Original

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Clinical characteristics and outcome of patients with pandemic 2009 Influenza A(H1N1)v virus infection admitted to hospitals with different levels of health-care

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ABSTRACT

Background. The outcome of patients with influenza A 2009 (H1N1)v virus infection taking into account hospital type has not been elucidated.

Objectives. To compare risk factors, clinical features and outcome of patients admitted to 3 public hospitals with different levels of health-care.

Methods: Prospective study of all non-pregnant adult patients admitted to 3 hospitals with pandemic H1N1 infection, from June 1 to December 31 and followed up until 1 month after discharge.

Results. During the study period, 111 patients with a mean age of 49 years (15-89) were hospitalized: 52 in hospital 1 (900-bed tertiary-teaching-hospital), 33 in hospital 2 (315-beds secondary-hospital) and 26 in hospital 3 (150-beds primary-care-hospital).Overall 80% of patients had at least 1 comorbid condition with no differences between hospitals. Symptoms or signs on admission were similar except for cough (P=0.01) more frequent in patients in hospital 1 and dyspnea (P=0.05), myalgia, arthralgia (P=0.04) and hypoxemia (P=0.009) present in more patients in hospital 2. In-hospital mortality rates were not statistically different between hospitals. In the stepwise analysis, independent predictors of mortality were pneumonia on admission (adjusted OR=8.68, 95%CI 1.0-82.43) and cardiac complications during hospitalization (adjusted OR=13.2, 95%CI 1.67-103.98).

Conclusions. Mortality of patients with pandemic H1N1 infection was influenced by patients underlying conditions, severity of disease (pneumonia) on admission and complications during hospitalization. Hospital-characteristics do not appear to have influenced severe outcome.

Keywords: pandemic H1N1 infection; Outcome; Hospital-characteristics.

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Características clínicas y evolución de los pacientes con infección por el virus pandémico influenza A (H1N1)v 2009 ingresados en hospitales con diferentes niveles de atención de salud

RESUMEN

Introducción. La evolución de los pacientes con infección por el virus de la influenza A (H1N1)v 2009, teniendo en cuenta el tipo de hospital donde ingresan no ha sido estudiada.

Objetivos. Comparar las características clínicas y la evolución de los pacientes con infección por el virus pandémico influenza A (H1N1)v 2009, teniendo en cuenta el tipo de hospital donde ingresan.

Métodos. Estudio prospectivo de todos los pacientes que ingresaron en 3 hospitales públicos con diferentes niveles de atención de salud con infección por el virus pandémico influenza A (H1N1)v entre el 1 de junio y el 31 de diciembre de 2009. Se excluyeron las mujeres embarazadas.

Resultados. Durante el período de estudio ingresaron 111 pacientes (edad media de 49 años; rango: 15-89): 52 en el hospital 1 (hospital universitario de 900 camas), 33 en el hospital 2 (315 camas) y 26 en el hospital 3 (150 camas). El 81% de los pacientes tenían al menos 1 enfermedad de base. Los síntomas o signos al ingreso fueron similares, excepto para la tos (P=0,01) más frecuente en los pacientes ingresados en el hospital 1 y disnea (P=0,05), mialgia, artralgia (P=0,04) e hipoxemia (P=0,009) presentes en más pacientes en el hospital 2. No hubo diferencias estadísticamente significativas en la tasa de mortalidad entre los pacientes ingresados en los 3 hospitales. En el análisis multivariante la neumonía al ingreso (OR ajustada=8,68; CI95% 1,0-82,43) y las complicaciones cardiacas durante la hospitalización (OR ajustada=13,2; CI95% 1,67-103,98) fueron predictores independientes de mortalidad.

Conclusiones. La mortalidad de los pacientes con infección por el virus de la gripe nueva (H1N1)v 2009 se

relacionó la comorbilidad de los pacientes, la gravedad de la enfermedad (neumonía) al ingreso y las complicaciones durante la hospitalización. Las características del hospital donde ingresaron los pacientes no influyeron en su evolución.

Palabras clave: Virus de la gripe H1N1 2009, Evolución, Tipo de hospital.

INTRODUCTION

On June 2009 the World Health Organization announced the first influenza pandemic of the 21st century[1-3]. Spain was the first country in Europe to report a laboratory-confirmed case of new influenza A (H1N1)v virus infection[4]. The number of hospitalizations and deaths due to pandemic (H1N1) 2009 increased continuously until December 2009.

The studies published indicate that there were differences between pandemic (H1N1) 2009 and seasonal influenza. Pandemic (H1N1) 2009 affects mainly adults under the age of 60 with chronic underlying diseases, pregnant women, and obese patients[4-9]. The overall mortality of this infection is similar to that presented by seasonal influenza and lower than previous pandemics[8-10]. Mortality varies considerably between countries[8-13]. However, there is no data about mortality taking into consideration the type of hospital the patients were admitted.

The aim of the present study was to compare the risk factors, clinical features, and outcome of patients admitted to 3 public hospitals with different levels of health-care in the Autonomous Community of Cantabria (Spain).

METHODS

Patients

A prospective cohort study was conducted in the 3 unique hospitals belonging to the Public Health Service of Cantabria (Spain). Hospital 1 is a 900-bed tertiary teaching hospital with a reference population of 315,197 persons; Hospital 2 is a 315-beds secondary hospital with a reference population of 162,762 persons and Hospital 3 is a 150-beds primary care hospital with a reference population of 96,381 persons.

All non-pregnant adult patients (≥ 15 years) admitted to the 3 hospitals for at least 24 hours with confirmed influenza A (H1N1)v virus infection from June 1 to December 31, 2009, were prospectively recruited. Pregnant woman were excluded from the study because only hospital 1 has mother-child care. Hospital admission, microbiological studies and treatment decisions were standardized according the criteria established for an Influenza Community Committee, which followed the recommendations of the Spanish Ministry of Health.

Specific laboratory tests for influenza A (H1N1)v virus were performed on all patients with community-onset pneumonia or influenza-like symptoms and underlying chronic conditions, morbid obesity, or in the presence of complications[14]. The results were available in less than 24 hours. A confirmed case was defined as a person with an influenza-like illness with laboratory-confirmed pandemic influenza A (H1N1)v virus infection using real-time polymerase chain reaction (RT-PCR)[15]. Pandemic influenza A (H1N1)v virus testing was performed to all patients in hospital 1. The study was approved by the Ethics Committee of the coordinating center, the hospital 1, and informed consent was obtained from patients.

Data collection

Data were prospectively collected using a standard form that included demographic characteristics, past-medical-history, comorbidities, pre-hospital medication, clinical presentation, body mass index, biochemical analysis, chest X-ray findings, antiviral and antibacterial therapy, care timelines, initial assessment, investigations and outcomes, including discharge and death. A follow-up visit was scheduled 1 month after discharge. For time calculations, the day of admission was considered to be hospital day 0, except for time to antiviral administration in which the day of symptoms onset was considered day 0.

Definitions

Comorbidities were assessed by the Charlson Comorbidity Index definitions[16]. Tobacco abuse was recorded when a patient had smoked more than 10 cigarettes per day for at least 1 year preceding the study. Alcohol abuse was considered if alcohol intake was > 3 standard drinks per day. Obesity was defined as a BMI ≥30–39.9 and morbid obesity as a BMI ≥40 or a subjective assessment by the physician if weight and height were not available. Pneumonia was defined as the presence of a new infiltrate on a chest radiograph plus fever (temperature ≥38.0°C) and/or respiratory symptoms. Concomitant and/or secondary bacterial coinfection was diagnosed in patients with one or more positive cultures obtained from blood, normally sterile fluids, or sputum and/or a positive urinary antigen. Complications were defined as any annoying circumstances occurring during hospitalization. Mortality was defined as death from any cause during hospitalization.

Statistical analysis

Descriptive statistics were performed for all study variables. All proportions were calculated as percentages of the patients with available data. Continuous variables were expressed as median and range. To detect significant differences between groups, we used the chi-square test or Fisher exact test for categorical variables and the ANOVA test or Kruskal-Wallis test for continuous variables, when appropriate. The size of the effect was determined by calculating the relative risk (RR) with 95% confidence interval (CI), taking hospital 1 as the reference. The multivariate logistic regression analysis of factors potentially associated with the mortality included all significant variables in univariate analysis and all clinically important variables, whether they were significant or not. Statistical significance was established at α=0.05. All reported P values are 2-tailed. The results were analyzed using a commercially available statistical software package (SPSS, version 17.0; SPSS Inc, Chicago, Illinois).

RESULTS

Patient characteristics

During the study period, 111 non-pregnant adult patients were admitted to the 3 hospitals: 52 (46.8%) in hospital 1 (hospitalization rate of 1.6 per 10.000 inhabitants), 33 (29.7%) in hospital 2 (hospitalization rate of 2.0 per 10.000 inhabitants), and 26 (23.4%) in hospital 3 (hospitalization rate of 2.7 per 10.000 inhabitants). The demographic and clinical characteristics are detailed in tables 1 and 2. All patients were admitted initially to their local hospital, except 1 patient who was sent from hospital 3 to hospital 1, because of severe disease. Of 111 patients 68 (61.3%) were men. Overall the mean age was 49 years (15-89) and half of patients were under age of 50.

Ninety (81.1%) patients had at least 1 comorbid condition, being chronic obstructive pulmonary disease (COPD) the most common, with no differences between hospitals. Only 6(5.4%) patients were morbidly obese: 1 admitted to hospital 1, 1 to hospital 2 and 4 to hospital 3 (15.4%) (RR 8, 95% CI 0.94-68;P=0.02) (table 1).

Overall, the median time from onset of symptoms to hospitalization was 5.1 days (range 1-8). The most frequent symptoms and signs on hospital admission were cough, shortness of breath, muscle aches and fever and were similar in patients admitted to hospital 1 and 3. However, more patients admitted to hospital 2 compared to hospital 1 had dyspnea (66.7% vs. 42.3%, RR 1.50, 95% CI 0.99-2.26;P=0.05) and myalgia-arthralgia (66% vs. 44.2%, RR 1.50, 95% CI 01.02-2.22;P=0.04) (table 2).

The laboratory and radiographic findings are shown in table 3. Hipoxemia was more frequent in patients in hospital 2 (P=0.009). Pneumonia was diagnosed in 36% of total of patients and these were mainly admitted in hospital 2 compared to hospital 1 (RR 1.66; 95% CI 1.01-2.74;P=0.04). A concomitant and/or secondary bacterial coinfection was present in 16% of patients and was more frequent in hospital 1 and 3 than in hospital 2 (21.2% and 19.2% vs 6.6%, RR 0.28; 95% CI 0.06-1.21;P=0.05). Sixteen microorganisms were isolated in 11 patients in hospital 1, 3 in 2 patients in hospital 2, and 5 in 5 patients in hospital 3. Overall, *Streptococcus pneumoniae* (4 cases isolated from blood, sputum and urine antigen test), Coagulase-negative *staphylococci* (4 cases isolated from blood) and *Candida albicans* (3 cases isolated from blood), were the most frequent causative bacteria. Other organisms isolated were: *Pseudomonas aeruginosa* (2 cases isolated from sputum) and methicillin-susceptible *Staphylococcus aureus*, *Candida parapsilosis*, *Proteus mirabilis, Acinetobacter baumannii* and *Aspergillus* one case each (isolated from tracheal aspirate, blood, sputum, blood and sputum respectively).

Treatment and outcome

One hundred (90.1%) of patients were treated with oseltamivir: 48 (92.3%) in hospital 1, 29 (87.9%) in hospital 2 and 23 (88.5%) in hospital 3, at a median of 3 days after the onset of symptoms (range 0-30 days) with a dosage of 75 mg bid in all but 10 patients (9.0%) who received 150 mg bid. Most patients (68%) in hospital 3 received oseltamivir in the first 48 h compared to 31.8% in hospital 1 (RR, 2.14, 95% CI 1.27-3.59; P=0.004) or 41.4% in hospital 2. Ninety seven patients (87.4%) received antibiotics with a median of 8 days (range 1-47 days) and this was similar in the 3 hospitals. Fifty-eight (52.3%) received corticosteroids, mainly in hospital 3 (69.2% hospital 3 vs 40.4% hospital 1; RR 1.71, 95%CI 1.12-2.60;P=0.01) (table 4).

The clinical outcomes are summarized in table 4. Overall, the median of length of hospital stay was 6 days (1-191) and there were no differences between hospitals. Eighteen patients (16.2%) required ICU admission and 11 (9.9%) mechanical ventilation. Five patients, 3 in hospital 1, and 2 in hospital 2, who were admitted to the ICU, presented septic shock. Eight patients, all of them admitted to hospital 1, had heart complications.

Total in-hospital mortality was 8.1% (9 of 111 patients); 6 (11.5%) in hospital 1 (one of the patients was sent from hospital 3 (age: 33, 51, 58, 58, 72 and 73), 2 (6.1%) in hospital 2 (age: 30 and 66) and 1(3.8%) in hospital 3 (age 79). The median time from admission to death was 10 days (range, 1–191). Patients in hospital 1 died on days 1, 4, 10, 17, 47 and 191 after admission. This last patient died because of nosocomial pneumonia. Therefore death seems not to be directly related to the influenza virus infection. Causes of death in the other 5 patients were respiratory failure/acute respiratory distress syndrome (3 patients), shock/multiorgan failure (1 patient) and decompensate comorbid condition (1 patient). Patients in hospital 2 and 3 died directly from influenza virus infection on days 9, 23 and 2 respectively after admission. All 3 died because of respiratory failure/acute respiratory distress syndrome.

All death patients received treatment with oseltamivir except one who died in the first 24 hours before a confirmed diagnosis was made. All had comorbid conditions: 9 had bacterial coinfection, 6 had multilobar pneumonia, 3 had solid neoplasms (2 in hospital 1 and 1 in hospital 2) and one had leukemia (hospital 3). None had morbid obesity.

In the follow-up visit 1 month after discharge all patients were alive and well except 1 patient from hospital 1, who died because a solid neoplasm 30 days after discharge.

Hospital type was not associated significantly with mortality, neither in the crude analysis nor adjusting for co-morbidities and variables related to the treatment and the outcome (age, sex, solid and hematological neoplasms, pneumonia on admission, thrombocytopenia, corticoids on admission, cardiac complications during hospitalization) (hospital 2 vs hospital 1: adjusted OR=1.44, 95%CI 0.05-36.5); (hospital 3 vs hospital 1: adjusted OR=1.11, 95%CI 0.005-246.05). However, in the univariate analysis other factors were related to mortality: solid neoplasm, haematological neoplasm, thrombocytopenia, pneumonia, admission to the ICU during hospitalization, respiratory distress, need for non-invasive ventilation, mechanical ventilation and inotropic therapy (Table 5). In the stepwise analysis independent predictors of mortality were: pneumonia on admission (adjusted OR=8.68, 95%CI 1.0-82.43), and cardiac complications

Table 1 **Demographic characteristics of patients with influenza A (H1N1)v virus infection.**

Variable	All patients (N=111)	Hospital 1 (n=52)	Hospital 2 (n=33)	Hospital 3 (n=26)	RR (95% CI) H2 vs H1 H3 vs H1	P-value+
Age. years - mean (range)	48,9 (15-89)	45.7 (15-87)	47.8 (22-84)	56.8 (23-89)		0.02
Age groups- n (%)						
15 – 49 years	57 (51.4)	30 (57.7)	19 (57.6)	8 (30.8)	0.99 (0.68-1.45)	0.99
					0.53 (0.28-0.99)	0.02
50 – 64 years	31 (27.9)	14 (26.9)	8 (24.2)	9 (34.6)	0.90 (0.42-1.9)	0.78
					1.28 (0.64-2.56)	0.48
≥ 65 years	23 (20.7)	8 (15.4)	6 (18.2)	9 (34.6)	1.18 (0.45-3.1)	0.73
					2.25 (0.98-5.14)	0.05
Male sex- n (%)	68 (61.3)	30 (61.5)	27 (81.8)	9 (34.6)	1.41 (1.06-1.88)	0.02
					0.6 (0.33-1.06)	0.05
Underlying conditions- n(%)						
Any one condition	90 (81.1)	43 (82.7)	24 (72.7)	23 (88.5)	0.87 (0.68-1.12)	0.27
					1.06 (0.88-1.28)	0.50
Diabetes mellitus	14 (12.6)	10 (19.2)	2 (6.1)	2 (7.7)	0.31 (0.07-1.34)	0.08
					0.4 (0.09-1.69)	0.18
Cardiovascular disease	12 (10.8)	6 (11.5)	3 (9.1)	3 (11.5)	0.78 (0.21-2.93)	0.72
					1 (0.27-3.68)	1
Chronic pulmonary disease- n(%)						
COPD	13 (11.7)	7 (13.5)	3 (9.1)	3 (11.5)	0.67 (0.18-2.42)	0.54
					0.85 (0.24-3.04)	0.81
Asthma	22 (19.8)	11 (21.2)	3 (9.1)	8 (30.8)	0.42 (0.12-1.42)	0.14
					1.45 (0.66-3.17)	0.35
OSAS	8 (7.2)	2 (3.8)	3 (9.1)	3 (11.5)	2.36 (0.41-13.40)	0.31
					3 (0.53-16.85)	0.19
Obesity	6 (5.4)	1 (1.9)	1 (3)	4 (15.4)	1.57 (0.10-24.33)	0.74
					8 (0.94-68)	0.02
Immunosuppressed- n(%)						
Transplant recipients	5 (4.5)	4 (7.7)	0 (0)	1 (3.8)	-	
					0.5 (0.05-4.25)	0.5
Cancer	14 (12.6)	6 (11.5)	5 (15.2)	3 (11.5)	1.31 (0.43-3.95)	0.6
					1 (0.27-3.68)	1

RR: risk ratio; CI: confidence interval; **COPD:** Chronic obstructive pulmonary disease; **OSAS:** Obstructive sleep apnoea syndrome.

+ *Two-tailed Chi-squared test for categorical variables or two-tailed ANOVA test for continuous variables*

Table 2 Clinical findings of patients with influenza A(H1N1)v infection.

Variable	All patients (N=111)	Hospital 1 (n=52)	Hospital 2 (n=33)	Hospital 3 (n=26)	RR (95% CI) H2 vs H1 H3 vs H1	P-value
Days since onset of symptoms-hospitalization - median (range)*	3 (1-30)	3 (1-30)	3 (1-14)	3 (1-10)		
Rhinorrhea - N (%)	5 (4.5)	3 (5.8)	1 (3)	1 (3.8)	0.52 (0.05-4.83)	0.56
					0.66 (0.07-6.09)	0.71
Sore throat - N (%)	13 (11.7)	5 (9.6)	5 (15.2)	3 (11.5)	1.57 (0.49-5.02)	0.44
					1.2 (0.31-4.63)	0.79
Chills - N (%)	37 (33.3)	20 (38.5)	8 (24.2)	9 (34.6)	0.9 (0.46-1.74)	0.76
					0.9 (0.47-1.69)	0.74
Cough - N (%)	87 (78.4)	46 (88.5)	22 (66.7)	19 (73.1)	0.75 (0.58-0.97)	0.01
					0.82 (0.64-1.06)	0.08
Dyspnea - N (%)	59 (53.2)	22 (42.3)	21 (63.6)	16 (61.5)	1.50 (0.99-2.26)	0.05
					1.45 (0.93-2.25)	0.1
Pleuritic chest pain - N (%)	17 (15.3)	7 (13.5)	5 (15.2)	5 (19.2)	1.12 (0.38-3.25)	0.82
					1.42 (0.50-4.06)	0.5
Gastrointestinal disorders - N (%)	16 (14.4)	8 (15.4)	7 (21.2)	1 (3.8)	1.37 (0.55-3.44)	0.49
					0.25 (0.03-2.22)	0.13
Myalgia-arthralgya - N (%)	54 (48.6)	23 (44.2)	22 (66.7)	9 (34.6)	1.50 (1.02-2.22)	0.04
					0.78 (0.42-1.44)	0.41
Headache - N (%)	23 (20.7)	9 (17.3)	10 (30.3)	4 (15.4)	1.75 (0.79-3.84)	0.16
					0.88 (0.30-2.61)	0.82
Fever at admission (≥38 ºC) - N (%)**	41 (37.6)	15 (29.4)	14 (43.7)	12 (46.2)	1.48 (0.83-2.65)	0.18
					1.56 (0.86-2.84)	0.14

*** Information was unavailable for 4 cases in hospital 1, and 1 case in hospital 3**
****Information was unavailable for 1 case in hospital 1, and 1 case in hospital 2**

during hospitalization (adjusted OR=13.2, 95%CI 1.67-103.98). No differences were observed in clinical signs.

DISCUSSION

This report provides details of the epidemiology, clinical characteristics and outcome of non-pregnant adult patients with influenza A (H1N1)v virus infection hospitalized in 3 public hospitals with different levels of health-care. Demographic characteristics were similar between patients admitted to the 3 hospitals and similar to data published previously[6,17-19]. Previous studies found that current and past pandemics affected mainly younger patients[5,10,20-23]. Similarly, adult patients younger than 50 years had a higher risk of death during the 1918 Spanish influenza pandemic[23] and during the recent H5N1 avian influenza[24]. In the present study, the median age of patients was 49 years. Patients admitted to hospital 1 and 2 were younger compared to patients admitted to hospital 3.

Overall mortality was 8.1% similar to that reported in the earliest studies of hospitalized patients[20,25,26]. When we compared mortality between patients admitted to the 3 hospitals we did not found statistical differences, although a higher percent (11.5%) of patients died in hospital 1 than in hospital 2 (6.1%) or 3 (3.8%). One could attribute this result to moving patients from hospital 2 or 3 to hospital 1, however, there were no patient's change between hospitals, except 1 patient admitted to hospital 3 who was sent to hospital 1 because a severe disease.

Univariate analyses showed that patients who died were more likely to be recorded as aged more than 65 years old, to have solid neoplasms, lymphoma, thrombocytopenia, ra-

Table 3 **Laboratory and radiological findings of patients with influenza A (H1N1)v virus infection.**

Category. Characteristic	All patients (N=111)	Hospital 1 (n=52)	Hospital 2 (n=33)	Hospital 3 (n=26)	RR (CI95%) H2 vs H1 H3 vs H1	P+
Leukocyte count* median (range) per mm^3	8,100 (500-27,400)	8,350 (500-21,800)	7,000 (1,300-27,400)	8,250 (3,400-13,800)		0.43
Leukopenia (<4000/mm3) – N (%)*	11 (10.1)	7 (14)	3 (9.1)	1 (3.8)	0.64 (0.18-2.33)	0.5
					0.27 (0.03-2.11)	0.17
Leukocitosis (>12000/mm3) - N (%)*	22 (20.2)	14 (28)	5 (15.2)	3 (11.5)	0.54 (0.21-1.36)	0.17
					0.41 (0.13-1.31)	0.10
Anemia (Hematocrit< 36%)** - N (%)	28 (25.9)	14 (28)	7 (21.9)	7 (26.9)	0.79 (0.36-1.75)	0.56
					0.98 (0.45-2.12)	0.96
Platelet count*** median (range) per mm^3	185,000 (11,000-395,000)	185,500 (67,000-395,000)	160,000 (70,000-352,000)	196,000 (11,000-333,000)		0.47
Thrombocytopenia (< 150000 per mm)*** N (%)	32 (29.4)	13 (26)	13 (39.4)	6 (26)	1.54 (0.82-2.90)	0.17
					0.91 (0.38-2.11)	0.81
Hypoxemia (Sat O_2 <90)**** - N (%)	19 (20)	6 (12.5)	10 (38.5)	3 (14.3)	3.07 (1.26-7.51)	0.009
					1.14 (0.31-4.14)	0.83
Concomitant and/or secondary bacterial coinfection - N (%)	18 (16.2)	11 (21.2)	2 (6.1)	5 (19.2)	0.28 (0.06-1.21)	0.05
					0.9 (0.35-2.34)	0.84
Pneumonia - N (%)	40 (36)	17 (32.7)	18 (54.5)	5 (19.2)	1.66 (1.01-2.74)	0,04
					0.58 (0.24-1.41)	0,21
Pathologic Radiology*****- N (%)	44 (40)	23 (44.2)	15 (45.5)	6 (24)	1.02 (0.63-1.66)	0.91
					0.54 (0.25-1.16)	0.08

+ Two-tailed Chi-squared test for categorical variables or two-tailed Kruskal-Wallis test for continuous variables

* Information was unavailable for 2 cases in hospital 1

**Information was unavailable for 2 cases in hospital 1, and 1 case in hospital 2

*** Information was unavailable for 2 cases in hospital 1

**** Information was unavailable for 4 cases in hospital 1 , 7 in hospital 2, and 5 cases in hospital 3

***** Information was unavailable for 1 case in hospital 3

diologically-confirmed pneumonia, respiratory distress, or to have required admission to the ICU, mechanical ventilation, non-invasive ventilation or inotropic therapy. These findings are similar to those of previous studies[5,26-28] and highlight the importance of underlying diseases as a risk factor for adverse outcome, as well as the fact that older patients had the lowest estimated incidence rate in this pandemic, however they had the highest case fatality rate[5,11]. In our study 78% of patients who died were older than 50 years of age. When we compared comorbidities between patients admitted to the 3 hospitals, we found that more than 80% of patients had at least one comorbid condition, being COPD the most common, but there were no major differences between patients admitted to 3 hospitals. Regarding clinical characteristics on admission more patients admitted to hospital 2 had myalgias, arthralgias, dyspnea, hipoxemia and findings consistent with pneumonia on chest radiography than patients hospitalized in hospital 1. These findings could be explained by the possibility that patients in hospital 2 were better selected, on the emergency room, to be admitted, or that more patients who developed pneumonia lived in the area of hospital 2. No other clinical differences were seen between the patients admitted to the 3 hospitals. Bacterial co-infections were similar reported to other case series[5,20,26] and were more frequent in patients hospitalized in hospital 1 (21%) and 3 (19%) than in hospital 2 (7%).

Early administration of antiviral treatment has been associated with favorable outcome and with lower development of respiratory failure in patients with influenza A (H1N1)v 2009 virus infection[5,29]. We found that 68% of patients in hospital 3 received oseltamivir in the first 48 h, compared to 31.8% of those in hospi-

Table 4 **Clinical and treatment outcomes of patients with influenza A (H1N1)v virus infection.**

Category-Characteristic	All patients (N=111)	Hospital 1 (n=52)	Hospital 2 (n=33)	Hospital 3 (n=26)	RR (95% CI) H2 vs H1 H3 vs H1	P-value+
Clinical outcomes						
Length of hospital stay median (range). Days	6 (1-191)	7 (1-191)	6 (2-23)	5.5 (2-15)		0.24
Mean (standard deviation). Days	9.6 (9.6)	13.5 (27)	7.3 (5.3)	6.3 (3.3)		0.18
In-hospital complications - N(%)						
Septic shock	5 (4.5)	3 (5.8)	0 (0)	2 (7.7)	-	
					1.33 (0.23-7.49)	0.74
Nosocomial infections	6 (5.4)	4 (7.7)	2 (6.1)	0 (0)	1.05 (0.32-3.44)	0.93
					-	
ICU admission	18 (16.2)	13 (25)	5 (15.2)	0 (0)	0.61 (0.23-1.54)	0.27
					-	
Need for mechanical ventilation	11 (9.9)	7 (13.5)	4 (12.1)	0 (0)	0.9 (0.28-2.83)	0.85
					-	
ARDS	10 (9)	8 (15.2)	2 (6.1)	0 (0)	0.39 (0.08-1.74)	0.19
					-	
In-hospital mortality	9 (8.1)	6 (11.5)	2 (6.1)	1 (3,8)	0.52 (0.11-2.44)	0.40
					0.33 (0.04-2.62)	0.26
- Time diagnosis to death Days. Median (range)*	10 (1-191)	13,5 (1-191)	16 (9-23)	2 (2-2)		
Treatment						
Antiviral therapy (Oseltamivir)– No (%)	100 (90.1)	48 (92.3)	29 (87.9)	23 (88.5)	0.95 (0.82-1.11)	0.49
					0.95 (0.81-1.12)	0.57
- Time since onset of symptoms to antiviral therapy - Days. Median (range)*	3 (0-30)	3.5 (0-30)	4 (1-9)	2 (0-10)		0.03
- Antiviral therapy within 48 hours since onset of symtomps – No (%)*	41 (43.2)	14 (31.8)	12 (41.4)	15 (68.2)	1.3 (0.71-2.39)	0.40
					2.14 (1.27-3.59)	0.005
Inotropic vasopressor – No (%)	12 (10.8)	10 (19.2)	2 (6.1)	0 (0)	0.31 (0.07-1.34)	0.08
					-	0.01
Corticosteroids > 300mg/day – No (%)	58 (52.3)	21 (40.4)	19 (57.6)	18 (69.2)	1.42 (0.91-2.21)	0.12
					1.71 (1.12-2.60)	0.01
- Duration in Days. Median (range)**	8 (1-47)	9 (1-47)	9 (1-45)	7.5 (2-12)		0.69

ARDS:Acute respiratory distress syndrome

+ Two-tailed Chi-squared test for categorical variables or two-tailed Kruskal-Wallis test for continuous variables

* Information was unavailable for 8 cases in hospital 1, 4 in hospital 2, and 4 in hospital 3.

** Information was unavailable for 7 cases in hospital 1.

Table 5 **Prognostic factors for in-hospital mortality in 111 non-pregnant adult patients with influenza A (H1N1)v virus infection: results of univariate analyses.**

Variable	Crude mortality		
	RR	95% CI	p value
Age > 65 years	4.55	(1.24–16.67)	0.015
Type of hospital			
Hospital 1 (reference category)	1		
Hospital 2	0.52	(0.11-2.44)	NS
Hospital 3	0.33	(0.04-2.62)	NS
Female gender	0.95	(0.24–3.77)	NS
Obesity	0	--	NS
Solid neoplasm	8.92	(2.55-31.15)	0.0007
Lymphoma	7.79	(1.64–37.06)	0.018
Thrombocytopenia (< 150000 per mm)*	4.01	(1.01–15.798)	0.033
Pneumonia	12.43	(1.58–97.40)	0.002
Inotropic vasopressor – No (%)	13.75	(3.75–50.45)	< 0.0001
Heart complications	12.88	(3.94–42.10)	< 0.0001
ICU admission	8.61	(2.26-32.87)	0.0002
Need for mechanical ventilation	9.09	(2.64–31.36)	0.0001
Need for non-invasive mechanical ventilation	12.0	(3.93–36.62)	0.0001
ARDS	16.83	(4.70–60.26)	< 0.0001

ARDS: Acute respiratory distress syndrome
*** Information was unavailable for 2 cases**

tal 1 or 41.4% in hospital 2. As described previously, there were no significant differences in mortality between 3 hospitals; however, mortality was lower in patients admitted to hospital 3, in which patients received earlier oseltamivir treatment. Although no solid conclusions can be drawn based in this observational study, these findings suggest that giving early antiviral treatment to hospitalized patients with pandemic (H1N1) 2009 might be more important that the process of care.

Previous reports have shown that obesity and pulmonary conditions other than asthma or COPD and radiologically-confirmed pneumonia were associated with a severe outcome[11,18,22,26]. In our study, multivariate analysis only revealed that pneumonia on admission and cardiac complications during hospitalization were the significant clinical risk factors for severe outcome. Risk factors for mortality were not associated with hospital type neither in the crude analysis, nor in the adjusted analysis for comorbidities and variables related to the treatment and the outcome.

This study is the first to examine the effect of hospital-level characteristics on the outcome of hospitalized adults with pandemic 2009 Influenza A (H1N1)v virus infection. Although, these findings are different to other studies outcomes as research on cardiovascular disease has some similarity[30]. Their results showed that after adjusting for hospital characteristics, the process of care was not significantly associated with outcomes. In the present study no association was seen between outcome and health-care related to hospital-level. Rather, other factors such as patients underlying conditions and severity of disease are the ones who influence the outcome.

The strengths of the present study are its prospective and multicenter design in a community area with standardized hospital admission, microbiological and treatment criteria. In addition, the comprehensive clinical and microbiological data collection was made for the same physicians. However, some limitations should be noted. First, patients who become infected in the community and did not go to hospital were not included. Second the sample size is small compared to other multi-centre studies, which can cause a lack of statistical power to detect small effects. This also prevented us to analyze differences of prognostic factors by hospital. Regardless of that, differences in the types of patients and treatment received based on hospital characteristics were detected. In addition, factors that have influenced mortality have been observed, while, conversely, no differences were found in mortality by hospital type, in the crude or confounders-adjusted analysis.

In summary, in the present study the outcome of patients with influenza A (H1N1)v virus infection was influenced by the patients underlying conditions, the severity of disease on admission and complications during the hospitalization. In our community the type of hospital where patients were admitted did not influence mortality.

ACKNOWLEDGEMENTS

The authors thank Dr. Luis Martinez-Martinez for critical revision of the manuscript.

POTENTIAL CONFLICTS OF INTERESTS

All authors declare that they have no conflicting interests that are relevant to this article.

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