ORIGINAL

First influenza season after the 2009 pandemic influenza: report of the first 300 ICU admissions in Spain

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Abstract
Introduction: During the 2009 influenza pandemic, several reports were published, nevertheless, data on the clinical profiles of critically ill patients with the new virus infection during this second outbreak are still lacking.
Material methods: Prospective, observational, multi-center study conducted in 148 Spanish intensive care units (ICU) during epidemiological weeks 50-52 of 2010 and weeks 1 - 4 of 2011.
Results: Three hundred patients admitted to an intensive care unit (ICU) with confirmed An/H1N1 infection were analyzed. The median age was 49 years [IQR = 38-58] and 62% were male. The mean APACHE II score was 16.9 ± 7.5 and the mean SOFA score was 6.3 ± 3.5 on admission. Comorbidities were present in 76% (n = 228) of cases and 111 (37.4%) patients were

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reportedly obese and 59 (20%) were COPD. The main presentation was viral pneumonia with severe hypoxemia in 65.7% (n = 197) of the patients whereas co-infection was identified in 54 (18%) patients. All patients received antiviral treatment and initiated empirically in 194 patients (65.3%), however only 53 patients (17.6%) received early antiviral treatment. Vaccination was only administered in 22 (7.3%) patients. Sixty-seven of 200 patients with ICU discharge died. Haematological disease, severity of illness, infiltrates in chest X-ray and need for mechanical ventilation were variables independently associated with ICU mortality.

Conclusions: In patients admitted to the ICU in the post-pandemic seasonal influenza outbreak vaccination was poorly implemented and appear to have higher frequency of severe comorbidities, severity of illness, incidence of primary viral pneumonia and increased mortality when compared with those observed in the 2009 pandemic outbreak.

Primera epidemia de gripe estacional después de la pandemia por gripe A en 2009: descripción de los primeros 300 ingresos en UCI españolas

Resumen

Introducción: Durante la pandemia de gripe A, se publicaron diferentes comunicaciones. No obstante, el perfil clínico de los pacientes críticos afectados por este virus durante este segundo brote epidémico es poco conocido.

Material y métodos: Estudio prospectivo, observacional y multicéntrico realizado en 148 UCI españolas entre las semanas epidemiológicas 50 de 2010 y 4 de 2011.

Resultados: Se incluyó a los primeros 300 pacientes ingresados en UCI con infección confirmada por An/H1N1. La media de edad fue de 49 [38-58] años y el 62% eran varones. La media de APACHE II fue $16,9 \pm 7,5$, con una media de SOFA de $6,3 \pm 3,5$. El 76% (n = 228) de los pacientes presentaron alguna comorbilidad, 111 (37,4%) eran obesos y 59 (20%) presentaban EPOC. La presentación clínica más habitual fue la neumonía viral con hipoxemia severa (65,7%; n = 197), mientras que se observó coinfección en 54 pacientes (18%). Todos recibieron tratamiento antiviral, de forma empírica en 194 (65,3%). Sólo 53 pacientes (17,6%) recibieron tratamiento antiviral precoz; 22 pacientes (7,3%) estaban vacunados. Cumplieron su evolución en UCI 200 pacientes, y fallecieron 67 de ellos. La enfermedad hematológica, la gravedad general, los infiltrados en la radiografía de tórax y la necesidad de ventilación mecánica fueron las variables asociadas de forma independiente con la mortalidad.

Conclusiones: Los pacientes críticos ingresados en UCI durante el brote estacional de gripe pospandémica evidenciaron escaso nivel de vacunación, mayor frecuencia de comorbilidades, un nivel gravedad más elevado, mayor incidencia de neumonía viral primaria y una mortalidad superior en comparación con lo observado durante la pandemia de 2009.

Introduction

During the 2009 influenza pandemic caused by the A(H1N1) 2009 virus, several reports were published regarding the presentation of this disease with severe acute respiratory symptoms in hospitalized patients[1–4]. Rapidly progressive viral pneumonia represents the primary cause of intensive care unit (ICU) admission with mortality rates ranging from 17.3% to 46% among different sites[1–3,5–9]. This disease represented a challenge for critical care physicians worldwide. In the 2010-11 winter a seasonal outbreak of influenza has been detected in Spain with most cases caused by the former A/H1N1 2009 pandemic virus, currently called ''new A/H1N1 virus'' (An/H1N1). Data on the clinical profiles of critically ill patients with the virus An/H1N1 infection during this outbreak are still lacking. Here, we present our experience in a series of the first 300 critically ill patients admitted to Spanish ICUs.

Material and methods

This prospective, observational cohort study of ICU patients was conducted across 148 ICUs in Spain. Data were obtained from a voluntary registry created by the Spanish Society of Intensive Care Medicine (SEMICYUC), the Spanish Network for Research on Infectious Disease (REIPI) and the Spanish Biomedical Research Center Network on Respiratory Diseases (CIBERES). The study was approved by the Joan XXIII University Hospital Ethics Committee (IRB NEU-MAGRIP/11809). Patient identification remained anonymous and the informed consent requirement was waived due to the observational nature of the study.

Data were reported by the attending physician reviewing medical charts and radiological and laboratory records. In this case series, data on all patients within the cohort consecutively diagnosed with An/H1N1 influenza between epidemiological weeks 50-52 of 2010 and weeks 1-4 of 2011 are presented (fig. 1). Children under 15
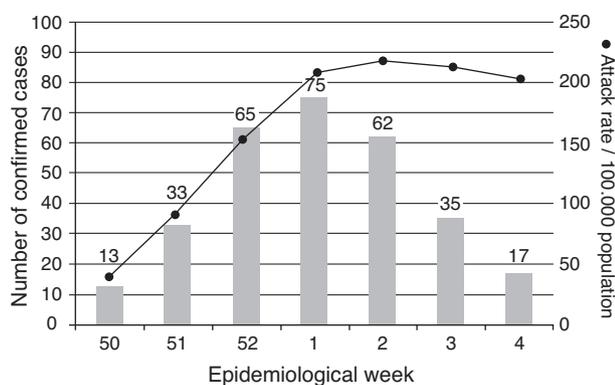
Figure 1 Number of confirmed cases of An/H1N1 virus infection admitted to intensive care unit and clinical attack rate in Spain (solid line).

years old were not enrolled in the registry. The An/H1N1 infection was confirmed by means of realtime reverse-transcription-polymerase chain reaction (RT-PCR) on either nasopharyngeal swab samples or tracheal secretions ordered by the attending physicians at ICU admission. An/H1N1 testing was performed in each institution or centralized in a reference laboratory when local resources were not available. A confirmed case was defined as an acute respiratory illness with laboratory-confirmed An/H1N1. Only confirmed cases were included in the current report.

The ICU admission criteria and treatment decisions for all patients, including determination of the need for intubation and type of antibiotic or antiviral therapy administered, were not standardized and were made by the attending physician. Systemic corticosteroid use was implemented when patients developed shock (hydrocortisone), or coadjuvant treatment was used for pneumonia (methyl-prednisolone). Orally administered oseltamivir (150 mg/24 h or 300 mg/24 h) or intravenous zanamivir (600 mg/12 h) was chosen by the attending physician.

Definitions

Primary viral pneumonia was defined in patients presenting illness with acute respiratory distress and unequivocal alveolar opacities involving two or more lobes with negative respiratory and blood bacterial cultures during the acute phase of influenza virus infection[5].

Community-Acquired Respiratory Co-infection (CARC) was defined as any infection diagnosed within the first 2 days of hospitalization[10]. Infections occurring later were considered nosocomial[11]. Definition of Hospital-Acquired Pneumoniae (HAP) was based on current American Thoracic Society and Infectious Disease Society of America guidelines[12]. Patients who presented healthcare-associated pneumonia (HCAP) were excluded from the present study[12]. Obese patients were defined as those with a body mass index (BMI) over 30[13].

Patient who had previously received Influenza A (H1N1) 2009 monovalent or seasonal influenza 2010-11 vaccination were considered to be ''vaccinated''.

Statistical analysis

Discrete variables are expressed as counts (percentage) and continuous variables as means ± standard deviation (SD) or medians [25th to 75th interquartile range (IQR)]. For the demographic and clinical characteristics of the patients, differences between groups were assessed using the χ^2 test and Fisher's exact test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables. Stepwise logistic regression analysis was used to determine the impact of each variable on ICU mortality. The variables included in the multivariate model were those that showed significant differences in the univariate analysis (Table 2), including the variable ''vaccination condition'' due to its potential clinical interest. Risk is expressed as odds ratio (OR) and its 95% confidence interval (CI).

Data analyses were performed using SPSS 15.0 for windows (SPSS, Chicago, IL, USA). Values of $P < .05$ were considered to indicate statistical significance.

Results

Data from the first 300 adults admitted to Spanish ICUs during the winter of 2010-11 due to An/H1N1 infection are the focus of the present report. Patients were young (median 49 years) and 62% were male. The mean APACHE II score was 16.9 ± 7.5 and the mean SOFA score was 6.3 ± 3.5 on admission. The baseline characteristics of the population are shown in Table 1. Comorbidities were present in 76% (n = 228) of cases. The main comorbid condition reported was obesity in 111 patients (37.4%) followed by chronic obstructive pulmonary disease (COPD) (n = 59; 20%), diabetes mellitus (n = 45; 15.2%) and haematological disease (n = 37, 12.5%) (fig. 2).

The main presentation was viral pneumonia with severe hypoxemia that was present in 65.7% (n = 197) of the patients. Forty (13.3%) patients had COPD exacerbation or severe asthma, and CARC was identified in 54 (18%) patients. *Streptococcus pneumoniae* (n = 21), *Pseudomonas aeruginosa* (n = 6), *Staphylococcus aureus* (n = 6) and *Streptococcus pyogenes* (n = 4) were the most frequent microorganisms isolated.

Two-hundred and thirty-seven patients (79%) required mechanical ventilation (MV). Non-invasive ventilation was used in 105 (35%), and failed in 53 patients (50.5%). One-hundred fifty-three patients (51.0%) required vasopressor drugs at ICU admission and 54 (18%) developed acute kidney injury. Forty-one (13.6%) of them received renal replacement techniques.

All patients received antiviral treatment for a median duration of 7 [6-10] days, which was initiated empirically in 194 patients (65.3%). Two-hundred and eighty-five (95%) received oseltamivir, whereas zanamivir was administered in 15 (5%) patients. Finally, eight patients (2.7%) received both antiviral drugs. The median time between the onset of symptoms and the first administered antiviral dose was 5 [3-7] days, with a dose of 75 mg/day in 50.3% (n = 151) of cases. Only 53 patients (17.6%) received early antiviral treatment (<48 h from symptoms onset).

One-hundred and thirty-one patients (43.6%) received early corticosteroid therapy at ICU admission for a median of

Table 1 Baseline demographic characteristics of critically ill patients with infection by influenza A(H1N1) virus (n = 300).

Variable	Overall (n = 300)	Non vaccinated (n = 278)	Vaccinated (n = 22)
Age, years, median (IQR)	49 (38.5-58)	48 (38-57)	55 (48.5-69.5)[a]
Male sex, n (%)	188 (62.6)	173 (62.2)	15 (68.2)
APACHE II score at day 1, mean (SD)	16.9 (7.5)	16.7 (7.4)	19 (7.9)
SOFA score al day 1, mean (SD)	6.3 (3.5)	6.2 (3.5)	7 (3.8)
Time between onset symptoms and hospital admission in days, median (IQR)	4 (3-7)	4 (3-7)	3.5 (1.5-7.5)
Time between hospital admission and ICU admission in days, median (IQR)	1 (1-2)	1 (1-3)	1.5 (1-4)[a]
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2.3 (1.2)	2.4 (1.2)	1.9 (1.4)
Mechanical ventilation, n (%)	239 (79.6)	222 (79.8)	17 (77.3)
Prone ventilation, n (%)	59 (19.6)	57 (20.5)	2 (9.1)
Shock at ICU admission, n (%)	153 (51)	143 (51.4)	10 (45.4)
Oseltamivir regimen (150 mg/day), n (%)	153 (51)	143 (51.4)	10 (45.4)
Steroid therapy at ICU admission, n (%)	131 (43.6)	122 (43.9)	9 (40.3)
Community-acquired respiratory co-infection at ICU admission, n (%)	54 (18)	50 (18)	4 (18.2)
ICU LOS, days, mean (SD)			
Survivors	8.5 (8)	9.1 (7.2)	5 (3.1)[a]
Non-survivors	8.8 (7.1)	8.4 (8.1)	9.2 (6.8)
Hospital LOS, days, mean (SD)			
Survivors	10.7 (9.1)	14.4 (8.5)	9.9 (5.2)[a]
Non-survivors	14.1 (8.4)	10.3 (9.1)	14 (10.1)
Days of mechanical ventilation, mean (SD)			
Survivors	8.3 (7.8)	8.2 (6.7)	3.4 (1.5)[a]
Non-survivors	7.9 (6.7)	8.3 (8)	7.7 (4.1)
Mortality rate, n (%)[b]	67 (33.5)	63 (22.6)	4 (18.2)

LOS: length of stay.

[a] P < .05.

[b] Only in 200 patients discharged from ICU.

duration of 7 [5-10], with 10.6% (n = 32) representing coadjuvant therapy for septic shock.

Interestingly, 278 (92.6%) of the patients had not been vaccinated. Vaccinated patients were older (P < .05) and with higher delay between hospital and ICU admission (Table 1). No significant differences in comorbidities were observed between patients with or without vaccination (fig. 2).
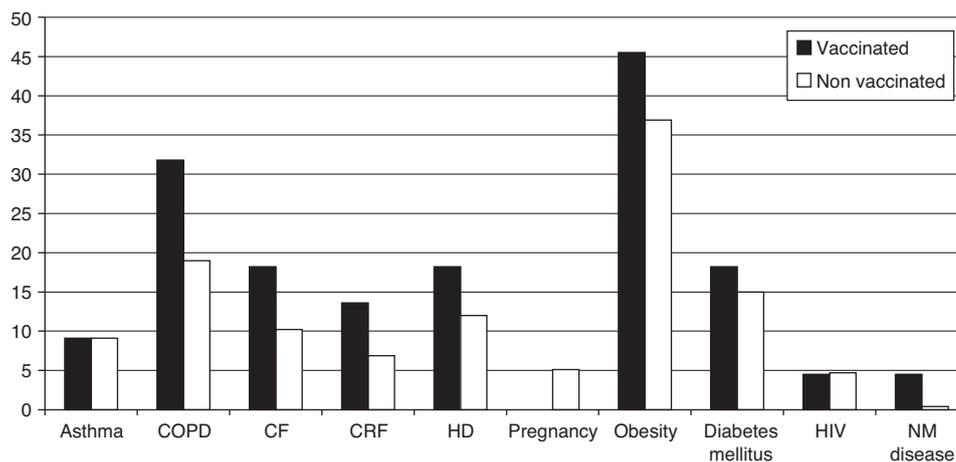

Figure 2 Most common comorbidities reported in confirmed cases of An/H1N1 virus infections, differentiating vaccinated patients from those who were not. CF: cardiovascular disease; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; HD: hematological disease; HIV: human immunodeficiency virus infection; NM disease: neuromuscular disease.

Table 2 Clinical characteristics of patients with infection by influenza A(H1N1) virus (only in 200 patients discharged from ICU).

Variable	Survival (n = 133)	Non-survival (n = 67)	P-value	OR (95%CI)
Age, years, mean (SD)	48.7 (14.9)	50.0 (13.5)	.34	—
Male sex, n (%)	83 (62.4)	46 (68.7)	.38	—
APACHE II score at day 1, mean (SD)	14.2 (6)	21.8 (7.8)	<.001	—
SOFA score al day 1, mean (SD)	4.6 (2.6)	8.6 (3.9)	<.001	—
Time between onset symptoms and hospital admission in days, mean (SD)	4.5 (3.2)	5.2 (3.7)	.2	—
Time between hospital admission and ICU admission in days, mean (SD)	1.8 (2.2)	2.6 (3.4)	.06	—
Quadrants infiltrated in chest X-ray at ICU admission, mean (SD)	2 (1.2)	2.7 (1)	<.001	—
Invasive Mechanical ventilation, n (%)	55 (42)	62 (92.5)	<.001	1.9 (1.6-2.4)
Prone ventilation, n (%)	13 (9.8)	26 (38.8)	<.001	2.2 (1.4-3.5)
Shock at ICU admission, n (%)	42 (31.6)	55 (82.1)	<.001	2 (1.6-2.6)
Steroid therapy at ICU admission, n (%)	50 (37.6)	40 (59.7)	<.05	1.3 (1.1-1.7)
Acute Kidney Injury, n (%)	21 (15.8)	33 (49.3)	<.001	1.9 (1.4-2.8)
Community-acquired respiratory co-infection at ICU admission, n (%)	16 (12)	21 (31.3)	<.05	1.6 (1.1-2.4)
Viral pneumonia, n (%)	84 (63.2)	44 (65.7)	.72	—
Time in days between onset of symptoms and first doses of antiviral received, mean (SD)	5.2 (3.2)	5.6 (3.1)	.33	—
Comorbidities, n (%)				
Asthma	16 (12.5)	3 (4.5)	.08	—
Chronic Obstructive Pulmonary Disease	26 (19.5)	16 (23.9)	.47	—
Cardiovascular disease	15 (11.3)	8 (11.9)	.89	—
Chronic Renal Failure	9 (6.8)	6 (9)	.57	—
Hematologic disease	9 (6.8)	16 (23.9)	<.05	1.9 (1.5-3.3)
Pregnancy	7 (5.3)	1 (1.5)	.2	—
Obesity	53 (39.8)	17 (25.4)	<.05	0.8 (0.6-0.9)
Diabetes mellitus	24 (18)	8 (11.9)	.26	—
Human immunodeficiency virus	1 (0.8)	9 (13.4)	<.001	6.9 (1.1-44.7)
Vaccinated, n (%)	8 (6)	4 (6)	.99	—

As of February 15 2011, 200 patients (66.6%) had been discharged from the ICU and 67 of them (33.5%) had died. The mortality rate was not different between patients who received vaccination (18.2%) compared to those who did not (22.6%; P = .79; OR = 1.32; 95%CI, 0.45-3.84). The 4 vaccinated patients who died had significant comorbidities (severe immunosuppression due to lung —n = 1— bone marrow transplantation —n = 1— and acute leukaemia —n = 2—). Among patients who underwent invasive mechanical ventilation (n = 117), the mortality was very high (n = 62; 53%).

The characteristics of patients at ICU admission according to survival or death (n = 200) are shown in Table 2. Patients who died presented higher APACHE II and SOFA scores at ICU admission. No differences in comorbidities were observed except for haematological disease (OR = 1.9; 95%CI, 1.5-3.3) and human immunodeficiency virus infection (OR = 6.9; 95%CI, 1.1-44.7) which were more frequent in non-survivors. Obesity was associated with a better prognosis (OR = 0.8; 95%CI, 0.6-0.9). Development of shock (OR = 2; 95%CI, 1.6-2.6); acute kidney injury (AKI) (OR = 1.9; 95%CI, 1.4-2.8), need for invasive MV (OR = 1.9; 95%CI, 1.6-2.4), number of quadrant infiltrates in chest X-ray (2.6 vs. 1.9; P < .05), steroid therapy (OR = 1.3; 95%CI,

1.1-1.7) and CARC (OR = 1.6; 95%CI, 1.1-2.4) were most frequent in non-survivors. APACHE II score, SOFA score, infiltrates in chest X-ray, invasive MV, shock at ICU admission, AKI, CARC, hematological disease, HIV infection and vaccination were variables included in the multivariate analysis to determine their association with the mortality. Stepwise logistic regression analysis showed that APACHE II score by point of increase (OR = 1.07; 95%CI, 1.01-1.14; P = .02), infiltrates in chest X-ray by quadrant (OR = 1.6; 95%CI, 1.08-2.4; P = .01), haematological disease (OR = 4.5; 95%CI, 1.2-17.5; P = .02) and invasive MV (OR = 9.4; 95%CI, 2.9-30.8; P < .001) were variables independently associated with mortality. The multivariate models had a Hosmer-Lemeshow goodness-of-fit test score of 13.04 (P = .11).

Discussion

To the best of our knowledge, this is the first study that presents a relatively large number of patients admitted to the ICU for severe infection due to the An/ H1N1 virus in the 2010-11 seasonal influenza outbreak, this being in the post-pandemic period.

In our series, the presenting features of An/H1N1 influenza during the winter of 2010-11 were quite similar to those described in the past 2009 A/H1N1 virus infection pandemic. Nevertheless some aspects need to be pointed out.

In this report, the severity of disease in patients (APACHE II score 16.9) was greater than that observed during the 2009 pandemic (APACHE II 13.8; $P < .001$)[5]. The frequency of comorbidities in the current series (76% of patients) was also higher than that observed in the 2009 pandemic (69.6%; $P = .01$)[5-7]. While obesity remained the most frequent comorbidity, there was an increase in the number of patients with haematological disease during the 2010-11 seasonal influenza outbreak compared to the pandemic period. This was the fourth most frequent comorbidity and it was the only one independently associated with mortality in the multivariate analysis.

Primary viral pneumonia was significantly more frequent (63.2%) during the 2010-11 seasonal influenza outbreak compared with recently published data for the previous (2009 pandemic) outbreak (54.8%; $P < .01$)[10]. The rapid progression of pulmonary viral infection from respiratory failure to Acute Respiratory Distress Syndrome (ARDS) may be related to a significant increase in the need for MV in the current seasonal outbreak (79%) compared to the 2009 pandemic outbreak (61.5%; $P < .01$)[14]. The mortality rate of ventilated patients was very high (53%) in the present study and invasive MV was independently associated with mortality in the multivariate analysis.

The implementation of early (<2 days) antiviral therapy was associated with a lower mortality rate in ventilated patients with 2009 H1N1[14]. While all patients received antiviral treatment, the present study showed a one-day delay (5 days instead of 4 days) in the administration of antiviral agents compared to previous studies[14].

All these variables must be considered in order to explain the higher mortality observed in the current seasonal outbreak (33%) compared to that reported during the 2009 pandemic (21%; $P < .01$)[14]. Although in the present study only haematological disease, the need for MV, APACHE II score and number of quadrants infiltrates in chest X-ray were factors associated with mortality, other variables cannot be excluded given that the study may be underpowered to identify other factors also associated with mortality.

The use of corticosteroids in the present report was very high (43% of cases). WHO guidelines for the management of human infection with pandemic (H1N1) Influenza A infection recommend that corticosteroid therapy should not be used routinely. Recently, Martin-Loeches et al[15] showed that the early use did not result in better outcomes and may be associated with an increased risk of super-imposed infections.

Many studies have demonstrated temporal relationships between influenza activity and CARC. During past pandemics, the bacteria most often recovered were common colonizers of the upper respiratory tracts of healthy persons, i.e., *Haemoohilus influenzae, S. pneumoniae, S. pyogenes* or *Staphylococcus aureus*[16-18]. Moreover, substantial laboratory evidence for synergism between influenza A and bacterial microorganisms has been suggested[19]. During the 2010-11 seasonal influenza outbreak, CARC was present in 18% of cases, this prevalence being similar to that reported in the 2009 outbreak (17.5%)[10].

Finally, in the present report, 92.6% of the patients admitted to the ICU were not vaccinated. The presentation of ARDS with severe refractory hypoxemia is particularly common in patients with this disease process and might be linked to an abnormal immune response[20]. Vaccination induces broad and improved cross protection against severe illness of multiple subtypes of influenza A virus. While vaccination has been a matter of debate, there has nevertheless been no evidence of harm or serious side effects in the vaccine trials that were conducted. In our study, the 4 vaccinated patients who died had severe risk factors and death was related to serious underlying comorbidities; given their immunosuppression status, it is possible that an inadequate immune response to the influenza vaccine had occurred. Moreover, Pregnancy was significantly associated with primary viral pneumonia due to An/H1N1[21] and it was recognized as important risk factor for developed severe hypoxemia. However, all pregnant women included in the present report were not vaccinated. No definitive conclusions can be drawn about the impact of vaccination based on our results given the small number of vaccinated patients included in the study. However, vaccinated patients seemed to have a more favorable outcome as evidenced by briefer stays in the ICU (4 days) and hospital (5 days) and fewer day under mechanical ventilation (5 days) (Table 1). Future studies are needed to clarify the impact of vaccination on outcome in critically ill patients.

The short follow up of the patients is a limitation of this study that should be further addressed. Indeed, the mortality rate in the present series could be underestimated given that 100 patients remained in the ICU at the time of this report, with a median follow up of 30 days in those patients. However, it is important to report in a timely manner our clinical experience with patients infected with the An/H1N1 virus to be aware of their clinical characteristics and possible differences with the previous 2009 outbreak, all of them pointing to a greater severity of illness and higher mortality as seen in the current series. In addition, early information on how recommendations on the management of critically ill patients with An/H1N1virus infection (i.e, on the use of antiviral agents or on the administration of corticosteroids) are being followed is of immediate practical relevance.

In conclusion, patients admitted to the ICU in the 2010-11 seasonal influenza outbreak appear to have a higher severity of illness, higher frequency of severe comorbidities, higher incidence of primary viral pneumonia and increased mortality compared with those observed in the 2009 pandemic outbreak. Hematological disease, severity of illness at ICU admission, number of quadrants infiltrates in chest X-ray and the requirement for mechanical ventilation were variables independently associated with mortality. Vaccination appears to be associated with improved outcomes. This report is aimed at providing a general description of the first An/H1N1 influenza patients admitted to Spanish ICUs. Further in-depth studies with a larger sample size are needed to confirm these preliminary results.

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Conflict of interests

Authors declare no conflict of interests regarding the present manuscript.

Authors' contributions

AR assisted in the design of the study, coordinated patient recruitment, analyzed and interpreted the data, and with IML assisted in writing the paper. JB, PO, FAL, RZ, JG, JB, FG, JR made an important contribution to acquisition and analysis of data. JC, JL, IML and EC were involved in revising it critically for important intellectual content. CL, FP and AE made a substantial contribution to the conception and interpretation of data, and revised the final manuscript version. They all approved the final version to be published.

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