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Original Article

Different prognosis in hospitalized patients with influenza one season after the pandemic H1N1 influenza of 2009–2010 in Spain

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Background The present report compares prognosis in hospitalized cases with the H1N1 pandemic virus in two seasons.

Methods Two series of hospitalized patients with laboratory-confirmed H1N1 pandemic influenza have been compared: 813 in the season 2009–2010 and 707 in the season 2010–2011. A detailed history of variables preceding hospital admission and during hospitalization was obtained by interview and clinical charts. A combined endpoint of death admission to intensive care was used as outcome due to the low number of deaths. Logistic regression was applied in the analysis for adverse outcome.

Results Patients of the second season had different characteristics than in the first one (older, more underlying conditions, more malfunctioning organs and more symptoms). Patients with H1N1 pandemic virus when hospitalized were more frequently directly admitted to ICU during the 2010–2011 season than in the previous season (RR = 2·10; 95% confidence intervals CI, 1·55–2·85), as a consequence of a higher presence of sepsis and respiratory distress. These patients also showed during hospitalization a higher risk of ICU admission or death (RR = 3·22, 95% CI, 2·15–4·83). After adjusting for the differences in risk factors of adverse outcome, patients in the second season showed a higher risk of ICU admission and/or in-hospital death odds ratio (OR = 3·77, 95% CI, 2·30–6·18).

Conclusion Hospitalized patients with H1N1 pandemic influenza during the second season were more severely affected at hospital admission and showed a worse prognosis than in previous season, independently of the differences found at hospital admission.

Keywords Hospitalization, influenza, mortality, prognosis.

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Introduction

Influenza A pandemic H1N1 2009 virus infections began to spread in Spain during spring, 2009. Early reports in Mexico,[1,2] Argentina,[3] USA[4] and Spain,[5] published between 2009 and 2010, suggested that the pandemic virus was more virulent and associated with an adverse outcome. Studies published later from Spain,[6,7] China,[8] USA[9] and Italy[10] have shown that mortality and admission to intensive care in hospitalized patients were lower than previously reported.

There is little information on whether the outcome of hospitalized patients across different seasons varies. A USA study carried out in two hospitals reported that hospitalized patients with the pandemic H1N1 virus for the period 2009/2010 had a worse prognosis than patients admitted in 2007–2008 with seasonal flu.[11] In a historical perspective, it has

been shown in some countries that pandemic waves during the past century showed an increased mortality in the seasons after the first wave (e.g. in the United States after the Asian pandemic of 1957),[12] and a deviation to higher mortality among younger groups in comparison with normal influenza seasons persists.[13] The objective of our research was to assess whether the prognosis of patients hospitalized with the H1N1 pandemic virus has changed after the first wave in the 2009–2010 season in Spain.

Methods

Study design

We carried out a multicenter study in 36 public hospitals from seven Spanish regions (Andalusia, Catalonia, Castile and Leon, Madrid, Navarre, Basque Country and Valencia). Hospitals were the reference centres for a population of about 21 million inhabitants. Hospitalized patients with influenza were selected in two seasons, between July 2009 and February 2010 – pandemic season – and between October 2010 and February 2011. The methods for the pandemic season have been published elsewhere.[6] Influenza infection was confirmed by real-time reverse-transcriptase polymerase chain reaction from nasopharyngeal swabs (RT-PCR). Influenza testing policy did not change across seasons (people with symptoms suggesting influenza). Also, public health administrators did not vary the policy for hospital admission between the two seasons.

We excluded patients who had nosocomial infection, defined as influenza virus infection in a patient that appears $\geq$48 hours after admission for another cause. All information collected was treated as confidential, in strict observance of legislation on observational studies. The study was approved by the Ethics Committees of the hospitals involved, following the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study.

Selection of patients

Within the next 48 hours, hospitalized patients were interviewed at the centre. One hundred and forty-eight patients rejected participation (23 in 2009/2010 and 125 in 2010/2011) and 17 were excluded because influenza had been acquired after hospital admission (12 in 2009/2010 and 5 in 2010/2011).

Data collection

The following demographic variables and pre-existing medical conditions were recorded for all study participants by trained interviewers (all health professionals, nurses and physicians) hired for this study, not involved in the care of hospitalized patients: age, sex, ethnicity, educational level, smoking, higher alcohol intake ($\geq$80 g/day of alcohol), pregnancy, history of pneumonia in the previous 2 years, chronic obstructive pulmonary disease (COPD), asthma, cardiovascular disease, renal failure, diabetes, HIV infection, disabling neurological disease, cancer, transplantation, morbid obesity (body mass index $\geq$40), use of neuraminidase inhibitors before hospital admission, and their timing with the onset of symptoms (verified after contacting the prescribing general practitioner), use of other medications in the 90 days before hospital admission (corticosteroids, antibiotics, etc.) and treatment received during hospitalization: medications, catheters, mechanical ventilation. The number of symptoms and malfunctioning organs at admission were also recorded. Data were collected from physician notes, by interview and from clinical charts during hospital admission; clinical charts were also reviewed after discharge.

The outcome variables were admission to an ICU and in-hospital death. Given that the number of deaths was very low, a combined endpoint was labelled as an adverse outcome: ICU admission and/or in-hospital death.

Statistical analysis

Bivariate comparisons were made using Pearson's chi-square test for categorical variables and Student's *t*-test for continuous variables. As a measure of association, the odds ratio (OR) and 95% confidence intervals (CI) were calculated. Logistic regression was applied in the multivariate analysis for dichotomous adverse outcomes. To determine the variables to be included in the multivariate analysis, the procedure described by Sun *et al.*[14] was followed. Intermediate variables were discarded. We ran two stepwise models, one backward and another forward, including variables with a value of $P < 0{\cdot}2$.[15,16] We constructed a list of predictors of mortality identified in other studies and all of the variables considered a priori which could explain a worse prognosis: sociodemographic and lifestyle variables – sex, age, obesity, smoking and alcohol intake – underlying conditions – chronic respiratory disease, hypertension, cardiovascular disease, diabetes mellitus, renal failure, neurological disease, liver failure, cancer, transplantation, haematological disease – treatment before hospital admission – influenza vaccination, antibiotics, corticosteroids, proton pump inhibitors, neuraminidase inhibitors – and characteristics of the disease at admission – pneumonia, sepsis, acute respiratory distress syndrome, symptoms and days between the beginning of symptoms and admission. Using information from stepwise models and the list of predictors, a saturated model was built, and using a heuristic approach, variables that did not change the coefficient of the bundles by more than 10% were discarded, to construct a parsimonious model retaining all important confounders. Analyses with length of hospital stay were carried out using a logarithmic transformation as this variable does not follow the normal distribution; in

multivariate analysis, the analysis of covariance was applied adjusting for the same confounders of previous analyses. All analyses were carried out using the Stata 12/SE (College Station, TX, USA) package.

Results

In the pandemic wave season (2009–2010), a total of 813 patients with H1N1 influenza was collected and 707 in the next season. Table 1 shows the characteristics of patients with pandemic H1N1 virus in the two seasons. In the second season, fewer women were hospitalized, mean age was higher, obesity and alcoholism were more frequent; patients suffered more hypertension, renal failure, sepsis, cardiovascular disease, acute respiratory distress syndrome, cancer, transplantation and haematological disease. As a consequence, the number of underlying conditions was also higher. Vaccination against influenza was clearly more frequent in the second period. In the analysis of treatments before admission, antibiotics and neuraminidase inhibitors were less used, whereas with the use of systemic corticoids and proton pump inhibitors, the opposite trend was seen. The number of symptoms, malfunctioning organs and presence of pneumonia at admission was higher in the second season. The length of hospital stay was by average 2·3 days longer in the second season.

Table 1. Differences between hospitalized patients with pandemic H1N1 influenza in two seasons. Numbers are *n* (%) unless otherwise indicated

Variable	2009–2010 season (*n* = 813)	2010–2011 season (*n* = 707)	*P* value
Sociodemographic and lifestyle			
Sex, female	410 (50·4)	301 (42·6)	0·002
Age, mean (SD)	38·5 (22·8)	42·9 (24·3)	<0·001
Obesity	84 (10·3)	128 (18·1)	<0·001
Smoking			
No	506 (62·2)	373 (52·8)	<0·001
Ex-smoker	129 (15·9)	165 (23·3)	
Yes	178 (21·9)	163 (23·9)	
High alcohol intake (>80 g/day)	44 (5·4)	81 (11·5)	<0·001
Underlying conditions			
Chronic respiratory disease	270 (33·2)	186 (26·3)	0·003
Hypertension	153 (18·8)	191 (27·2)	<0·001
Cardiovascular disease	99 (12·2)	108 (15·3)	0·079
Renal failure	38 (4·7)	58 (7·9)	0·009
Diabetes mellitus	98 (12·1)	104 (14·7)	0·128
Liver failure	35 (4·3)	42 (5·9)	0·147
Cancer	69 (8·5)	98 (13·9)	0·001
Transplantation	36 (4·4)	54 (7·6)	0·008
Haematological disease	42 (5·2)	55 (7·8)	0·038
No of underlying conditions, mean (SD)	1·4 (1·5)	1·7 (1·6)	<0·001
Treatment before admission			
Vaccine against influenza	13 (1·6)	124 (17·4)	<0·001
Antibiotics	207 (25·5)	235 (33·2)	0·001
Systemic corticosteroids	72 (8·9)	92 (13·0)	0·009
Proton pump inhibitors	131 (16·1)	161 (22·8)	0·001
Neuraminidase inhibitors $\leq$48 hours after beginning flu			
Yes	429 (52·8)	188 (26·6)	<0·001
Later	66 (8·1)	46 (6·5)	
No use	318 (39·1)	473 (66·9)	
Characteristics of the disease at admission			
Pneumonia	204 (25·1)	202 (28·6)	0·126
Sepsis	3 (0·4)	57 (8·1)	<0·001
Acute respiratory distress syndrome	22 (2·7)	96 (13·6)	<0·001
Number of symptoms, mean (SD)	4·8 (2·0)	5·1 (2·1)	0·004
Days between the beginning of symptoms and admission, mean (SD)	4·2 (4·3)	4·8 (4·5)	0·023
>2 organs malfunctioning	12 (1·5)	66 (9·3)	<0·001
Length of stay at hospital, mean (SD)	5·8 (2·4)	8·1 (2·5)	<0·001

SD, standard deviation.

During the 2010–2011 season, patients show a higher risk of admission directly to ICU (RR = 2·10, 95% CI, 1·55–2·85) (Table 2). A logistic regression analysis for predicting admission directly to ICU showed that during the 2010–2011 season, the crude result was explained by the presence of sepsis and respiratory distress syndrome at admission, and the relationship was not longer significant (OR = 1·20, 95% CI, 0·81–1·76). Patients in the second period showed a higher rate of admission to ICU, apart from those directly admitted to ICU, and death during hospitalization.

Given that hospital admission directly to ICU was explained by underlying conditions, we focused on the patients hospitalized during the two seasons who had not been directly admitted to ICU. The results of a predictive model to predict an adverse outcome (admission to ICU or mortality) are presented in Table 3, excluding those patients admitted directly to ICU. The worse prognosis of patients with the pandemic H1N1 strain admitted during the 2010–2011 season was not explained by other variables. The addition to this model of other variables (such as age in different models: linear, quadratic, spline function, sex, smoking, high alcohol intake, use of neuraminidase inhibitors, time between the beginning of symptoms and hospital admission, neurological disease and other variables listed in Table 1) did not change the association. Length of stay was also higher for patients in the second period (5·6–5·3, 6·0 versus 7·1–6·6, 7·6, $P < 0·001$) after adjusting for the same variables.

Table 2. Risk of adverse outcome in patients hospitalized with H1N1 pandemic influenza in two seasons

	2009–2010 season (*n* = 813)	**2010–2011 season (*n* = 707)**
Hospital admission directly to ICU, *n* (%)	58 (7·1)	106 (15·0)
RR (95% CI)	1 (reference)	2·10 (1·55–2·85)
Admission to ICU during hospitalization, *n* (%)	21 (2·6)	68 (9·6)
RR (95% CI)*	1 (reference)	3·72 (2·3–6·01)
Death during hospitalization, *n* (%)	10 (1·3)	22 (3·1)
RR (95% CI)*	1 (reference)	2·53 (1·21–5·31)
Admission to ICU or death during hospitalization, *n* (%)	30 (3·7)	84 (11·9)
RR (95% CI)*	1 (reference)	3·22 (2·15–4·83)

*Confidence intervals estimated by exact procedures with Stata 12/SE.

Discussion

Our main goal has been to compare the prognosis of hospitalized patients between the pandemic and the next season and understand the factors influencing the observed differences; the general predisposing factors of a higher probability of adverse outcome during hospitalization were broadly similar to those found in other studies.[17,18] The results presented here show that the likelihood of an adverse outcome in hospitalized patients with H1N1 influenza increased 1 year after the beginning of the disease. The results suggest that the profile of hospitalized patients with influenza in 2010/2011 was different from those hospitalized during the pandemic season.

Some form of selection bias cannot be completely ruled out, as in our study, patients had to give written consent to be enrolled and interviewed. First, one question is whether our patients are comparable with other series. In a study carried out in Catalonia (north-east Spain), of 773 cases hospitalized, 37·9% were admitted to the ICU,[19] higher than our ICU admission rate in H1N1 patients during the second season (27·6%). In contrast, in Andalusia (southern Spain), 28 of 311 hospitalized cases (9%) received intensive care.[20] In another Spanish study of patients admitted to the ICU, the mortality rate was 22%,[21] much than that observed during the second season. Taken together, these data suggest that patients who died shortly after admission were not picked up by our study. Likewise, the rate of ICU admission (9·7%) was lower than that found in the USA (25%)[4] and Canada (16%),[17] although similar to the 8% reported in New Zealand Maoris.[22] Regarding selection bias, the second question is, 'Are there any differences between the recruitment of patients between the two seasons?' The methods for the selection of participants have been strictly the same for the two seasons, and influenza testing policy did not change between seasons.

Patients hospitalized during the second season showed a higher illness severity. This cannot be due to a change in influenza testing policy in the second season (for more severe patients), as it was the same as before. Although health administrators did not alter criteria for hospital admission, patient's likelihood of attending for hospital admission could change across the two seasons. It may be possible that patients behaved differently across the 2 years – in the second year, as people were less afraid of influenza, they were less likely to present to hospital unless they were unwell; in the first year, their threshold for attending was much lower; that is, in the first year, patients might attend with mild illness, leading to more patients presenting with mild illness, and this would give the impression of a worse prognosis in the second year. There is no information about changes in patients' disease severity perception across seasons (in fact, the general impression was that people were less afraid about influenza).

Table 3. Multivariate model of the risk of an adverse outcome (ICU admission and/or in-hospital death) among hospitalized patients with pandemic H1N1 influenza in two consecutive seasons (patients directly admitted to ICU have been excluded)

Variable	Crude analysis OR (95% CI)	*P* value	Multivariate model* OR (95% CI)	*P* value
2010–2011 season: reference (2009–2010)	3·55 (2·30–5·49)	<0·001	3·77 (2·30–6·18)	<0·001
Age (ref. ≤ 18 years)				
19–30	0·86 (0·31–2·38)	0·763	1·02 (0·33–3·16)	0·969
31–45	1·54 (0·80–2·97)	0·200	1·52 (0·74–3·13)	0·258
46–65	1·91 (1·04–3·50)	0·037	1·43 (0·72–2·86)	0·306
66–75	2·94 (1·45–5·96)	0·003	1·12 (0·47–2·66)	0·803
>75	2·39 (1·02–5·63)	0·046	1·07 (0·38–2·99)	0·903
Respiratory failure	2·14 (1·12–4·08)	0·021	1·70 (0·77–3·76)	0·190
Cardiovascular disease	3·10 (1·89–5·09)	<0·001	2·24 (1·18–4·27)	0·014
Cancer	2·61 (1·61–4·24)	<0·001	2·53 (1·41–4·54)	0·002
Systemic corticosteroids before admission	4·69 (2·46–8·95)	<0·001	2·97 (1·32–6·71)	0·009
Pneumonia at admission	1·98 (1·332–95)	0·001	1·55 (0·99–2·44)	0·058
Number of malfunctioning organs at admission (cont.)	3·31 (2·62–4·20)	<0·001	3·13 (2·41–4·08)	<0·001
High alcohol intake (>80 g/day)	1·99 (1·09–3·64)	0·025	1·62 (0·78–3·36)	0·197

002AArea under the ROC curve = 0·82; goodness of fit (Hosmer–Lemeshow) = 2·39, *P* = 0·967.

Another reason that could alter patient's comparability between the two seasons may be due to doctors' behaviour: they knew less about the influenza illness in the first season (and regardless of 'objective' thresholds set for admission) and they would have been more likely to admit people with milder illness in the first season than the second season.

We would like to emphasize that there was not any outbreak of other disease implying hospital bed scarcity for influenza patients; the availability of beds was similar across the two seasons. Vaccination increased in the second season, but this variable did not explain the higher severity at admission and during hospitalization. The maximum peak of influenza incidence in the first season was 372 cases/100 000 people for the weeks 38–50 of 2009 and in the second season was lower, 240/100 000, for the weeks 1–8 of 2011, with a shift of mortality to more advanced ages in the second season.[23] Co-infection is unlikely to explain the higher severity in the second period; it was similar to the previous one; nevertheless, pneumonia at admission was more frequent in the second season, but it did not explain the worse prognosis after hospital admission. Weather was slightly milder in the second season, and temperatures were 0·5°C higher in January and February 2011 than in November–December 2009, when most of pandemic cases in the first wave occurred;[24] therefore, it is unlikely that a colder winter could affect influenza patient's severity.

Once discarded several explanations for a higher severity of influenza patients at admission, another one remains. May it be that physicians changed their own opinion about the severity of H1N1 influenza during the second season after knowing that mortality during the pandemic wave was lower than predicted? If this is true, it would imply that more severe patients would be admitted to hospital.

Notwithstanding, the differences in underlying conditions, failing organs and symptoms did not explain the worse prognosis of patients with pandemic H1N1 influenza during the second season (and neither the treatments given during hospitalization, results not shown). In a report from Greece, it is suggested that the severity of clinical illness in the first post-pandemic influenza season was comparable or even higher than during the pandemic, showing also a significant increase in ICU admissions;[25] something similar occurred in England with a higher admission to critical care during the year after the pandemic wave.[26] Although these results agree with ours, these studies did not report the characteristics of patients at hospital admission; therefore, they cannot establish whether patients were more severe at hospital admission than during the pandemic wave. However, a report of the FLU-CIN study in England agrees with our report: patients in the second wave were older and showed a higher severity at hospital admission.[27]

It may be likely that we have failed in measuring all the variables related to an adverse outcome, although efforts were made in collecting all the known data on it. An additional explanation for this fact may be that in the pandemic season, a great public and media alarm was created, which led to an excess of not-severe cases to be

admitted to hospital, thus reducing the severity score of persons hospitalized during that season. In contrast, in the second season, when the alarm disappeared, patients attended later to the hospital and so the severity was higher and the prognosis worse.

The differences could also be in theory due to changes in the H1N1 virus and not only to criteria for hospital admission. Although this hypothesis could not be tested as virus strains of subjects enrolled were not studied, no changes in the virus strain have been reported in Spain;[23] and therefore, it is unlikely that this fact could explain our results.

In summary, we found that patients with H1N1 influenza admitted to hospital were more severe in the next season after the pandemic wave. One possible explanation for this fact, after discarding other reasons, is that patients during the pandemic wave were admitted with a less severe disease due to the alarm created by the new virus. In the next season after the spread of H1N1 pandemic flu, a worse prognosis in hospitalized patients, independently of known risk factors, was observed.

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Contribution

Angela Domínguez, Miguel Delgado-Rodríguez, Jesús Castilla, Pere Godoy, Vicente Martín contributed to study design. Nuria Soldevila, Jordi Alonso, Jenaro Astray, Juan Carlos Galán, Ady Castro, José María Mayoral, José María Quintana, Sonia Tamames involved in data collection. Maretva Baricot is a Data Manager. Tomás Pumarola, Fernando Gónzález-Candelas performed the microbiological analyses. Miguel Delgado-Rodríguez, Marc Sáez carried out the statistical analyses, All the authors involved in data interpretation. A draft was prepared by Miguel Delgado-Rodríguez. It was revised and approved by the all the remaining authors.

Conflict of interests

All the authors declare that there is no conflict of interest, and no one of them has received any support from the industry manufacturing drugs against influenza.

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