respiratory disease (asthma not included)	5	2·3 (0·3–4·3)	36	3·7 (2·5–4·9)	0·61
Asthma	1	0·9 (0·0–2·6)	14	0·8 (0·4–1·2)	1·06 (0·13–8·14)
Obesity	12	4·7 (2·1–7·3)	37	5·1 (3·5–6·7)	0·91 (0·47–1·77)
Endocrine disease	4	5·4 (0·2–10·5)	15	3·7 (1·8–5·4)	1·50 (0·48–4·66)
Cancer	4	8·7 (0·5–16·8)	54	11·6 (8·6–14·4)	0·73 (0·25–2·10)
Hematological disease**	7	10·4 (3·1–17·7)	75	9·1 (7·1–11·0)	1·17 (0·51–2·64)
Epilepsy	1	7·1 (0·0–20·6)	14	5·8 (2·8–8·6)	1·25 (0·15–10·32)
Diseases of the CNS	0	0 (–)	15	15·9 (8·5–23·3)	NA
Chronic liver disease	0	0 (–)	8	26·6 (10·8–42·49	NA
Chronic renal disease	7	6·5 (1·8–11·2)	21	7·5 (4·4–10·5)	0·86 (0·35–2·09)

CFR In-hospital case fatality risk.
*No chronic disease excludes all listed diseases.
**Incidence rate ratios and 95% CI comparing non-diabetic (ref category) versus diabetic patients using Poisson regression.

Table 4 shows the characteristics of those diabetic patients who died and those who survived according to study variables. Bivariate analysis shows that patients with diabetes who died during hospitalization with influenza A(H1N1)pdm09 were significantly older, suffered more hematological diseases, and had a longer LOHS and higher costs. Three factors were found, on multivariate logistic regression analysis, to be associated with the death among diabetic patients, namely age (odds ratio, 1·03; 95% CI, 1·01–1·05; $P = 0·02$), hematological disorders (odds ratio, 3·49; 95% CI, 1·46–8·37; $P < 0·01$), and obesity (odds ratio, 1·88; 95% CI, 1·07–3·92; $P = 0·04$).

Discussion

To the best of our knowledge, there are still little published, countrywide data describing the characteristics of patients admitted to hospitals because of A(H1N1)pdm09.[22] Most published studies are based on surveillance and notification systems and usually only include severe patients or those critically ill patients admitted to ICUs.[6–14,23–27] This may lead to an under-notification of patients who are without, or who suffer less severe, underlying conditions.

In this investigation, we have identified all patients admitted to any Spanish hospital who were hospitalized with A(H1N1)pdm09 infection and who suffered diabetes regardless of the severity or outcome of the infection. Using this methodology, we found that the prevalence of diabetes was 9%. Diabetes is a chronic condition that has been previously reported in patients hospitalized during 2009 with A(H1N1)pdm09.[6–14,23–27] In the Netherlands, the prevalence of diabetes in hospitalized non-ICU patients was 8·6%.[13] However, in several countries, the reported prevalence among those critically ill was significantly higher and ranged from around 10 to 25%.[12,23–28] To date, the largest published sample, which included data of approximately 70 000 laboratory-confirmed hospitalized A(H1N1)pdm09 patients from many countries, described a median prevalence among hospitalized patients identical to ours (9%).[6]

In Spain, studies based on surveillance data have estimated the prevalence of diabetes as 9·4% for patients not

Table 4. Characteristics of diabetic patients (grouped as type 1 and type 2) hospitalized with confirmed 2009 A(H1N1)pdm09 who died and survived according to study variables

	Died during hospitalization			
	Yes (*n* = 38)		No (*n* = 996)	
	% (Mean)	95% CI	*n* (Mean)	95% CI
Age[a]	(62·1)	57·5–66·7	(56·9)	55·8–57·9
Age groups (years)				
<18	0	–	3·7	2·7–5·1
18–30	0	–	4·0	3·1–5·4
31–45	15·8	7·3–30·1	13·2	11·2–15·4
46–60	28·9	16·8–45·1	34·1	31·3–37·2
61–75	39·5	25·4–55·6	32·3	29·4–35·2
76 and over	15·8	7·3–31·0	12·7	10·7–14·9
Sex				
Men	52·6	37·0–67·8	51·9	48·7–54·9
Women	47·4	32·2–63·0	48·1	45·0–51·2
Pregnancy	0	–	5·6	4·7–7·0
No chronic disease[*]	23·7	12·8–39·6	32·4	29·7–35·4
Chronic cardiovascular disease	10·5	4·0–24·9	8·0	6·5–9·9
Chronic respiratory disease (asthma not included)	13·2	5·6–28·0	21·11	18·7–23·8
Asthma	2·6	0·4–16·5	11·1	9·2–13·2
Obesity	31·6	18·9–47·8	24·3	21·7–27·1
Endocrine disease	10·5	4·0–24·9	7·0	5·6–8·8
Cancer	10·5	4·0–24·8	4·2	3·1–5·7
Hematological disease[a]	18·4	9·3–33·9	6·0	4·7–7·7
Epilepsy	2·6	0·4–16·5)	1·3	0·7–2·2
Diseases of the CNS	0	–	2·5	1·7–3·7
Chronic liver disease	0	–	0·7	0·3–1·4
Chronic renal disease	18·4	9·0–33·9)	10·0	8·3–12·1
LOHS[a]	(12·53)	9·6–15·4	(7·6)	7·21–8·06
Cost per patient (Euros)[a]	(9306)	5760–12853	(3472)	3176–3768

[a]*P*-value < 0·05 Comparing survivals versus non-survivals.
[*]No chronic disease excludes all listed diseases.

admitted to an ICU who survived and 13·8% for patients admitted to an ICU who died.[9]

The possibility of diabetes being indicative of worse outcomes from A(H1N1)pdm09 infections remains unsolved. One possible strategy to assess the effect of diabetes is to compare the prevalence of this disease in the general population with that found among patients hospitalized for or who died from A(H1N1)pdm09. Van Kerkhove *et al.*[6] found that in pooled data from several countries, the relative risk of hospitalization for diabetes was 0·9 (95% CI; 0·5–1·7).

As can be seen in Table 1, the prevalence of diabetes by age groups and sex among those hospitalized in Spain with A(H1N1)pdm09 frequently lies between the prevalences of ''Known (diagnosed) diabetes'' and ''Known and unknown (un-diagnosed) diabetes'' (obtained from a very recently published investigation (di@bet.es Study) conducted with the target population being the entire Spanish population aged 18 years or over.[20] The results of the di@bet.es Study yield an adjusted prevalence of ''Known and Unknown diabetes'' for this age group of 13·8% and for ''Known diabetes'' of 7·8%. We estimated adjusted diabetes prevalence in our sample of 13·6%. The results of the chi-square test show that for ''Known and unknown diabetes,'' no significant differences are found (13·8% versus 13·6% *P*-value = 0·877) and for ''Known diabetes,'' the prevalence among hospitalized patients was significantly higher. (7·8% versus 13·6%; *P*-value < 0·001). However, as can be seen in Table 1, when we compare our prevalence of diabetes among persons hospitalized with A(H1N1)pdm09 infections, stratified by sex and age groups, with the prevalence of known diabetes reported in the di@bet.es Study[20], we found that in almost all possible comparisons (8/10), our prevalences were significantly higher. On the other hand, when comparing our prevalences with the prevalence of ''Known and unknown diabetes'' according to the

di@bet.es Study[20], we found our prevalences significantly higher in 3 of 10, significantly lower in 3 of 10 and no differences in the remaining four groups.

In other studies conducted in Spain, the estimated prevalence among adults for T2DM also ranges from 10 to 15% suggesting that diabetes is not overrepresented among A(H1N1)pdm09 hospitalized patients.[29,30] Furthermore, another study has found that in Spain, 9·7% of all hospital discharges are subjects with a diagnosis of diabetes.[31] This data suggest that diabetes may not significantly increase the risk of being hospitalized from this infection in Spain. A study conducted in Australia and New Zealand that also compared the prevalence of risk factors among severely ill A(H1N1)pdm09 cases with the prevalence of the same risk factors in the general population found no relevant differences for diabetes.[28] On the other hand, in Canada, the prevalence ratio (diabetes among hospitalized patients/ diabetes in the general population) was 3·10 (95% CI 2·04–4·71).[7]

The result our multivariate analysis showed that among patients with diabetes, age, obesity, and hematological disorders were independent risk factors for dying from A(H1N1)pdm09. These high risk conditions also showed significant results for the entire sample. Using age as a continuous variable is possibly not the best option to adjust multivariate model. We did so because we had a very small number of people with diabetes who died ($n = 38$) and for some age groups, there were no cases <18 and 18–30 years, so the role of age must be interpreted with precaution. In any case when data were stratified by age groups, no difference in CFR between those with and without diabetes was found. The association of obesity with a higher incidence of hospitalizations with A(H1N1)pdm09 infection has been described in data from different populations.[13,23,28,32]

Another relevant aspect of our investigation is that we were able to differentiate type of diabetes. According to our data, only 97 patients with T1DM were hospitalized in Spain during 2009, most of whom did not have any concomitant chronic conditions (71%) and only two of whom died (2%). An Italian study found that among children with diabetes, the outbreak of A(H1N1)pdm09 has increased pediatric consultation rates and hospitalizations compared with previous epidemics, although without causing deaths, and noted that the children at highest risk of severe infection were those with comorbidities.[10] The main strengths of this study are that the CMBD database has the advantage of being mandated by the National Public Health System and includes over 95% of hospital (public and private) admissions in Spain.[6] Furthermore, all cases were laboratory-confirmed A(H1N1)pdm09. Finally, we could distinguish between types of diabetes and identify a large number of concomitant diagnoses.

However, several limitations must be identified. First, some important clinical variables are not recorded in the CMBD including (i) characteristics of diabetes such as duration, glycemic control measurements (HbA1c), or insulin use; (ii) severity of the underlying diseases or medications used by the patients. Second, hospital admission can be influenced by social and healthcare-related factors. We have no information addressing whether diabetics were more likely than others to be tested for A(H1N1)pdm09 infection or whether diabetic patients may have been hospitalized more readily or with less serious coexisting illnesses, all of which could have resulted in overrepresentation in our study population.

Third, data from other countries have estimated that around 1 per 1000 population were hospitalized in the first wave of A(H1N1)pdm09, and we have estimated a cumulative incidence of around only 0·25 per 1000.[33,34] Data from the CDC, for the period September 1, 2009 to January 16, 2010, estimate a total number of 87 529 laboratory-confirmed hospitalized cases of A(H1N1)pdm09 infection in United States, and this would result in and incidence of around 0·28 cases per 1000 population.[33] According to the CDC methodology, extrapolations of hospitalizations to the entire United States have to be corrected for under-reporting, and this correction is conducted by multiplying the estimated total number of laboratory-confirmed hospitalization cases by 2·7, so this would result in an incidence of around 0·84 per 1000 population.[33]

Jules *et al.*[34] using two independent methods provided consistent results on the burden of pandemic virus in Davidson County and suggested that the overall incidence of A(H1N1)pdm09-associated hospitalization was 1 per 1000 county residents.

However, when we analyze reports obtained using only hospital discharge data, the results are similar to ours.[22,35] In Canada, between April and December 2009, 10 406 cases with an A(H1N1)pdm09 diagnosis were discharged from Canadian acute care hospitals. Hospital discharge data also revealed that 4800 patients were diagnosed with influenza, but not specifically with A(H1N1)pdm09. According to these numbers, the incidence of hospitalizations in Canada would have been between 0·31 and 0·46 per 1000 population.[35]

Unfortunately, we do not have the information on the proportion of hospitalized cases with respiratory infection during the pandemic who were able to be tested by PCR in a timely manner in Spain. Therefore, considering all previous comments, we belief that possibly we underreport the total number of hospitalizations, and that patients in CMBD database may be those with more severe infection and more comorbid conditions. In any case, we think that underreport does not affect the validity of our study with regard to the association between diabetes and A(H1N1)pdm09 infection outcomes.

We conclude that among individuals hospitalized in Spain with A(H1N1)pdm09 infections, the age-specific prevalence of diabetes was higher than the general population in most age groups, and the results of multivariate analysis suggest that possibly concomitant conditions such as obesity and cardiovascular disease increase the risk of dying with the infection, but not diabetes itself.

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Conflict of interest

The authors have no conflicts of interest to declare.

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