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Original Article

Clinical features, complications and mortality in critically ill patients with 2009 influenza A(H1N1) in Sfax,Tunisia

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Purpose Africa, as the rest of the world, was touched by the 2009 pandemic influenza A(H1N1). In the literature, a few publications covering this subject emerged from this continent. We prospectively describe baseline characteristics, treatment and outcomes of consecutive critically ill patients with confirmed 2009 influenza A(H1N1) in the intensive care unit (ICU) of Sfax hospital.

Methods From 29 November 2009 through 21 January 2010, 32 patients with confirmed 2009 influenza A(H1N1) were admitted to our ICU. We prospectively analysed data and outcomes of these patients and compared survivors and dead patients to identify any predictors of death.

Results Patients were young (mean, 36·1 [SD], 20·7 years) and 21 (65·6%) of whom had co-morbidities. During ICU care, 29 (90·6%) patients had respiratory failure; among these, 15 (46·9%) patients required invasive ventilation with a median duration of 9 (IQR 3–12) days. In our experience, respiratory dysfunction can remain isolated but may also be associated with other dysfunctions or complications, such as, septic shock, seizures, myasthenia gravis exacerbation, Guillan–Barre syndrome, acute renal failure, nosocomial infections and biological disturbances. The nine patients (28·1%) who died had greater initial severity of illness (SAPS II and sequential organ failure assessment (SOFA) scores) but also a higher SOFA score and increasing severity of organ dysfunction during their ICU evolution.

Conclusion Critical illness from the 2009 influenza A(H1N1) in Sfax occurred in young individuals and was associated with severe acute respiratory and additional organ system failure. SAPS II and SOFA scores at ICU admission, and also during evolution, constitute a good predictor of death.

Keywords 2009 influenza A(H1N1), intensive care, multiple organ failure, outcome, SOFA.

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Introduction

The 2009 pandemic influenza A(H1N1) emerged in March 2009, and it quickly spread worldwide in the subsequent months.[1,2] On 7 May 2010, more than 214 countries and overseas territories or communities had reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18 000 deaths.[3]

There were some reports that dealt with the clinical picture, pathogenesis and treatment of critically ill patients with confirmed 2009 influenza A(H1N1). The risk of influenza complications is believed to be higher in certain populations, and some patients developed severe complications requiring intensive care unit (ICU) admission. Mortality was also associated with pandemic A(H1N1) 2009 influenza which had been reported with variable completeness worldwide[4] and in particular subgroups, including patients in intensive care,[1,5,6] pregnant women[7] and children.[8] To our knowledge, there have been no publications from Tunisia relating to this subject. We conducted this study to describe clinical features and complications of the 2009 influenza A(H1N1) and to elucidate possible predictors for poor prognosis for those affected who became critically ill.

Methods

Study design

We prospectively collected and analysed observations of all critically ill patients with confirmed 2009 influenza A(H1N1) admitted between 29 November 2009 (the first case) and 21 January 2010 (the last case), in the intensive care unit of Habib Bourguiba hospital (22 beds).

Case definition

Cases of 2009 H1N1 influenza were confirmed by testing nasal aspirates or combined nasal and throat swabs with

the use of a real-time reverse transcriptase–polymerase chain reaction (RT–PCR) assay at the Tunisian National Laboratory. According to their evolutions in the ICU, eligible patients were subdivided into the survivor and the non-survivor groups.

Data collection and analysis

Eligible patients included all adults and paediatric critically ill cases with confirmed 2009 H1N1 influenza. Data collection included patients' characteristics, presence of pre-existing medical conditions, initial symptoms and signs, laboratory and radiographic findings at admission, time course of the acute illness, treatment modalities, complications during hospitalization, and discharges status. The severity of the illness was assessed by the simplified acute physiology score (SAPS II)[9] for adults and by the paediatric risk of mortality (PRISM)[10] for children. Sequential organ failure assessment (SOFA) scores[11] were performed at ICU admission, on days 3 and 7 and (for non-survivors) on day of death. We also calculated the outcome variables including duration of mechanical ventilation, ICU and hospital length of stay, ICU mortality and hospital mortality. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared: $18{\cdot}5 \leq \text{BMI} < 25$ is normal, $25 \leq \text{BMI} < 30$ is overweight; $\text{BMI} \geq 30$ kg/m^2 in adults, BMI percentile above 95th percentile in children older than 2 years old and body weight above 95th percentile on a development curve in children <2 years old were defined as obese. PaO_2/FiO_2 ratio (PaO_2: partial O_2 pressure; FiO_2: fraction of inspired O_2) was calculated. Acute respiratory distress syndrome (ARDS) was defined as having $PaO_2/FiO_2 < 200$ accompanied by acute and diffuse pulmonary infiltrates but without evidence of left heart failure,[12] When $200 \leq PaO_2/FiO_2 < 300$, we defined the case as an Acute Lung Injury (ALI). (FiO_2 for patients in spontaneous ventilation was calculated by $[(VO_2 \times 4) + 21\%)]$.[13] Acute kidney injury was defined as a serum creatinine level greater than 110 μm and/or a serum urea level greater than 8·5 mm. Liver function abnormality was identified if the increase in aspartate amino transferase was more than twofold of normal upper limit. Myocardial dysfunction was defined as having symptoms or/and electrocardiographic or/and enzymatic or/and echocardiographic evidence of heart failure. At admission, we systematically performed, in all cases, bacterial cultures of blood, urine and sputum and serology of atypical respiratory pathogens, such as, mycoplasma pneumoniae, chlamydia psittacii, chlamydia pneumoniae and legionella pneumophila. We repeated bacterial cultures of blood and/or urine and/or sputum each time when the patients developed signs of infection. A scoring system was used to identify the presence of disseminated intravascular coagulation (DIC).[14] Multiple organ failure (MOF) is defined as a SOFA score of ≥4 with involvement of ≥2 organ systems.[11,15] At admission, we systematically prescribed neuraminidase inhibiters (oseltamivir or zanamivir) (for the patients who had not previously received it) to all patients admitted for A(H1N1) 2009 influenza suspicion. Antivirals were discontinued if the RT–PCR returned negative; If not (RT–PCR positive), they would be maintained for 10 days. We also systematically prescribed antibiotics to treat possible co-infections (cefotaxime + spiramycine) which were also stopped if the bacterial culture and serological reaction were reported negative. Finally, we must announce that all pregnant women in our series had a gestational term above 5 months with low risk to the developing foetus following ionizing radiation.[16] Moreover, in our practice for pregnant women, a lead shielding was used to protect the abdominal area before performing chest radiographs. This measure seems to be the easier method to reduce radiation exposure.[16]

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science (version 13.0; SPSS, Chicago, IL, USA). Descriptive data are presented as frequencies (percentages) for discrete variables and as means (SDs) or medians interquartile ranges [IQRs] for continuous variables. We compared all variables in patients who survived or who died. Fisher's exact test was utilized to compare categorical variables if any cell was <5; otherwise, the chi-square test was used; Mann–Whitney *U* test was used to test continuous variables. A two-sided *P*-value of <0·05 was considered statistically significant. We also performed odds ratios and 95% confidence intervals to determine the predictors of death in patients with 2009 H1N1 Influenza. The receiver operating characteristics (ROC) curve was performed – as the layout of the values of the sensitivity according to 1-Sp- to evaluate the performance of SOFA score to predict mortality by comparing the area under the ROC curve (AUC) for SOFA score and number of organs failure (according to SOFA score) at admission, day 3 and 7.

Results

Characteristics of study patients

During this period, 32 patients with confirmed 2009 influenza A(H1N1) were admitted in our ICU and they were all included. None of them had been vaccinated for seasonal or for 2009 A(H1N1) influenza. The mean age was 36·1 (SD, 20·7) years (minimum 4 and maximum 72 years) (Figure 1). Fourteen (43·7%) were women. Seven (21·9%) children [mean age of 8·1 (SD, 3) years] were admitted with median PRISM scores of 3 (IQR, 0–7). In adult cases [25 patients (78·1%)], the mean age was 43·9 (SD, 16·1) and median SAPS II score was 22 (IQR, 11·5–40·5). Only

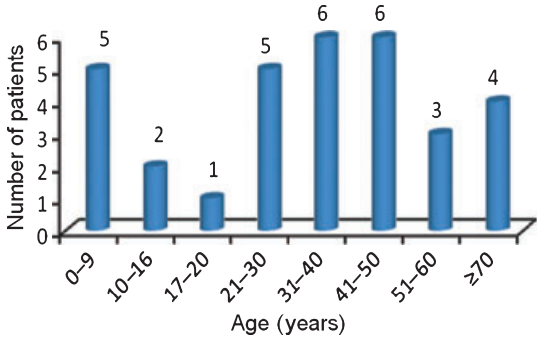

Figure 1. Age (per years) distribution of patients with the 2009 A(H1N1) influenza Infection.

21 (65·6%) patients had co-morbid conditions. Pregnant women represented 9·4% (three cases). The mean body mass index [BMI] was at 23·8 (SD, 4·8); 13 patients (40·6%) had an overweight; 2 (6·2%) were morbidly obese (Table 1). All patients had initial symptoms including fever in 32 (100%), cough in 23 (71·9%), rhinorrhea in 6 (18·8%), generalized weakness in 9 (28·1%), myalgias in 9 (28·1%), arthralgia in 8 (25%), headache in 12 (37·5%), gastrointestinal symptoms, nausea and vomiting in 3 (9·4%) and diarrhoea in 2 (6·3%). Patients developed first symptoms at a median of 4 (IQR, 2–5) days prior to hospitalization and a median of 5 (IQR 3–7) days prior to ICU admission (Figure 2). The median time from hospitalization to ICU admission was 1 (IQR, 0–2) day.

Course of illness and received treatments

Respiratory features

Seven patients (21·9%) were ventilated just before ICU admission. On the first day in ICU, 25 (78·1%) patients were in spontaneous ventilation. Among them, 22 (88%) had polypnea, 9 (36%) had dyspnoea with fight signs and only 2 (8%) had cyanosis (Table 2). X-ray was normal in 2 (6·2%) patients and showed bilateral interstitial abnormality in 3 (9·4%), bilateral alveolo-interstitial abnormality in 18 (56·32%), bilateral alveolar abnormality in 5 (15·6%) and unilateral alveolar abnormality in 4 (12·5%).

Oxygen therapy was sufficient in 14 (43·7%) patients. Eighteen (56·3%) patients had required ventilation; it was invasive in 15 (46·9%) and non-invasive in 3 (9·4%). Median time between ICU admission and invasive mechanical ventilation was 0 day (IQR, 0–1) and between first symptoms and invasive mechanical ventilation was 6 (IQR, 3–8). The median of duration of invasive mechanical ventilation was 9 (IQR, 3–12) days. During their ICU hospitalization, 11 patients (34·4%) developed ALI and 21 (65·6%) developed ARDS. One patient developed pulmonary fibrosis (confirmed with CT imaging) complicated with pneumothorax.

Table 1. Characteristics of patients with confirmed 2009 A(H1N1) influenza infection

Characteristics	(*N* = 32)
Age (year), Mean (SD)	36·1 (20·7)
Paediatric cases, (N°)(%)	7 (21·9)
Female sex, N° (%)	14 (43·7)
SAPS II, Median (IQR)	22 (11·5–40·5)
PRISM, Median (IQR)	3 (0–7)
BMI, Mean (SD)	23·8 (4·8)
Overweight, N° (%)	13 (40·6)
Obesity, N° (%)	2 (6·2)
Pregnancy, N° (%)	3 (9·4)
Co-morbidities, N° (%)	21 (65·6)
Smoker, N° (%)	5 (15·6)
Diabetes (type 1 or 2), N° (%)	4 (1·5)
Chronic renal insufficiency, N° (%)	3 (9·4)
Cardio-vascular co-morbidity, N° (%)	9 (28·1)
Systemic arterial hypertension N° (%)	6 (18·8)
Ischaemic heart disease, N° (%)	1 (3·1)
Arrhythmia, N° (%)	1 (3·1)
Interauricular communication, N° (%)	1 (3·1)
Pulmonary co-morbidity, N° (%)	9 (28·1)
Restrictive respiratory syndrome, N° (%)	2 (6·3)
Restrictive and obstructive respiratory syndrome, N° (%)	1 (3·1)
Obstructive respiratory syndrome, N° (%)	6 (18·8)
Chronic obstructive pulmonary disease (COPD), N° (%)	2 (6·3)
Asthma, N° (%)	3 (9·4)
Bronchiectasis, N° (%)	2 (6·3)
Pulmonary emphysema, N° (%)	1 (3·1)
Neurologicals or neuro-musculars co-morbidity, N° (%)	6 (18·8)
Epilepsy, N° (%)	2 (6·3)
Ischaemic stroke, N° (%)	1 (3·1)
Cerebral palsy N° (%)	2 (6·3)
Scoliosis, N° (%)	2 (6·3)
Myasthenia, N° (%)	1 (3·1)

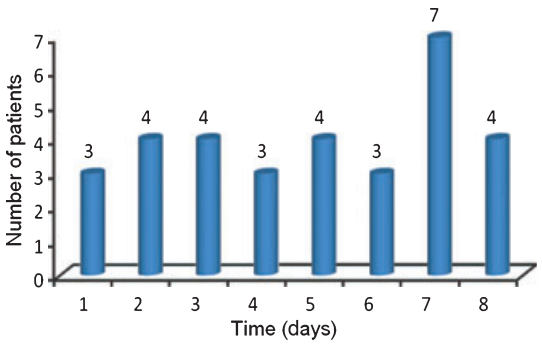

Figure 2. Time (per day) between the first symptoms and the ICU admission.

Table 2. Ventilation and gazometric parameters in patients with confirmed 2009 A(H1N1) influenza infection

Characteristics	Admission (*N* = 32)	Day 3 (*N* = 28)	Day 7 (*N* = 15)	Death day (*N* = 9)
Bilateral crackles	26 (81·2)	22 (78·6)	10 (66·7)	8 (88·9)
Spontaneous ventilation N° (%)	25 (78·1)	15 (53·6)	6 (40)	0
Polypnea, N° (%)	22 (68·8)	12 (80)	4 (66·7)	–
VO_2 (l/min), Median (IQR)	6 (6–8)	4 (2–4)	4 (2·75–6)	–
FIO_2 (%), Median (IQR)	45 (45–53)	37 (29–37)	37 (32–45)	–
SpO_2 (%), Median (IQR)	94 (92–98)	97 (94–98)	97·5 (95·5–98)	–
PaO_2 (mmHg), Median (IQR)	86 (69·5–135·5)	87 (79–113)	104 (77–127·5)	–
PaO_2/FIO_2, Median (IQR)	204 (153–309)	283 (230–400)	254 (240–300)	–
$PaO_2/FIO_2 < 200$, N° (%)	12 (48)	0	0	–
$200 \leq PaO_2/FIO_2 < 300$, N° (%)	6 (24)	8 (53·3)	5 (83·3)	–
$PaO_2/FIO_2 \geq 300$, N° (%)	7 (28)	7 (46·7)	1 (16·7)	–
Mechanical ventilation, N° (%)	7 (21·9)	13 (46·4)	9 (60)	9 (100)
Tidal volume per body weight (mL/kg), Median (IQR)	7·5 (6·3–8·3)	6·6 (6·1–7·9)	6·5 (6·2–7·7)	6·7 (6·1–7·5)
PEEP (cmH_2O), Median (IQR)	4 (2–6)	4 (4–6)	5 (4–6·5)	7 (6–9)
FIO_2 (%), Median (IQR)	60 (50–80)	60 (50–65)	60 (50–65)	80 (70–100)
PaO_2 (mmHg), Median (IQR)	117 (89–145)	98 (85–133)	89 (81·5–120)	91 (66–108)
PaO_2/FIO_2, Median (IQR)	161 (148–234)	182 (134–283)	147 (131 - 255)	91 (66–180)
$PaO_2/FIO_2 < 200$, N° (%)	5 (71·4)	8 (61·5)	6 (66·7)	8 (88·9)
$200 \leq PaO_2/FIO_2 < 300$, N° (%)	2 (28·6)	3 (23·1)	1 (11·1)	0
$PaO_2/FIO_2 \geq 300$, N° (%)	0	2 (15·4)	2 (22·2)	1 (11·1)

Haemodynamic features

On the day of ICU admission, seven patients (21·9%) presented shock and required catecholamine therapy. During their ICU course, six other patients developed septic shock, five of whom also required catecholamine. The initial ECG revealed a sinus tachycardia in 28 patients (87·5%). ST depression/elevated was noted in two patients (6·2%) and T-wave changes in 6 (18·7%). Troponine levels were performed for 22 patients and were positive (>0·01 ng/ml) in 12 (54·5%). Trans-thoracic echocardiography was performed beyond the second day of ICU evolution in six patients (18·7%). In three patients, heart function was normal; hypertensive cardiopathy with systolic dysfunction was detected in one case, diastolic dysfunction diagnosed in one case and interauricular communication confirmed in one case.

Neurological features

Thirty patients had normal initial CGS (15/15) and two patients had neurological dysfunction (CGS at 6 and 13/15). One patient who had epilepsy as co-morbidity presented with generalized status epilepticus requiring mechanical ventilation and clonazepam and phenobarbital administration. Another patient had decompensated myasthenia requiring mechanical ventilation and five sessions of plasmapheresis. Two other patients, a child (4 years) and a woman (37 years), had a Guillan–Barre syndrome with a symmetrical flaccid ascending paralysis and acute respiratory failure confirmed by electromyography (which confirmed a reduction in motor conduction velocity and prolonged distal latencies which were more severe in the lower limbs). The diagnosis was retained in the absence of another obvious aetiology. Neither of the two patients had received any recent vaccination or infection. Both required mechanical ventilation and immunotherapy. All patients with neurological manifestations had a good outcome.

Biological analysis

In the first 24 hours, biological perturbations included leucopenia (<4000 cells/mm^3) in 2 (9·4%), hyperleucocytosis (>10000 cells/mm^3) in 18 (56·3%), thrombopenia (<1 50 000 E/mm^3) in 7 (21·9%), CIVD in 6 (18·7%), hyponatraemia (<135 mm) in 16 (50%), hyperkalaemia (>5 mm) in 4 (12·5%), hypokalaemia (<3·5 mm) in 10 (31·3%), hyperglycaemia (>6·5 mm) in 16 (50%), hyperprotidaemia (>70 g/l) in 16 (50%), hypoprotidaemia (<60 mm) in 10 (31·3%), elevated urea (>8·5 mm) in 13 (40·6%), elevated creatinine (>110 μm) in 12 (37·5%), cytolysis (ALAT >two fold of normal upper limit) in 5 (15·6%) and rhabdomyolysis (CPK > 500 UI/l) in 6 (21·4%) (CPK was performed for 28 patients).

Organ dysfunction

At admission, the median SOFA score was 4 (IQR, 3–6) (minimum 0 and maximum 12), the median number of organ failure was 2 (IQR, 1–2·75) (minimum 0 and maximum 5) and 16 patients (50%) had MOF (Table 3).

Table 3. Sequential organ failure assessment score in patients with confirmed 2009 A(H1N1) influenza infection

Organ Dysfunction	Admission (*N* = 32)	Day 3 (*N* = 28)	Day 7 (*N* = 15)	Death day (*N* = 9)
Respiratory dysfunction (Yes), N° (%)	29 (90·6)	24 (85·7)	15 (100)	9 (100)
Score Respiratory dysfunction (points), Median (IQR)	3 (2–3)	3 (1–3)	3 (2–3)	3 (3–4)
Haemodynamic dysfunction (Yes), N° (%)	9 (21·8)	13 (46·4)	7 (46·7)	7 (77·8)
Score Haemodynamic dysfunction (points), Median (IQR)	0 (0–1)	0 (0–3)	0 (0–3)	4 (0·5–4)
Neurological dysfunction (Yes), N° (%)	2 (6·3)	1 (3·6)	3 (20)	3 (33·3)
Score of neurological dysfunction (points), Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)
Renal dysfunction (Yes), N° (%)	12 (37·5)	9 (32·1)	3 (20)	7 (77·8)
Score Renal dysfunction (points), Median (IQR)	0 (0–1·75)	0 (0–2)	0 (0–0)	2 (0·5–4)
Liver dysfunction (Yes), N° (%)	2 (6·3)	2 (7·1)	1 (6·7)	2 (22·2)
Score liver dysfunction (points), Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)
Haematological dysfunction (Yes), N° (%)	7 (21·9)	6 (21·4)	3 (20)	7 (77·8)
Score of haematological dysfunction (points), Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	2 (0·5–2·5)
SOFA score (points), median (IQR)	4 (3–6)	4 (2–6)	3 (2–6)	12 (6–14)
Number of Organ dysfunction, Median (IQR)	2 (1–2·75)	2 (1–3)	1 (1–3)	4 (3–5)
MOF (Yes), N° (%)	16 (50)	16 (57·1)	7 (46·7)	9 (100)

Infections complications

In all cases, co-infection was excluded by negative bacterial cultures of blood, urine and sputum and negative serological reaction for atypical respiratory pathogens. Six (18·8%) patients developed nosocomial infections, 5 (83·3%) developed nosocomial pneumonia (3 were septisaemic) and one developed a septisaemic catheter-related infection. In all cases, BGN were commonly identified as the cause of nosocomials infections (*Pseudomonas Aergenosa* in two cases, Acinetobacter Baumanii, Stenotrophomonas Maltophilia and Klepsiella Pneumoniae in one case for each one).

Other medical therapies

All patients received neuraminidase inhibitors; 29 (90·6%) received oseltamivir (tamiflu*) and 3 (9·4%) received zanamivir (relenza*). Neuraminidase inhibitors were begun at a median of 5 (IQR 2–5·75) days after first symptoms. At admission, all patients received antibiotics which were stopped when initial bacteriological cultures were proved negative. The three patients who developed nosocomial infections were treated by an adapted antibiotherapy. Eighteen patients (56·3%) received corticosteroids, hydrocortisone in 6 (33·4%), dexamethasone in 11 (61·1%) and Solumedrol in 1 (5·5%). Five patients (15·6%) needed intermittent haemodialysis.

Outcomes

In our series, the median ICU length of stay was 6 (IQR 3–11) days (Figure 3) and median hospital stay was 11 (IQR 6–18). Nine patients (28·1%) died, among whom only one paediatric case (10 years old). Most patients [8 (88·9%)] died within the first 2 weeks after ICU admission; however, one patient died at day 45. All deaths were noted in ICU and no death was noted among patients discharged from ICU.

Comparison of survivors and non-survivors

Patients who died were more likely to have a higher SAPS II, a respiratory obstructive syndrome as co-morbidity and an acute mode of installation (ICU hospitalization within 24 hours from first symptoms). At admission, these patients were already ventilated; they were likely to have a shock and required catecholamines. Dead patients had also more biological disturbances (Tables 4 and 5). The SOFA score and the number of organ dysfunctions were significantly high at ICU admission, and in days 3 and 7 in the non-survivors group (Table 5) (Figures 4 and 5). In addition, in our series, the SOFA score and the number of organ dysfunction were respectively a good predictor of mortality at admission (AUC 0·78 and 0·79), day 3 (AUC 0·94 and 0·92) and day 7 (AUC 1 and 0·98) (Figures 6 and 7).

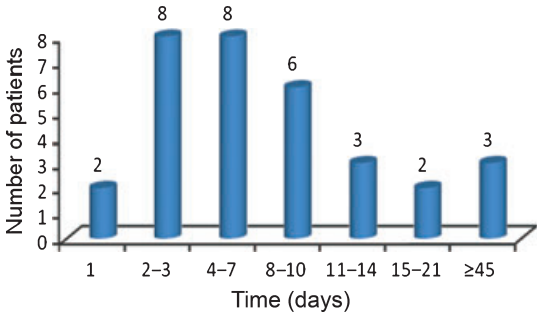

Figure 3. Length of stay in the intensive care unit (ICU) among patients with the 2009 A(H1N1) influenza Infection.

Table 4. Comparison of survivors and non-survivors among patients with the 2009 A(H1N1) influenza infection

Characteristics	Survivors (*N* = 23)	Died (*N* = 9)	*P* Value *OR [IC 95%]
Age (Years), Mean (SD), year	34·1 (20·4)	41·3 (21·9)	0·40
Age (Years), Mean (SD), year (adult cases)	43·3 (14·7)	45·5 (19·8)	0·88
Age (Years), Mean (SD), year (child cases)	7·8 (3·2)	10	0·29
Children (Yes), No (%)	6 (26·1)	1 (11·1)	0·64
Female sex (Yes), No (%)	12 (52·2)	2 (22·2)	0·23
SAPS II (Points), Mean (SD)	18 (10)	46 (17)	0·001
PRISM (Points), Mean (SD)	3·5 (3·8)	7	0·44
BMI, Mean (SD)	23·3 (4·9)	25·1 (4·7)	0·38
Obesity (Yes), N° (%)	0	2 (22·2)	0·073
Pregnancy (Yes), N° (%)	3 (13)	0	0·54
Co-morbidities (Yes), N° (%)	14 (60·9)	7 (78·8)	0·44
Obstructive pulmonary disease co-morbidity (Yes), N° (%)	2 (8·7)	4 (44·4)	0·038 *8·4 (1·2–59·5)
Time course of illness, (First symptoms to ICU admission) (Days), Mean (SD)	4·7 (2·2)	5·1 (2·7)	0·60
Time course of illness, (Hospitalization to ICU admission) (Days), Mean (SD)	1·22 (1·2)	1·22 (0·9)	0·83
Acute mode, N° (%)	0	3 (33·3)	0·017
ICU Admission			
Temperature (°C), Mean (SD)	37·8 (0·9)	37 (1·5)	0·085
Shock (Yes), N° (%)	2 (8·7)	5 (55·6)	0·01 *13·1 (1·8–92·9)
Catecholamins (Yes), N° (%)	2 (8·7)	5 (55·6)	0·01 *13·1 (1·8–92·9)
ARDS (Yes), N° (%)	11 (47·8)	6 (66·7)	0·44
ALI (Yes), N° (%)	7 (30·4)	1 (11·1)	0·38
Invasive mechanical ventilation at ICU admission (Yes), N° (%)	2 (8·7)	5 (55·6)	0·01 *13·1 (1·8–92·9)
Peep (cmH_2O), Mean (SD)	3 (1·4)	4·6 (2·8)	0·32
FiO2 (%), Mean (SD)	55 (7·1)	70 (20)	0·31
Tidal volume per body weight (ml/kg), Mean (SD)	7·3 (1·4)	7·8 (1·4)	0·84
Temperature (°C), Mean (SD)	37·8 (0·9)	37 (1·5)	0·085
Ph, Mean (SD)	7·39 (0·10)	7·22 (0·15)	0·009
Potassium (mm), Mean (SD)	3·7 (0·7)	4·6 (1·0)	0·005
Glycaemia (mm), Mean (SD)	6·3 (2·2)	10·7 (5·6)	0·026
White blood cell count $*10^3$ (E/mm^3), Mean (SD)	12·413 (7·642)	13·800 (8·051)	0·60
Platelet count $* 10^3$ (E/mm^3), Mean (SD)	248 (108)	204 (108)	0·30
Creatinine (μm), Mean (SD)	106·4 (120·2)	378·3 (307·5)	0·001
ASAT (UI/l), Mean (SD)	311·9 (902·2)	297·1 (548·5)	0·098
CPK (UI/l), Mean (SD)	286·6 (405·5)	1281·7 (2744·8)	0·258
ALAT (UI/l), Mean (SD)	121·6 (313·9)	221·2 (509·8)	0·038
Bilirubin (mg/l), Mean (SD)	14·4 (5·4)	19·4 (10·1)	0·22
Troponines elevated (troponines elevated/troponines normal) (%)	(5/10) (50%)	(7/0) (100%)	0·005
Troponines (ng/l), Mean (SD)	0·33 (0·4)	0·48 (0·6)	0·74
Duration of invasive mechanical ventilation (Days), Mean (SD)	15·8 (17·7)	10·4 (13·5)	0·19
ICU length of stay (Days), Mean (SD)	10·8 (14·6)	10·9 (13·4)	0·86

Comment

In spring 2009, a new variant of influenza (H1N1) made its appearance in Mexico. It was caused by an A(H1N1) virus resulting from a genetic restocking between several viruses of porcine, avian and human origin.[17,18] The incubation period for the 2009 H1N1 virus has been estimated to be between 1 and 7 days. However, patients requiring ICU had a short median time of 4 days between symptom onset and hospitalization.[1,5,17,19–20] Most cases occurred in patients with a median age from 12 to 18 years.[2,17,21] However, severe cases also occurred in slightly older populations. More recent reports indicate that the median age of cases may increase as infection becomes more widespread in the population.[17] Patients requiring ICU had an older median age of 21–44 years.[1,5,6,21,22] The number of patients requiring ICU varies from one country to another and from one study to another from 6·5% to 31%.[5,21,23] According to the literature, the mean age of our patients was of 36·1 (SD, 20·7) years and the median time between symptom onset and hospitalization was at 4 days (IQR 2–5).

Patients requiring hospitalization or ICU admission for the 2009 H1N1 infection are much more likely to have underlying medical conditions, especially asthma, chronic obstructive pulmonary disease, immunosuppression,

Table 5. Sequential organ failure assessment organ dysfunction through time among patients with the 2009 A(H1N1) influenza infection. Comparison of survivors and non-survivors

Characteristics	Admission (*N* = 32)			Day 3 (*N* = 28)			Day 3 (*N* = 15)		
Organ Dysfunction	**Survivors (*N* = 23)**	**Died (*N* = 9)**	***P* Value *OR [IC 95%]**	**Survivors (*N* = 21)**	**Died (*N* = 7)**	***P* Value *OR [IC 95%]**	**Survivors (*N* = 10)**	**Died (*N* = 5)**	***P* Value**
SOFA Score (Points), Mean (SD)	3·4 (1·5)	7·3 (3·3)	0·002	2·8 (1·8)	10·4 (4·4)	<0·001	2·2 (1·1)	10 (3·9)	0·002
N° of Organ dysfunction, mean (SD)	1·5 (0·7)	3·0 (1·3)	0·002	1·4 (0·7)	3·6 (1·1)	<0·001	1·2 (0·4)	4 (1·6)	0·001
MOF (Yes), N° (%)	8 (34·8)	8 (88·9)	0·015 15·0 (1·5–142·2)	7 (33·3)	7 (100)	0·006	2 (20)	5 (100)	0·007
Respiratory dysfunction (Yes), N° (%)	21 (91·3)	8 (88·9)	NS	16 (76·2)	7 (100)	0·29	10 (100)	5 (100)	–
Respiratory dysfunction Score (Points), Mean (SD)	2·3 (1·1)	2·2 (1·3)	0·96	1·5 (1·0)	2·7 (0·9)	0·013	1·8 (0·6)	3 (0·0)	0·003
Haemodynamic dysfunction (Yes), N° (%)	3 (13)	6 (66·7)	0·006 13·3 (2·1–84·1)	7 (33·3)	6 (85·7)	0·029 12·0 (1·2–120·1)	2 (20)	5 (100)	0·007
Haemodynamic dysfunction Score (Points), Mean (SD)	0·2 (0·6)	2·2 (1·9)	0·001	0·7 (1·1)	3·3 (1·5)	0·001	0·4 (0·8)	3 (1·2)	0·002
Neurological dysfunction (Yes), N° (%)	2 (8·7)	0	NS	1 (4·8)	0	NS	0	3 (60)	0·022
Neurological dysfunction Score (Points), Mean (SD)	0·2 (0·6)	0	0·37	0·05 (0·2)	0	0·56	0	0·8 (0·8)	0·009
Renal dysfunction (Yes), N° (%)	4 (17·4)	8 (88·9)	<0·001 38·0 (3·6–395·2)	4 (19)	5 (71·4)	0·02 10·6 (1·5–76·1)	0	3 (60)	0·022
Renal dysfunction Score (Points), Mean (SD)	0·4 (1·1)	2·2 (1·5)	<0·001	0·5 (1·1)	2·6 (1·9)	0·005	0	2 (2)	0·009
Liver dysfunction (Yes), N° (%)	0	2 (22·2)	0·073	0	2 (28·6)	0·06	0	1 (20)	0·33
Liver dysfunction Score (Points), Mean (SD)	0	0·2 (0·4)	0·022	0	0·6 (0·9)	0·013	0	0·4 (0·9)	0·16
Haematological dysfunction (Yes), N° (%)	4 (17·4)	3 (33·3)	0·37	1 (4·8)	5 (71·4)	0·001 50 (3·7–668·3)	0	3 (60)	0·022
Haematological dysfunction Score (Points), Mean (SD)	0·2 (0·5)	0·4 (0·7)	0·32	0·05 (0·2)	1·3 (1·2)	<0·001	0	0·8 (0·8)	0·009

diabetes, obesity, or chronic heart conditions.[1,5,23] Obesity was more frequent in those with associated co-morbidities and was found in 24–38% of the cases.[20,21,24] As in prior reports,[1,5,21] more than 60% of our patients had co-morbid conditions, especially pulmonary, cardiovascular and neurological, but we found few with morbid obesity. In our cohort, 9·4% (three patients) were pregnant women, similar to prior reports of a frequency between 6% and 10% of affected patients, and between 5% and 9% of those admitted to ICU.[18,21] Pregnant women are not known to have an increased risk of becoming infected by the H1N1 2009 influenza. However, owing to the changes in their immune systems, they are at greater risk of severe diseases and of developing complications if they get the illness.[19,25] The term of the pregnancy seems to be a determining factor for serious risk of severe complications or death from the influenza A(H1N1) 2009. Ninety-five per cent of the pregnant patients were infected in the second or third trimester.[21,25,26] In our study, pregnant women represent 50% of these between 25 and 45 years, and the term of the pregnancy was, respectively, 20–24 and 32 weeks of gestation.

Seven cases (21·9%) of our cohort were children, with only one death. Hospitalized children with the 2009 H1N1 influenza had a median age from 10 months[27] to 9 years[23] and high rates of pre-existing illness, especially asthma and neurological disorders. In addition, children under the age of 4–5 years are prone to have increased risk for severe diseases.[21,23,27,28] Children requiring ICU for the 2009 H1N1 influenza represented 7–19% of all related ICU admissions[23,27] with 7·5% paediatric deaths.[23]

Clinical manifestations of the 2009 H1N1 influenza and seasonal influenza are similar.[17] Patients usually develop symptoms within a week of exposure and are infected for about 8 days after the onset.[29] Hospitalized patients with confirmed 2009 H1N1 often presented with a polymorphic clinical picture gathering to variable frequencies, fever

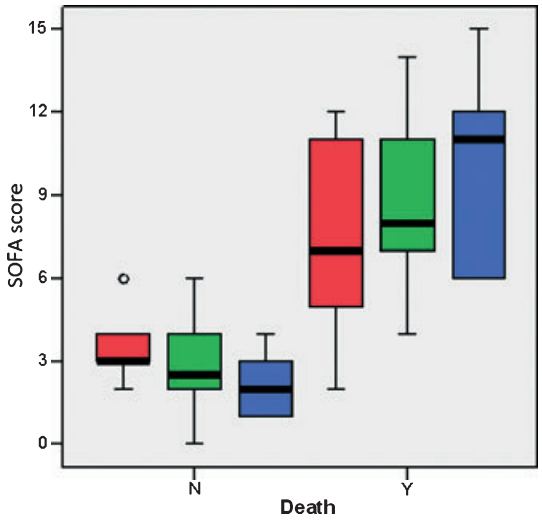

Figure 4. Sequential organ failure assessment score through time among patients with the 2009 A(H1N1) influenza infection. Comparison of survivors and non-survivors [at admission (red), day 3 (green) and day 7 (blue)].

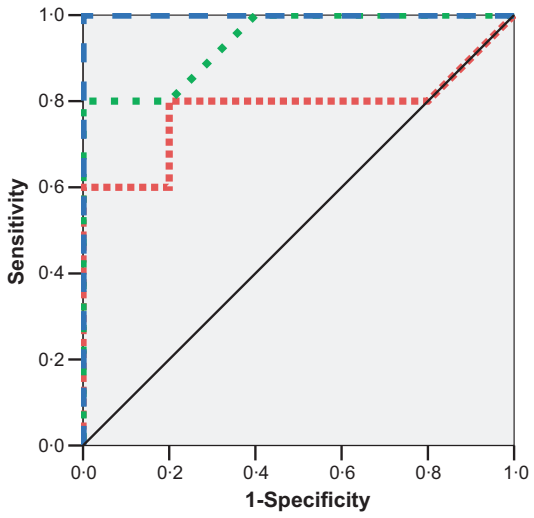

Figure 6. Receiver operating characteristics curve of sequential organ failure assessment score at admission (red), day 3 (green) and day 7 (blue).

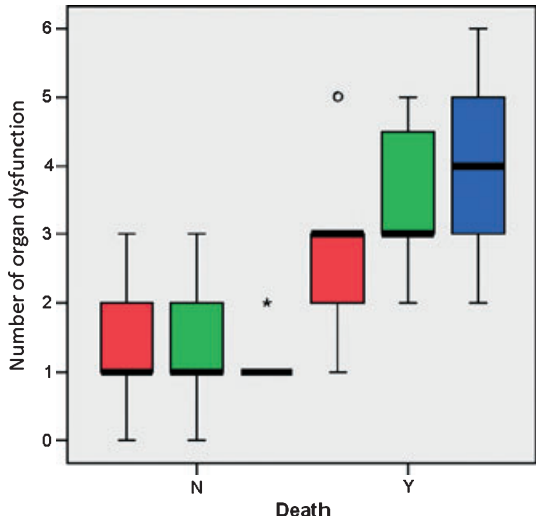

Figure 5. Number of organ dysfunction through time among patients with the 2009 A(H1N1) influenza infection. Comparison of survivors and non-survivors [at admission (red), day 3 (green) and day 7 (blue)].

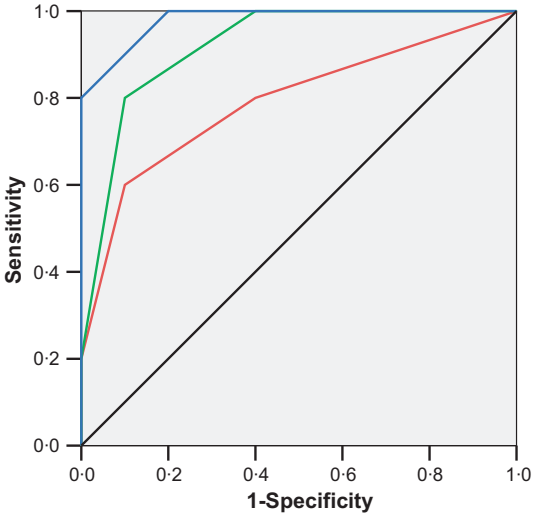

Figure 7. Receiver operating characteristics curve of number of organ dysfunction at admission (red), day 3 (green) and day 7 (blue).

(95–96%), chills (80%), cough (88–98%), shortness of breath (60%), dyspnoea (48%), headache (34–82%), sore throat (31–82%), rhinorrhea (82%), runny nose (38%), and myalgia (36%), joint pain (46%), or stomach ache (36%), arthralgia, fatigue (43%) and muscle aches (80%).[17,21] A proportion of affected patients also presented with gastrointestinal symptoms, such as, nausea (55%), diarrhoea (48%) and vomiting. Small subsets of patients presented solely with gastrointestinal or neurological symptoms without fever or cough.[21] Symptoms and signs that have been associated with more severe diseases include dyspnoea, fever for >3 days, abdominal pain, persistent vomiting, hypotension, bloody sputum and altered mental state.[19]

The median or mean time between symptoms' apparition and the first consultation at the hospital was relatively long, generally between 4 and 7 days. On the other hand, aggravation was fast and the time from hospital admission to ICU admission was short, with a median of 1 day;[1,5,17,19,20] this finding was confirmed in our study [median 1 (IQR 0–2) day]. In most cases, patients requiring critical care presented with rapidly progressing respiratory failure and refractory hypoxaemia.[1,5,19] Nevertheless,

they can be hospitalized in ICU for other (often associated and seldom isolated) extra-pulmonary failures.[17,19]

The respiratory failure is often in the foreground and consists of ALI or ARDS, which causes hypoxaemia and can be refractory, requiring early invasive mechanical ventilation with a lung-protective ventilation strategy, high levels of FiO_2 and of positive expiratory pressure (PEEP) in 60–100% of cases.[1,5,20,21,24,30,31] Non-invasive ventilation was used without real success in many studies, with the 75% rate of failure justifying quick intubation and invasive ventilation.[1,5,20] Refractory forms of SDRA can lead to the use of extracorporeal membrane oxygenation 'ECMO'.[20,24] The initial chest X-rays were normal in more than half of the patients with proven A(H1N1) 2009 influenza infection. The evolution is rapidly marked by the appearance of radiological anomalies in the form of interstitial and/or alveolar infiltrates in 75% of cases.[1,5,20,30,32]

During their stays in ICU, all our patients developed a P/F ratio lower than 300; this ratio remained between 200 and 300 in 11 patients (34·4%) and lower than 200 in 21 patients (65·6%); only 15 (71·4%) of the latter had necessitated mechanical ventilation. In our series, we did not find significant differences between non-survivors and survivors in the number of patients having a respiratory failure. Nevertheless, non-survivors were significantly more serious with significant hypoxaemia and a higher respiratory SOFA score in J3 and 7. Independently of a decompensation of chronic respiratory or cardiac diseases, three mechanisms can explain the respiratory compromise. First, the direct viral pneumonia, which can cause viral pneumonitis or haemorrhagic pneumonitis.[33] Second, the co-infection of pneumonia by the bacterial agents; approximately 10–30% of the patients had a bacterial co-infection (generally in *Staphylococcus aureus* or *Streptococcus pneumoniae*). These patients can be presented in the form of severe bacterial pneumonia, preceded by influenza.[20] In our study, we sought any bacterial or atypical co-infection. The third mechanism related to a cardiac dysfunction with haemodynamic pulmonary oedema and cardiogenic shock. Probable mechanisms of cardiovascular dysfunction are influenza myocarditis, exacerbation of pre-existing coronary disease or worsening of congestive heart failure.[34–37] Fulminant myocarditis because of viral infection is an uncommon form of acute myocarditis and may present with fatal arrhythmias, atrioventricular block and/or varying degrees of cardiogenic shock.[38] The prevalence of myocardial involvement in influenza infection ranges from 0 to 11%, depending on the diagnostic criteria used to define myocarditis.[34] Myocardic suffering explains also the shock and is regarded as an element of severity.[17,19,23,35,37] Circulatory compromise can also be attributed to the requirement for high sedative doses to assist ventilation[1,5,19] or to septic complications (pulmonary co-infection or nosocomial infection). In our series, the haemodynamic status was significantly predictive of mortality. Dead patients had more haemodynamic failures as well as a higher haemodynamic SOFA score. At admission, seven patients developed shock, and all had ECG re-polarization disorders as well as elevated troponine levels, leading to a diagnosis of a cardiogenic origin.

Neurological complications of the 2009 A(H1N1) influenza are rarely described. Kevin Tan *et al.*[39] reported nine cases of neurological complication among 826 hospitalized patients with the diagnostic of 2009 A(H1N1) influenza in Singapore from June to October 2009. These complications included six cases with a seizure (one with a recurrent seizure), one case of myasthenia gravis exacerbation, one case of migraine exacerbation and one case of ischaemic stroke. We reported four cases of neurological complications: two patients with decompensation of their chronic diseases (epilepsy and myasthenia) and two other who presented with acute complications relating to Guillain–Barre syndrome. This last diagnosis was retained on the data of the clinical and neurophysiological examination in view of the absence of other obvious aetiologies (absence of recent vaccination and/or recent infection). All these patients required invasive ventilation with specific treatments.

Acute renal failure (ARF) is rarely reported as an A(H1N1) influenza complication.[40,41] It was often initiated during the first week, with refractory oliguria requiring renal replacement therapy in 10–50% of the cases.[40] ARF can be attributed to a systemic inflammatory response syndrome because of sepsis ('viral sepsis'), shock, rhabdomyolysis but may also have been initiated by hypoxaemia and volume depletion. The necessity for renal replacement therapy (RRT) was associated with an elevated risk of death.[19,30,40–43] In our cohort, 12 (37·5%) patients developed ARF; among them 5 (41·7%) needed RRT (intermittent dialysis). Eight (66·7%) patients with ARF died, 4 (50%) in them had required RTT. These four survivors had recovery of their renal function. In addition, involvement of renal function is a significant predictor of death according to the SOFA Score.

Biologically, the literature reports rhabdomyolysis as an A(H1N1) influenza complication,[5,30,42,44,45] CPK would generally increase moderately in the first week because of a myosite; it can be associated with myalgia or muscle weakness.[5,30] However, severe rhabdomyolysis with ARF was reported mainly in children.[45] It remains unclear whether the mechanism of rhabdomyolysis is by direct viral invasion of muscle or by an immune-mediated action.[30,42] We report six cases of rhabdomyolysis (21·4%), five among them with ARF. In addition, the biological assessment reveals that the majority of the patients did not have hyperleucocytosis.[20,30,46] Lymphopenia was reported in two-thirds of the patients.[20,30] In our series, we also noted many disturbances, such as acidaemia, hyperglycaemia,

hyponatraemia, thrombopenia, and cytolysis, which may be due essentially to hypotension, severe hypoxaemia and systemic inflammatory response syndrome.

The A(H1N1) 2009 influenza virus is sensitive to neuraminidase inhibitors, oseltamivir and zanamavir, but resistant to Adamantine.[17,31] Antiviral treatment is recommended for all hospitalized patients with confirmed, probable or suspected 2009 H1N1 infection and patients at high risk of complications. Treatment benefit is greatest if antiviral medications are started within 48 hours of the illness onset (reduction in the mortality and the duration of stay, faster reduction of the viral load than among untreated patients). The delay of start-up of the treatment was associated with over-morbidity and over-mortality. However, studies have suggested that hospitalized patients still benefit from treatment initiation even later.[16,20,31,47] The median time of institution of the treatment was of 4–8 days, and the duration of administration was of 5–10 days according to severity.[17,20,31,47] All our patients received neuraminidase inhibitors, commenced immediately in the hospital when A(H1N1) 2009 influenza infection was suspected. In our study, the median time of institution of antiviral was of 5 days. Compared with the non-survivor group, neuraminidase inhibitors were begun earlier in the survivor group [(mean ± SD) 3·9 ± 2·0 days versus 4·7 ± 2·4 days] but we do not found significant difference between the two groups ($P = 0·39$). This result can be explained by the relatively late start (median 5 days) of treatment.

In the literature, corticotherapy was instituted at 18–100% of the patients and several protocols were tested,[1,5,20,21,24,30] Quispe-Laime. AM *et al.*[22] studied the effect of the corticotherapy among 13 patients having A(H1N1) 2009 influenza with ALI or ARDS, with the authors reporting a significant improvement of oxygenation and the number of failures after 7 days of treatment as well as a weak mortality of 15%. It was thus concluded that a prolonged low-to-moderate dose corticosteroid treatment was well tolerated and associated with significant improvement in lung injury and multiple organ dysfunction scores, and a low hospital mortality, but they recommended multicentric studies to evaluate the benefit of corticotherapy in the treatment of pulmonary complications of A(H1N1) 2009 influenza. However, prolonged use of high-dose corticosteroids may increase the susceptibility of the patients to opportunistic infections[19,31] and may also increase the viral shedding time.[31,33] Nevertheless, corticosteroids do have a beneficial treatment for severe bronchospasm or asthma.[19] In our study, 18 (56·3%) patients received corticosteroids, and no significant difference was found between those who died and those who survived with regard to steroid administration or the nature of used molecules.

Mortality in ICU patients ranged between 17·3%[1] and 39·3%.[5] This death rate did not seem to be different from that of the seasonal influenza.[48] In the literature, factors associated with an increased risk of mortality are extreme ages,[1,21] raised scores of revolved APACHE II and SOFA at admission, higher severity of illness and greater organ dysfunction at presentation,[1,5,21] presence of a renal failure,[5,21] severe hypoxaemia and arterial hypotension,[5] absence of antiviral treatment[5] and delay in its start-up.[21] On the other hand, obesity was not found as a risk factor of mortality.[1,5] Many studies[1,5] also validated the use of either SOFA or Acute Physiology and Chronic Health Evaluation (APACHE II) scores to identify patients at risk of death.

Our analysis of critically ill patients with the 2009 influenza A(H1N1) reveals that this disease predominantly affected a young patient group. Fever and respiratory symptoms were suggestive of disease in almost all cases. There was a relatively long period of illness before coming to hospital, which was followed by a short period of acute and severe respiratory deterioration requiring admission in ICU. Patients who had ARDS or ALI required high oxygen flow or invasive ventilation with high levels of FiO2 and PEEP. The mortality rate of 28·1% appears to have been directly related to respiratory problems but also to other organs failure. We found that certain baseline characteristics of critically ill patients with the 2009 influenza A(H1N1) may be associated with increased mortality, including cardiovascular, respiratory and renal organ dysfunction. We also found in this cohort that either SOFA or SAPSII scores may help to identify patients at high risk of death.

Conclusion

Our analysis suggests that the 2009 influenza A(H1N1) infection requiring ICU affects predominantly young patients, with greater risks to those with co-morbidities. Respiratory failure was the major cause of ICU admission, but it was often associated with other organ system failures. Mortality in our series was comparable with existing publications and significantly correlates with the gravity of the patients – which we evaluated by SAPS II and SOFA score – at ICU admission but also in their evolution.

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