



## Original article

# Prognostic Factors and Analytical Abnormalities in Patients Admitted With the Diagnosis of Influenza in a Third Level Hospital During the 2015–2016 Season



Néstor Vázquez-Agra<sup>a</sup>, Vanesa Alende-Castro<sup>b</sup>, Cristina Macía-Rodríguez<sup>c</sup>, Ana-Teresa Marques-Afonso<sup>a</sup>, Martín Vidal-Vazquez<sup>a</sup>, Vanesa Riveiro Blanco<sup>d</sup>, Ignacio Novo-Veleiro<sup>a,\*</sup>

<sup>a</sup> Internal Medicine Department, University Hospital of Santiago de Compostela, A Coruña, Spain

<sup>b</sup> Internal Medicine Department, Hospital do Salnés, Vilagarcía de Arousa, Pontevedra, Spain

<sup>c</sup> Internal Medicine Department, POVISA Hospital, Vigo, Pontevedra, Spain

<sup>d</sup> Pneumology Department, University Hospital of Santiago de Compostela, A Coruña, Spain

## ARTICLE INFO

## Article history:

Received 25 July 2019

Accepted 23 February 2020

Available online 19 March 2020

## Keywords:

Influenza A

Influenza B

Multiple comorbidity patient

Elderly

## ABSTRACT

**Introduction:** Influenza is an acute respiratory illness due to influenza A or B viruses, which is associated with an increased morbidity and mortality in certain high-risk populations, like children, elderly patients and those with multiple comorbidities.

**Methods:** We conducted a cross-sectional retrospective analysis including all patients identified with the following ICD 10 codes: J10.0, J10.1, J10.8–11.0, J11.1, J11.8. 258 patients were included.

**Results:** The most frequent strain was influenza A H1N1 (81.8%). We found alterations in blood count in 163 (63.2%) patients and they were more frequent in men. In the case of liver enzymes, we found alterations in 155 (60.1%) patients, being more frequent in men, smokers or former smokers and non-A cases. 22 patients were admitted to the ICU and 20 died during hospital stay. We performed a multivariable logistic regression analysis that showed an association between ICU admission and the presence of infiltrates in chest radiography (OR = 4.1, IC 95% 1.55–10.87;  $P = 0.004$ ), previous antibiotic treatment (OR = 5.84, IC 95% 1.32–25.69;  $P = 0.020$ ), anemia (OR = 7.29, IC 95% 1.38–38.41;  $P = 0.019$ ) and no initial suspicion of influenza (OR = 8.07, IC 95% 1.48–43.89;  $P = 0.016$ ). We also found an association between mortality and age (OR = 1.04, IC 95% 1.01–1.09;  $P = 0.026$ ), the presence of infiltrates in chest radiography (OR = 2.19, IC 95% 1.26–3.81;  $P = 0.005$ ) and no initial suspicion of influenza (OR = 5.43, IC 95% 1.60–18.47;  $P = 0.007$ ). Finally, our analysis showed that the variables linked to a length of hospital-stay >5 days were concomitant antibiotic treatment during admission (OR = 14.36, IC 95% 2.23–92.35;  $P = 0.005$ ) and liver enzymes alterations (OR = 3.01, IC 95% 1.26–7.12;  $P = 0.013$ ).

© 2020 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Neumología y Cirugía Torácica (SEPAR). This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Factores pronósticos y alteraciones analíticas en pacientes ingresados por gripe en un hospital de tercer nivel en el periodo 2015-2016

## RESUMEN

**Introducción:** La gripe es una enfermedad respiratoria aguda debida a los virus de la influenza A o B que se asocia con un aumento de la morbilidad y la mortalidad en ciertas poblaciones de alto riesgo como niños, ancianos y personas con comorbilidades múltiples.

**Métodos:** Realizamos un análisis retrospectivo transversal que incluyó a todos los pacientes identificados con los códigos ICD10: J10.0, J10.1, J10.8–11.0, J11.1, J11.8. Se incluyeron 258 pacientes.

## Palabras clave:

Gripe A

Gripe B

Paciente pluripatológico

Anciano

\* Corresponding author.

E-mail address: [ignacio.novo.veleiro@gmail.com](mailto:ignacio.novo.veleiro@gmail.com) (I. Novo-Veleiro).

**Resultados:** La cepa más frecuente fue la influenza A H1N1 (81.8%). Encontramos alteraciones en el hemograma en 163 pacientes (63.2%); estas alteraciones fueron más frecuentes en hombres. En el caso de las enzimas hepáticas, encontramos alteraciones en 155 pacientes (60,1%), que fueron más frecuentes en hombres, fumadores o exfumadores y en casos no-A. 22 pacientes ingresaron en la UCI y 20 fallecieron durante la estancia hospitalaria. Se realizó un análisis de regresión logística multivariable que mostró una asociación entre el ingreso en la UCI y la presencia de infiltrados pulmonares en la radiografía de tórax ( $OR=4,1$ , IC 95% 1,55–10,87;  $P=0,004$ ), el tratamiento antibiótico previo ( $OR=5,84$ , IC 95% 1,32–25,69;  $P=0,020$ ), la anemia ( $OR=7,29$ , IC 95% 1,38–38,41;  $P=0,019$ ) y ausencia de sospecha inicial de gripe ( $OR=8,07$ , IC 95% 1,48–43,89;  $P=0,016$ ). También encontramos una asociación entre la mortalidad y la edad ( $OR=1,04$ , IC 95% 1,01–1,09;  $P=0,026$ ), la presencia de infiltrados en la radiografía de tórax ( $OR=2,19$ , IC 95% 1,26–3,81;  $P=0,005$ ) y ausencia de sospecha inicial de gripe ( $OR=5,43$ , IC 95% 1,60–18,47;  $P=0,007$ ). Finalmente, nuestro análisis mostró que las variables relacionadas con una estancia hospitalaria >5 días fueron el tratamiento antibiótico concomitante durante el ingreso ( $OR=14,36$ , IC 95% 2,23–92,35;  $P=0,005$ ) y alteraciones de las enzimas hepáticas ( $OR=3,01$ , IC 95% 1,26–7,12;  $P=0,013$ ).

© 2020 Publicado por Elsevier España, S.L.U. en nombre de Sociedad Española de Neumología y Cirugía Torácica (SEPAR). Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Influenza is an acute respiratory illness due to influenza A or B viruses, which cause outbreaks and epidemics worldwide.<sup>1</sup> Signs and symptoms of upper and/or lower respiratory tract involvement are usually present, along with fever, headache, myalgia and weakness.<sup>2</sup> Influenza is a self-limited infection in the general population; however, it is associated with an increased morbidity and mortality in certain high-risk populations, like children, elderly patients and those with multiple comorbidities.<sup>3</sup>

Several analytical abnormalities have been described in the literature related to viral infections, like those caused by the herpes virus family.<sup>4,5</sup> Regarding influenza viruses, the presence of leukocyte count or liver enzymes abnormalities are frequent, nevertheless, there are lack of studies analyzing laboratory abnormalities caused by influenza virus infection and the results are dissenting. Thus, the real relevance of these abnormalities in the development of complications during influenza infection process remains unknown. There are no recommendations regarding the clinical usefulness of determining these and other parameters. Moreover, in spite of the high frequency of these abnormalities in patients with influenza, there are no validated scores or indexes based on them which predict severity.

Due to the lack of data available regarding the potential relationship of frequent analytical abnormalities in patients with influenza and prognosis, the aim of this study was to analyze laboratory abnormalities during influenza infection and to investigate the potential relationship between those abnormalities and the type of influenza virus, prognosis outcomes like intensive care unit admission (ICU) and increased length of hospital stay or mortality.

## Material and methods

We conducted a cross-sectional retrospective analysis, which included all patients admitted with the diagnosis of influenza virus infection at the Santiago de Compostela University Teaching Hospital (NW Spain), from January 1st to June 31st 2016. All patients were identified through the electronic admission database, searching for the following ICD 10 (International Classification of Diseases, 10th edition) codes: J10.0, J10.1, J10.8–11.0, J11.1, J11.8.<sup>6</sup> After that, all electronic medical histories were reviewed to confirm that the diagnosis criteria applied for the inclusion were those published in current guidelines.<sup>7–9</sup> All patients with a clinical and microbiological diagnosis of influenza infection were included. Patients with clinical suspicion of influenza which was not confirmed by the microbiology laboratory were excluded. We conducted the study

after the approval of the Autonomic Investigation Ethics Committee of Galicia.<sup>10</sup>

We recorded socio-demographic, epidemiological, clinical, analytical, microbiological and prognosis characteristics of all included patients through revision of their medical electronic history. The grade of physical dependence was established by using the Barthel's index (BI).<sup>11</sup>

We categorized patients by age in three ranges: <30, 30–60 and >60. Then, we summarize age in two ranges: under and over sixty.

We used the variable chronic pulmonary pathology, which includes presence of any obstructive or restrictive chronic pulmonary disease.

We considered as fever a corporal temperature higher than 37.8 °C. To measure respiratory function failure, we used gasometrical data and considered acute respiratory failure an oxygen pressure (pO<sub>2</sub>) under 60 mmHg.

We divided the radiological patterns in six categories: radiography not performed, normal radiography, bronco-vascular web enhancement, presence of infiltrates, interstitial involvement and pleural effusion.

For laboratory values, we considered the first blood extraction performed in emergency department in patients admitted with the diagnosis on influenza infection and the first blood extraction after the beginning of influenza symptoms in patients considered as nosocomial cases.

We also divided the cases into two groups, respectively, depending on the presence or absence of the following characteristics: leukopenia (<4500/μl), neutropenia (<1500/μl), lymphopenia (<700/μl) and general blood count abnormalities (presence of at least one blood count abnormality).

We defined anemia as hemoglobin concentration lower than 12 g/dl. Regarding liver enzymes, we considered as upper limit of normality the value of 45 UI/l for glutamate-oxalacetate aminotransferase (GOT) and glutamate-pyruvate aminotransferase (GPT). We considered as upper limit of normality 45 UI/l for alkaline phosphatase (AP) and 150 UI/l for gamma glutamil transpherase (GGT).

Nosocomial transmission was considered in those patients whom the infection symptoms started more than 48 h after admission for any other cause, an infection that occurred in less than 72 h before being discharged or an infection in patients who lived in nursing homes and other institutions. We considered as cases with clinical suspicion if the diagnostic hypotheses of influenza infection had been coded in the hospital admission request and as unsuspected if not. In nosocomial cases the clinical suspicion was established since the appearance of influenza infection symptoms.

**Table 1**  
Baseline characteristics.

| Baseline characteristics, n = 258 (%) | Gender                |                     | Total      |
|---------------------------------------|-----------------------|---------------------|------------|
|                                       | Women, n = 126 (48.8) | Men, n = 132 (51.1) |            |
| Age:                                  |                       |                     |            |
| Average                               | 63.29                 | 65.87               | 64.55      |
| <60 years old                         | 34.9 (34.9)           | 49 (37.1)           | 93 (36)    |
| Barthel (<20):                        | 14 (11.1)             | 9 (6.8)             | 23 (8.9)   |
| Risk factors:                         |                       |                     |            |
| Obesity                               | 53 (42.1)             | 46 (34.8)           | 99 (38.4)  |
| Tobacco abuse                         | 22 (17.5)             | 59 (44.7)           | 81 (31.4)  |
| HT                                    | 64 (50.8)             | 60 (45.5)           | 124 (48.1) |
| DLP                                   | 57 (45.2)             | 52 (39.4)           | 109 (42.2) |
| Comorbidities:                        |                       |                     |            |
| Diabetes mellitus                     | 27 (21.4)             | 26 (19.7)           | 53 (20.5)  |
| CHF                                   | 26 (20.6)             | 25 (18.9)           | 51 (19.8)  |
| CPD                                   | 35 (27.8)             | 48 (36.4)           | 83 (32.2)  |
| Chronic renal failure                 | 12 (9.5)              | 10 (7.6)            | 22 (8.5)   |
| Chronic liver disease                 | 4 (3.2)               | 14 (10.6)           | 18 (7)     |

HT: hypertension; DLP: dyslipidaemia; CHF: chronic heart failure; CPD: chronic pulmonary disease.

**Table 2**  
Analytical abnormalities.

| n = 258                  | Leukopenia (<4500/ $\mu$ l) |             |        | Neutropenia (<1500/ $\mu$ l) |             |       | Liver enzymes alteration<br>(GOT/GOTref > 1.1)<br>to (GPT/GPTref > 1.1) |              |       |
|--------------------------|-----------------------------|-------------|--------|------------------------------|-------------|-------|-------------------------------------------------------------------------|--------------|-------|
|                          | No, n = 183                 | Yes, n = 75 | P      | No, n = 231                  | Yes, n = 27 | P     | No, n = 103                                                             | Yes, n = 155 | P     |
| Age (<60 years)          | 52 (28.4)                   | 41 (54.7)   | <0.001 | 110 (47.6)                   | 16 (59.3)   | 0.002 | 35 (34.0)                                                               | 58 (37.4)    | NS    |
| Gender (male)            | 93 (50.8)                   | 39 (52.0)   | NS     | 121 (52.4)                   | 11 (40.7)   | NS    | 41 (39.8)                                                               | 91 (58.7)    | 0.003 |
| Smoker (or former)       | 60 (32.8)                   | 21 (28.0)   | NS     | 76 (32.9)                    | 5 (18.5)    | NS    | 25 (24.3)                                                               | 56 (36.1)    | 0.044 |
| CLD                      | 7 (3.8)                     | 11 (14.7)   | 0.002  | 14 (6.1)                     | 4 (14.8)    | NS    | 8 (7.8)                                                                 | 10 (6.5)     | NS    |
| Liver enzymes alteration | 100 (54.6)                  | 55 (73.3)   | 0.005  | 138 (59.7)                   | 17 (63.0)   | 0.013 |                                                                         |              |       |
| Leukopenia               |                             |             |        |                              |             |       | 20 (19.4)                                                               | 55 (35.5)    | 0.005 |

CLD: chronic liver disease; NS: no significant.

All patients were tested for viral respiratory infections, which included influenza A, influenza B and respiratory syncytial virus (RSV). All positive cases in microbiological rapid influenza diagnostic test (RIDT) were confirmed by polymerase chain reaction (PCR). According to these tests, patients were classified in 4 groups: influenza A, influenza B, co-infection AB and indeterminate. We considered as prolonged length of hospital stay if it exceeded 5 days, since reference value in our hospital for mean hospital stay in uncomplicated respiratory tract infections. All patients deceased during their hospitalization were included as in-hospital mortality.

A descriptive analysis was performed, by calculating qualitative variable rates plus mean and standard deviation. We conducted a univariate analysis to identify factors associated with blood count abnormalities, liver enzymes alterations, virus influenza strains and age ranges as well as to compare the distribution of the different variables in relation to different prognostic factors (ICU, length of hospital stay and death). We used the Chi-square test or Fisher's exact test, as appropriate (expected frequency value <5), to compare qualitative variables, always considering a *P*-value <0.05 for statistical significance. A multivariate logistic regression analysis was conducted to identify factors associated with prognosis variables, including all variables with *P*<0.1 in univariate analysis. All analyses were performed using the SPSS v. 22.0 software package (SPSS Inc., Chicago, IL, USA).

## Results

A total of 258 patients were included, 51.1% were men and mean age was 64.5 years (standard deviation [SD]=16.7). The main comorbidity conditions were chronic pulmonary disease and

diabetes mellitus. One third of patients were active or former smokers. There were 25 cases (10.1%) of nosocomial infection. The rest of baseline characteristics are shown in [Table 1](#).

### Analytical abnormalities

We found alterations in blood count in 163 (63.2%) patients, being the most frequent abnormality the presence of lymphopenia (131 patients). In the case of liver enzymes, we found alterations in 155 (60.1%) patients, with a predominance of cholestasis pattern (141 patients).

Liver enzymes alterations were more frequent in men, smokers or former smokers and non-A cases. Regarding blood count alterations, they were also more frequent in men and the only association with previous comorbidities was the higher frequency of leukopenia in patients with chronic liver disease. The complete analysis is detailed in [Table 2](#).

### Virus strain

The most frequent strain was influenza A H1N1 with more than 81.8% of the cases. A total of 44 patients (17.2%) were non-influenza A infected ones. Although not statistically significant, non-A infection was clinically significantly higher than A infection in patients older than 60 and men. Moreover, we saw that non-A infection had more analytical abnormalities, especially for neutropenia and hepatic biochemistry without achieving statistical significance. The complete comparative analysis between A and non-A infection is shown in [Table 3](#). All patients showed negative tests for RSV.

**Table 3**  
Factors linked to Influenza A strain.

| Univariate analysis, n = 258      | Influenza A |              |       |
|-----------------------------------|-------------|--------------|-------|
|                                   | No, n = 47  | Yes, n = 211 | P     |
| Age (>60)                         | 34 (72.3)   | 131 (62.1)   | NS    |
| Gender (male)                     | 28 (59.6)   | 104 (49.3)   | NS    |
| Barthel (<20)                     | 6 (12.8)    | 17 (8.1)     | NS    |
| <b>Risk factors</b>               |             |              |       |
| Obesity                           | 20 (42.6)   | 79 (37.4)    | NS    |
| Tobacco                           | 16 (34)     | 65 (30.8)    | NS    |
| HT                                | 25 (53.2)   | 99 (46.9)    | NS    |
| DLP                               | 21 (44.7)   | 88 (41.7)    | NS    |
| <b>Comorbidities</b>              |             |              |       |
| Diabetes                          | 9 (19.1)    | 44 (20.9)    | NS    |
| Heart failure                     | 15 (31.9)   | 36 (17.1)    | 0.021 |
| Chronic pulmonary                 | 14 (29.8)   | 69 (32.7)    | NS    |
| Renal failure                     | 4 (8.5)     | 18 (8.5)     | NS    |
| Chronic liver disease             | 3 (6.4)     | 15 (7.1)     | NS    |
| <b>Clinical features</b>          |             |              |       |
| Fever                             | 26 (55.3)   | 141 (66.8)   | NS    |
| Respiratory failure               | 31 (67.4)   | 139 (68.8)   | NS    |
| Rx infiltrates                    | 11 (23.4)   | 66 (31.3)    | NS    |
| <b>Analytical features:</b>       |             |              |       |
| Blood count                       | 35 (74.5)   | 128 (60.7)   | NS    |
| Leukopenia                        | 17 (36.2)   | 58 (27.5)    | NS    |
| Neutropenia                       | 8 (17)      | 19 (9)       | NS    |
| Lymphopenia                       | 24 (51.1)   | 107 (50.7)   | NS    |
| Liver enzymes                     | 33 (70.2)   | 122 (57.8)   | NS    |
| <b>Prognosis</b>                  |             |              |       |
| ICU admission                     | 7 (14.9)    | 15 (7.1)     | NS    |
| Death                             | 6 (12.8)    | 15 (7.1)     | NS    |
| Death cause (respiratory failure) | 3 (6.0)     | 10 (4.7)     | NS    |
| <b>Other features:</b>            |             |              |       |
| Vaccine                           | 19 (40.4)   | 61 (29)      | NS    |
| No initial suspicion              | 5 (10.6)    | 29 (13.7)    | NS    |
| Nosocomial                        | 4 (8.5)     | 22 (10.4)    | NS    |
| Admission days (>5)               | 18 (38.4)   | 97 (46)      | NS    |
| Symptoms days (>5)                | 40 (85.1)   | 184 (87.2)   | NS    |

HT: hypertension; DLP: dyslipidaemia; NS: no significant.

### Prognostic variables

A total of 22 patients were admitted to the ICU and 20 died during hospital stay in our series. Among the causes of death, respiratory failure was responsible of 68% of them. 224 patients (86.8%) required more than 5 days of hospital stay.

The main factors linked to ICU admission were previous antibiotic treatment, no initial clinical suspicion of influenza, the presence of infiltrates in chest radiography, liver enzymes alterations and the presence of anemia. If we focus on mortality, the univariate analysis showed association with Barthel's index <20 points, the presence of infiltrates in chest radiography, no initial suspicion of influenza, nosocomial acquisition, a higher age, lymphopenia and liver enzymes alterations. Regarding a length of hospital stay over 5 days, the following variables reached statistical significance after univariate analysis: previous chronic heart failure, the presence of infiltrates in chest radiography, concomitant antibiotic treatment during admission and liver enzymes alterations (Table 4).

We performed a multivariable logistic regression analysis that showed an association between ICU admission and the presence of infiltrates in chest radiography (OR=4.1, IC 95% 1.55–10.87;  $P=0.004$ ), previous antibiotic treatment (OR=5.84, IC 95% 1.32–25.69;  $P=0.020$ ), anemia (OR=7.29, IC 95% 1.38–38.41;  $P=0.019$ ) and no initial suspicion of influenza (OR=8.07, IC 95% 1.48–43.89;  $P=0.016$ ). We also found an association between mortality and age (OR=1.04, IC 95% 1.01–1.09;  $P=0.026$ ), the

presence of infiltrates in chest radiography (OR=2.19, IC 95% 1.26–3.81;  $P=0.005$ ) and no initial suspicion of influenza (OR=5.43, IC 95% 1.60–18.47;  $P=0.007$ ). Finally, our analysis showed that the variables linked to a length of hospital stay over 5 days were concomitant antibiotic treatment during admission (OR=14.36, IC 95% 2.23–92.35;  $P=0.005$ ) and liver enzymes alterations (OR=3.01, IC 95% 1.26–7.12;  $P=0.013$ ).

### Discussion

We conducted a cross-sectional retrospective analysis which showed the association of some relevant variables with a poorer prognosis in patients diagnosed with influenza infection. The presence on infiltrates in chest radiography, an early clinical suspicion and concomitant antibiotic treatment during admission seem to be the more useful variables to identify high-risk patients, although the presence of laboratory values variations, like liver enzymes alterations, could have a capital role in the detection of these patients and help physicians to make decisions.

### Descriptive results

#### Baseline characteristics

The representative patient in our study was a male, older than 60 years with multiple comorbidities, among which the most frequent were hypertension, obesity and chronic lung disease. Cheng et al.,<sup>12</sup> Sharma et al.<sup>13</sup> and Cheng et al.<sup>14</sup> showed a lower percentage of patients over 60, which could be explained at least in part by the inclusion of pediatric and juvenile patients. By gender, influenza was more frequent in males with higher differences than ours. Another one report by Albarran-Sanchez et al.<sup>15</sup> showed a greater proportion of women. The Report on Surveillance of Influenza in Spain<sup>16</sup> showed an average age 7 years lower than ours in their series with 20% less patients over 60 years old. Regarding age, it is necessary to consider that Galicia is an aging community compared with other regions within Spain and Europe.<sup>17</sup>

#### Virus strain

In the reviewed studies, Influenza A was always more frequent than Influenza B. Cheng et al.<sup>12</sup> showed that the AH3N2 strain was the most foreseeable one, while Sharma et al.<sup>13</sup> demonstrated that the most frequent AH1N1 was pdm09. According to the national registry,<sup>16</sup> in Spain a total of 80% of the confirmed cases of influenza were due to subtype AH1N1 pdm09 with a total of 15% cases of influenza B. The results of our study were consistent with the figures provided by the national registry for that year.

#### Form of presentation

**Clinical features.** In our study, the most frequent clinical features were fever and respiratory failure affecting more than 50% of patients respectively, although it should be mentioned that up to 35% of patients had been pauci-symptomatic. These results contrast with those obtained by other authors like Tabarsi et al.,<sup>17</sup> Iorio et al.,<sup>18</sup> Rovina et al.<sup>19</sup> and Chawla et al.,<sup>20</sup> in which the percentage of febrile syndrome was significantly higher and the presence of respiratory insufficiency was lower. These dissensions could be due to the fact that the samples used in these studies were composed of a younger population with lower comorbidities. It is also remarkable that in elderly patients with multiple comorbidities, the typical manifestations of an infectious disease such as fever or cough appear less frequently.<sup>21,22</sup>

**Radiological pattern.** The most frequent radiological pattern was the bronco-vascular web enhancement. If we compare the results with the literature, Shi et al.,<sup>23</sup> Iorio et al.<sup>18</sup> and Chawla et al.<sup>20</sup> found that the dominant pattern was the presence of pulmonary

**Table 4**

Factors linked to prolonged admission and mortality.

| Univariate analysis, n = 258 | >5 days admission |              |       | Dead        |             |        | ICU admission |             |        |
|------------------------------|-------------------|--------------|-------|-------------|-------------|--------|---------------|-------------|--------|
|                              | No, n = 34        | Yes, n = 224 | P     | No, n = 237 | Yes, n = 21 | P      | No, n = 236   | Yes, n = 22 | P      |
| Age (>60)                    | 18 (52.9)         | 147 (65.6)   | NS    | 147 (62)    | 18 (85.7)   | 0.030  | 152 (64.4)    | 13 (59.1)   | NS     |
| Gender (male)                | 13 (38.2)         | 119 (53.1)   | NS    | 123 (51.9)  | 9 (42.9)    | NS     | 118 (50)      | 14 (63.6)   | NS     |
| Barthel (<20)                | 1 (2.9)           | 22 (9.8)     | NS    | 19.8 (7.6)  | 5 (23.8)    | 0.012  | 21 (8.9)      | 2 (9.1)     | NS     |
| <b>Risk factors</b>          |                   |              |       |             |             |        |               |             |        |
| Obesity                      | 12 (35.3)         | 87 (38.8)    | NS    | 93 (39.2)   | 6 (28.6)    | NS     | 87 (36.9)     | 12 (54.5)   | NS     |
| Tobacco                      | 9 (26.5)          | 72 (32.1)    | NS    | 75 (31.6)   | 6 (28.6)    | NS     | 71 (30.1)     | 10 (45.5)   | NS     |
| HT                           | 14 (41.2)         | 110 (49.1)   | NS    | 112 (47.3)  | 12 (57.1)   | NS     | 114 (48.3)    | 10 (45.5)   | NS     |
| DLP                          | 15 (44.1)         | 94 (42)      | NS    | 102 (43)    | 7 (33.3)    | NS     | 101 (42.8)    | 8 (36.4)    | NS     |
| <b>Comorbidities</b>         |                   |              |       |             |             |        |               |             |        |
| Diabetes                     | 5 (14.7)          | 48 (21.4)    | NS    | 50 (21.1)   | 3 (14.3)    | NS     | 47 (19.9)     | 6 (27.3)    | NS     |
| Heart failure                | 2 (5.9)           | 49 (21.9)    | 0.029 | 44 (18.6)   | 7 (33.3)    | NS     | 48 (20.3)     | 3 (13.6)    | NS     |
| CPD                          | 12 (35.3)         | 71 (31.7)    | NS    | 76 (32.1)   | 7 (33.3)    | NS     | 76 (32.2)     | 7 (31.8)    | NS     |
| Renal failure                | 5 (14.7)          | 17 (7.6)     | NS    | 21 (8.9)    | 1 (4.8)     | NS     | 22 (9.3)      | 0 (0)       | NS     |
| CLD                          | 1 (2.9)           | 17 (7.6)     | NS    | 16 (6.8)    | 2 (9.5)     | NS     | 17 (7.2)      | 1 (4.5)     | NS     |
| <b>Clinical features</b>     |                   |              |       |             |             |        |               |             |        |
| Fever                        | 27 (79.4)         | 140 (62.5)   | NS    | 158 (66.7)  | 9 (42.9)    | <0.029 | 155 (65.7)    | 12 (54.5)   | NS     |
| RF                           | 18 (54.5)         | 152 (70.7)   | NS    | 152 (67)    | 18 (85.7)   | NS     | 151 (66.8)    | 19 (86.4)   | NS     |
| Rx infiltrates               | 5 (14.7)          | 72 (32.1)    | 0.019 | 69 (29.1)   | 8 (38.1)    | <0.001 | 63 (26.7)     | 14 (63.6)   | <0.001 |
| <b>Analytical features:</b>  |                   |              |       |             |             |        |               |             |        |
| Blood count                  | 17 (50)           | 146 (65.2)   | NS    | 146 (61.6)  | 17 (81)     | NS     | 146 (61.9)    | 17 (77.3)   | NS     |
| Anemia                       | 9 (26.5)          | 45 (21.5)    | NS    | 52 (21.9)   | 2 (33.3)    | NS     | 48 (20.8)     | 6 (50)      | 0.018  |
| Leukopenia                   | 7 (20.6)          | 68 (30.4)    | NS    | 68 (28.7)   | 7 (33.3)    | NS     | 66 (28)       | 9 (40.9)    | NS     |
| Neutropenia                  | 3 (8.8)           | 24 (10.7)    | NS    | 25 (10.5)   | 2 (9.5)     | NS     | 24 (10.2)     | 3 (13.6)    | NS     |
| Lymphopenia                  | 13 (38.2)         | 118 (52.7)   | NS    | 116 (48.9)  | 15 (71.4)   | 0.048  | 116 (49.2)    | 15 (68.2)   | NS     |
| Liver enzymes                | 12 (35.3)         | 143 (63.8)   | 0.002 | 138 (58.2)  | 17 (81)     | 0.042  | 134 (56.8)    | 21 (95.5)   | <0.001 |
| <b>Prognosis</b>             |                   |              |       |             |             |        |               |             |        |
| ICU admission                | 0 (0)             | 22 (9.8)     | NS    | 11 (4.6)    | 11 (52.4)   | <0.001 | 10 (4.2)      | 11 (50)     | <0.001 |
| Death                        | 1 (2.9)           | 20 (8.9)     | NS    |             |             |        | 6 (66.7)      | 7 (70)      | NS     |
| <b>Other features:</b>       |                   |              |       |             |             |        |               |             |        |
| PATB                         | 8 (23.5)          | 69 (30.9)    | NS    | 69 (29.2)   | 8 (38.1)    | NS     | 65 (27.7)     | 12 (54.5)   | 0.008  |
| ATB                          | 30 (88.2)         | 218 (97.3)   | 0.011 | 227 (95.8)  | 21 (100)    | NS     | 226 (95.8)    | 22 (100)    | NS     |
| Non-A strain                 | 7 (20.6)          | 40 (17.9)    | NS    | 41 (17.3)   | 6 (28.6)    | NS     | 40 (16.9)     | 7 (31.8)    | NS     |
| Vaccine                      | 6 (17.6)          | 74 (33.2)    | NS    | 73 (30.9)   | 7 (33.3)    | NS     | 74 (31.5)     | 6 (27.3)    | NS     |
| No suspicion                 | 3 (8.8)           | 31 (13.8)    | NS    | 25 (10.5)   | 9 (42.9)    | <0.001 | 25 (10.6)     | 9 (40.9)    | <0.001 |
| Nosocomial                   | 1 (2.9)           | 25 (11.2)    | NS    | 20 (8.4)    | 6 (28.6)    | NS     | 21 (8.9)      | 5 (22.7)    | NS     |
| <b>Stay &gt; 5 d</b>         |                   |              |       |             |             |        |               |             |        |
| Symptoms > 5 d               | 14 (41.2)         | 101 (45.1)   | NS    | 108 (45.6)  | 7 (33.3)    | NS     | 104 (44.1)    | 11 (50)     | NS     |

HT: hypertension; DLP: dyslipidaemia; NS: no significant; AB: antibiotic; CP: chronic pulmonary disease; ICU: intensive care unit; ATB: concomitant antibiotic treatment; PATB: previous antibiotic treatment; RF: respiratory failure; CLD: chronic liver disease; CPD: chronic pulmonary disease.

infiltrates. In our study there were a significant percentage of patients with some type of underlying lung disease that could at least partially justify the discrepancies.

**Liver enzymes alterations.** In our study, we observed liver enzymes alterations in more than a half of patients. Previous studies found fewer alterations of the hepatic profile, although they included younger and healthier patients. Yingying et al.<sup>24</sup> stated that a total of 58% of patients had one or more abnormalities in liver profile although the percentage of patients with elevated transaminases were lower than ours (GOT: 13%, GPT: 9%). Papic et al.<sup>25</sup> established a comparison between two groups of patients (Pandemic influenza AH1N1 and seasonal influenza) in terms of hepatic biochemistry and concluded the existence of greater alterations in the group of the pandemic AH1N1 infection, although the percentage of patients with liver enzymes alterations were lower than ours. Most studies, like the one by Zarogoulidis et al.<sup>26</sup> found a predominance of liver enzymes alterations in patients infected by AH1N1 strain. In this sense, it is necessary to emphasize the higher frequency of general biochemical alterations in our study and also the higher frequency of these alterations in non-A cases, differing from previous data.

### Mortality

In our study, the overall mortality rate reached 8.1%, with a total of 21 deaths, 85.7% of them in patients over 60 years old. These results are consistent with those found by other authors like Ramos et al.<sup>27</sup> and Lynfield et al.,<sup>28</sup> with mortality rates around 8%. Elderly patients (>60 years) had a higher mortality in the multivariate analysis, which is consistent with several previous studies such as Ramos et al.<sup>27</sup> (over 80 years old), Huang et al.<sup>29</sup> (over 50 years old) or Zhang et al.,<sup>30</sup> including multivariate analysis too.

We found that patients with higher grades of dependence had a worse prognosis in terms of mortality. There are lack of data regarding a possible relationship between Barthel's index and a worst prognosis in influenza infection, the only work we had found was a study published by Murcia et al.,<sup>31</sup> which described an association with a worse prognosis in terms of mortality but not specifically for influenza.

In our study, patients who presented with radiological infiltrates had higher mortality. The development of viral pneumonia or associated bacterial pneumonia, defined by radiological criteria, are factors previously linked to poorer prognosis in influenza infection.<sup>32,33</sup> In addition, we have observed studies that provide results consistent with ours, such as Maruyama et al.<sup>17,34</sup>

The initial non-suspicion of the condition usually leads to a diagnostic delay that, in our study, seemed to be linked to a poorer prognosis and greater mortality in the multivariate analysis. Other studies such as Álvarez-Lerma et al.<sup>35</sup> and Lynfield et al.<sup>28</sup> showed similar results.

#### ICU admission

Overall, our study had lower ICU admission rates (8.5% of patients) compared with other studies, despite the inclusion of a sample of patients predominantly over 60 years old and with multiple comorbidities. This could be due in part to the low percentage of cases with no initial suspicion (13%), which would lead to an early treatment as well as to the presence of a not insignificant group of very elderly patients, with many comorbidities and a poor baseline state, which would imply not meeting criteria for ICU admission.

As we said, some studies reported a 15% and 17% of patients admitted to the ICU respectively<sup>25,26</sup> and data from the national epidemiology center in Spain<sup>16</sup> showed a global percentage of 35%. Regarding the factors associated with ICU admission, the studies of Iorio et al.<sup>18</sup> and Tabarsi et al.<sup>17</sup> obtained similar results to ours.

We observed a relationship between the presence of anemia and ICU admission in univariate and multivariate analysis. The study by Lorio et al.<sup>18</sup> showed a greater presence of anemia in patients who were admitted to ICU, but without reaching statistical significance.

As for mortality, the presence of radiological infiltrates was a factor associated with ICU admission in a statistically significant way in our study. Other studies like Rovina et al.<sup>19</sup> showed results in the same line.

Our results point to an increase in ICU admission in patients with absence of initial suspicion. When reviewing the literature, we found some studies that support this finding<sup>35</sup> in which a comparison between early and late diagnosis was specifically established and patients with a diagnosis delay had a worse prognosis. Other studies referred to the time of delay at admission, with results that suggested that greater lapses of time in the diagnosis implied greater complications and admission to ICU.<sup>28,36</sup>

#### Length of stay

We found a length of stay with a median of 8 days and a total of 86.8% of patients. The studies by Ramos et al.<sup>27</sup> and Chawla et al.<sup>20</sup> referred about 10–11 days, whereas the study by Bernal et al.<sup>37</sup> showed a median of 6 days. Both the Papic et al.<sup>25</sup> and Al-Busaidi et al.<sup>38</sup> studies showed statistically significant results in the multivariate analysis for the association between alterations in liver enzymes, especially ALT, and the length of hospital stay, just like our study.

It is remarkable that, although it did not reach the statistical significance in the multivariable analysis, the presence of alterations in liver enzymes values was also linked to mortality and ICU admission in univariate analysis.

We consider that the main strengths of our work are the high number of patients included and the extremely low frequency of missing values, which reinforces the relevance of our findings. We also must recognize the potential limitations of a retrospective study, limited relevant data availability, the development in a single center and the only inclusion of inpatients.

In light of our findings, there could be several variables such as lymphopenia, liver enzymes alterations, chest radiography abnormalities, use or former use of antibiotic treatment or no initial suspicion of infection that could help to identify patients with a higher risk of death, ICU admission and prolonged length of stay. Further studies will be necessary to develop useful tools based on these data which could help physicians to identify and classify high-risk patients diagnosed with influenza infection.

## Conclusions

The presence of infiltrates in chest radiography, an early clinical suspicion and concomitant antibiotic treatment during admission could be useful to identify high-risk patients. The presence of laboratory values variations, mainly liver enzymes alterations, could have a capital role in the detection of these patients and help physicians to make decisions.

## Conflict of interest

The authors declare that they have no conflict of interest.

## References

- Bresee J, Hayden FG. Epidemic influenza – responding to the expected but unpredictable. *N Engl J Med*. 2013;368:589–92. <http://dx.doi.org/10.1056/NEJMp1300375>.
- Loeb M, Singh PK, Fox J, Russell ML, Pabbaraju K, Zarra D, et al. Longitudinal study of influenza molecular viral shedding in Hutterite communities. *J Infect Dis*. 2012;206:1078–84. <http://dx.doi.org/10.1093/infdis/jis450>.
- Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004;292:1333–40. <http://dx.doi.org/10.1001/jama.292.11.1333>.
- Pinna AD, Rakela J, Demetris AJ, Fung JJ. Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci*. 2002;47:750–4. <http://dx.doi.org/10.1023/a:1014779614525>.
- Miura H, Kawamura Y, Ozeki E, Ihira M, Ohashi M, Yoshikawa T. Pathogenesis of severe neutropenia in patients with primary human herpesvirus 6B infection. *Pediatr Infect Dis J*. 2015;34:1003–7. <http://dx.doi.org/10.1097/INF.0000000000000777>.
- WHO | International Classification of Diseases, 11th revision (ICD-11). WHO. <http://www.who.int/classifications/icd/en/> [accessed 06.11.19].
- Call SA, Vollenweider MA, Hornung CA, Simel DL, McKinney WP. Does this patient have influenza? *JAMA*. 2005;293:987–97. <http://dx.doi.org/10.1001/jama.293.8.987>.
- Govaert TM, Dinant GJ, Aretz K, Kottner JA. The predictive value of influenza symptomatology in elderly people. *Fam Pract*. 1998;15:16–22. <http://dx.doi.org/10.1093/fampra/15.1.16>.
- Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. Seasonal influenza in adults and children – diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48:1003–32. <http://dx.doi.org/10.1086/598513>.
- Red de comités de ética de la investigación – Agencia de Conocimiento en Salud. <https://acis.sergas.es/Paxinas/web.aspx?tipo=paxict&idTax=15534&idioma=es> [accessed 06.11.19].
- Collin C, Wade DT, Davies S, Horne V. The Barthel ADL index: a reliability study. *Int Disabil Stud*. 1988;10:61–3. <http://dx.doi.org/10.3109/09638288809164103>.
- Cheng W, Yu Z, Liu S, Zhang X, Wang X, Cai J, et al. Comparison of influenza epidemiological and virological characteristics between outpatients and inpatients in Zhejiang Province, China, March 2011–June 2015. *Int J Environ Res Public Health*. 2017;14. <http://dx.doi.org/10.3390/ijerph14020217>.
- Sharma P, Gupta S, Singh D, Verma S, Kanga A. Influenza A(H1N1)pdm09 cases in sub-Himalayan region, 2014–2015 India. *Indian J Pathol Microbiol*. 2016;59:63–5. <http://dx.doi.org/10.4103/0377-4929.178222>.
- Cheng AC, Holmes M, Senenayake S, Dwyer DE, Hewagama S, Korman T, et al. Influenza epidemiology in adults admitted to sentinel Australian hospitals in 2014: the Influenza Complications Alert Network (FluCAN). *Commun Dis Intell Q Rep*. 2015;39:E355–60.
- Albarrán-Sánchez A, Ramírez-Rentería C, Huerta-Montiel F, et al. Clinical features of patients with influenza-like illness who went to a third level center in the winter of 2013–2014. *Rev Med Inst Mex Seguro Soc*. 2017;54:162–7.
- Informe Vigilancia.GRIPE.2016–2017.v.28septiembre2017.pdf. [http://vgripe.isciii.es/documentos/20162017/InformesAnuales/Informe\\_Vigilancia.GRIPE.2016–2017.v.28septiembre2017.pdf](http://vgripe.isciii.es/documentos/20162017/InformesAnuales/Informe_Vigilancia.GRIPE.2016–2017.v.28septiembre2017.pdf) [accessed 06.11.19].
- Tabarsi P, Moradi A, Marjani M, Baghaei P, Hashemian SM, Nadjji SA, et al. Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection. *Ann Thorac Med*. 2011;6:91. <http://dx.doi.org/10.4103/1817-1737.78429>.
- Iorio AM, Camilloni B, Basileo M, Monaldi L, Lepri E, Neri M, et al. An observational retrospective study provide information on hospitalization and severe outcomes of the 2009 A(H1N1) infection in Italy. *J Clin Med Res*. 2013;5:286–93. <http://dx.doi.org/10.4021/jocmr883w>.
- Rovina N, Erifaki M, Katsaounou P, Lyxi G, Koutsoukou A, Koulouris NG, et al. Subjects hospitalized with the 2009 pandemic influenza A (H1N1) virus in a respiratory infection unit: clinical factors correlating with ICU admission. *Respir Care*. 2014;59:1560–8. <http://dx.doi.org/10.4187/respcare.03049>.
- Chawla R, Kansal R, Chauhan M, Jain A, Jibhake BN. Predictors of mortality and length of stay in hospitalized cases of 2009 influenza A (H1N1):

- experiences of a tertiary care center. *Indian J Crit Care Med.* 2013;17:275–82, <http://dx.doi.org/10.4103/0972-5229.120318>.
21. Berman P, Hogan DB, Fox RA. The atypical presentation of infection in old age. *Age Age.* 1987;16:201–7, <http://dx.doi.org/10.1093/ageing/16.4.201>.
  22. Lam PP, Coleman BL, Green K, Powis J, Richardson D, Katz K, et al. Predictors of influenza among older adults in the emergency department. *BMC Infect Dis.* 2016;16:615, <http://dx.doi.org/10.1186/s12879-016-1966-4>.
  23. Shi SJ, Li H, Liu M, Liu YM, Zhou F, Liu B, et al. Mortality prediction to hospitalized patients with influenza pneumonia: PO<sub>2</sub>/FiO<sub>2</sub> combined lymphocyte count is the answer. *Clin Respir J.* 2017;11:352–60, <http://dx.doi.org/10.1111/crj.12346>.
  24. Yingying C. Abnormal liver chemistry in patients with influenza A H1N1. *Liver Int.* 2011;31:902, <http://dx.doi.org/10.1111/j.1478-3231.2011.02519.x>.
  25. Papic N, Pangercic A, Vargovic M, Barsic B, Vince A, Kuzman I. Liver involvement during influenza infection: perspective on the 2009 influenza pandemic. *Influenza Other Respir Viruses.* 2012;6:e2–5, <http://dx.doi.org/10.1111/j.1750-2659.2011.00287.x>.
  26. Zarogoulidis P, Constantinidis T, Steiropoulos P, Papanas N, Zarogoulidis K, Maltezos E. Are there any differences in clinical and laboratory findings on admission between H1N1 positive and negative patients with flu-like symptoms? *BMC Res Notes.* 2011;4:4, <http://dx.doi.org/10.1186/1756-0500-4-4>.
  27. Ramos JM, García-Navarro MM, González de la Aleja MP, Sánchez-Martínez R, Gimeno-Gascón A, Reus S, et al. Seasonal influenza in octogenarians and nonagenarians admitted to a general hospital: epidemiology, clinical presentation and prognostic factors. *Rev Esp Quimioter.* 2016;29:296–301.
  28. Lynfield R, Davey R, Dwyer DE, Losso MH, Wentworth D, Cozzi-Lepri A, et al. Outcomes of influenza A(H1N1)pdm09 virus infection: results from two international cohort studies. *PLoS ONE.* 2014;9:e101785, <http://dx.doi.org/10.1371/journal.pone.0101785>.
  29. Huang WT, Chang CH, Hsu YF, Chuang JH. Prognostic factors for mortality in patients hospitalized with influenza complications, in Taiwan. *Int Health.* 2015;7:73–5, <http://dx.doi.org/10.1093/inthealth/ihu083>.
  30. Weng G, Han S, Pu R, Pan WH, Shi L. Risk factors for adult death due to 2009 pandemic influenza A (H1N1) virus infection: a 2151 severe and critical cases analysis. *Chin Med J.* 2013;126:2222–8.
  31. Murcia J, Llorens P, Sánchez-Payá J, Reus S, Boix V, Merino E, et al. Functional status determined by Barthel Index predicts community acquired pneumonia mortality in general population. *J Infect.* 2010;61:458–64, <http://dx.doi.org/10.1016/j.jinf.2010.08.006>.
  32. Viral pneumonia. UF Health, University of Florida Health; 2012. <https://ufhealth.org/viral-pneumonia> [accessed 06.11.19].
  33. Márquez MG, Castro MS, de Villagómez AJ, et al. Neumonía grave por virus AH1N1: revisión de la bibliografía a propósito de un caso. *Actualidades. Med Int Mex.* 2010;26:516–23.
  34. Maruyama T, Fujisawa T, Suga S, Nakamura H, Nagao M, Taniguchi K, et al. Outcomes and prognostic features of patients with influenza requiring hospitalization and receiving early antiviral therapy: a prospective multicenter cohort study. *Chest.* 2016;149:526–34, <http://dx.doi.org/10.1378/chest.14-2768>.
  35. Álvarez-Lerma F, Marín-Corral J, Vila C, Masclans JR, González de Molina FJ, Martín Loeches I, et al. Delay in diagnosis of influenza A (H1N1)pdm09 virus infection in critically ill patients and impact on clinical outcome. *Crit Care.* 2016;20:337, <http://dx.doi.org/10.1186/s13054-016-1512-1>.
  36. Jiang H, Yu D, Ruan F, et al. [Clinical characteristics of adult influenza inpatients in ten provinces in China and analysis of severe risk factors]. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2015;36:216–21.
  37. Bernal E, Muñoz A, Cano A. [Factor associated with prolonged hospital stay in patients with H1N1 virus influenza]. *Arch Bronconeumol.* 2010;46:660–1, <http://dx.doi.org/10.1016/j.arbres.2010.06.010>.
  38. Al-Busaidi M, Al Maamari K, Al'Adawi B, Ba Alawi F, Al-Wahaibi A, Belkhair A. Pandemic Influenza A H1N1 in Oman: epidemiology clinical features, and outcome of patients admitted to Sultan Qaboos University Hospital in 2009. *Oman Med J.* 2016;31:290–7, <http://dx.doi.org/10.5001/omj.2016.56>.