Original Article

Factors Associated with Death Due to 2009 Influenza A (H1N1) Virus Infection and Acute Respiratory Distress Syndrome in Beijing, 2009 - 2011

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Objective Patients with H1N1 virus infection were hospitalized and quarantined, and some of them developed into acute respiratory failure, and were transferred to the medical intensive care unit of Beijing Ditan Hospital, Capital Medical University in Beijing, China.

Methods The clinical features and preliminary epidemiologic findings among 30 patients with confirmed H1N1 virus infection who developed into acute respiratory failure for ventilatory support were investigated.

Results A total of 30 patients (37.43 ± 18.80 years old) with 2009 influenza A (H1N1) related acute respiratory distress syndrome (ARDS) received treatment with mechanical ventilation, 15 cases of whom were male and 17 cases died of ARDS. Fatal cases were significantly associated with an APACHE II score ($P = 0.016$), but not with $\text{PaO}_2/\text{FIO}_2$ ($P = 0.912$) and chest radiograph ($P = 0.333$). The most common complication was acute renal failure ($n = 9$). Five patients received extracorporeal membrane oxygenation (ECMO), 3 of whom died and the others survived. The major causes of death were multiple organ dysfunction syndrome (MODS) (39%), intractable respiratory failure (27%) and sepsis (20%).

Conclusions Most patients with respiratory failure due to influenza A (H1N1) virus infection were young, with a high mortality, particularly associated with APACHE II score, secondary infection of lung or type 2 diabetes mellitus.

Key words: H1N1; Acute respiratory distress syndrome; APACHE II; Extracorporeal membrane oxygenation; Risk factor

In early April 2009, cases infected with 2009 pandemic influenza A (H1N1) virus were identified in the United States^{1,2} and Mexico.³ The 2009 novel swine-origin influenza A (H1N1) virus was identified as its cause and rapidly led to a worldwide pandemic.⁴ The 2009 H1N1 virus is at triple-reassortant influenza virus containing genes from human, swine and avian influenza viruses.⁵⁻⁸

The first case of confirmed infection with H1N1 virus in China was documented at May 10, 2009. Since this was a new and potentially serious infectious disease, all patients with 2009 pandemic influenza A (H1N1) virus infection who had been hospitalized were quarantined in the hospital and were isolated from the

general population. Real-time reverse-transcription polymerase chain reaction (RT-PCR) detection was applied to confirm infection. A proportion of these patients presented with, or developed into severe acute respiratory distress syndrome (ARDS).

Total of 30 patients confirmed as 2009 pandemic influenza A (H1N1) virus infection who developed into acute respiratory failure for ventilatory support were enrolled to hospitals in Beijing, 28 of whom were from October 2009 to February 2010, and 2 were from February 2011 to May 2011.

The clinical features, results of laboratory detection, radiographic tests, and severity of respiratory failure, pneumonia or complications, causes of death, management and outcomes (cured or died) in those patients were collected.

All these patients with confirmed influenza A (H1N1) virus infection and complicated by respiratory failure were treated with oseltamivir, immunosuppressive, mechanical ventilation and rescue ARDS therapies. In some severe cases, extracorporeal

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membrane oxygenation (ECMO) was commenced for the treatment of refractory hypoxemia, hypercapnia, which still occurred despite mechanical ventilation and rescue ARDS therapies.

In addition, we discussed the relevance among the outcome, the factors associated with the death due to 2009 influenza A (H1N1) virus infection and ARDS.

METHODS

Patients

In China, the national guideline, adapted from guidelines provided by the U.S. Centers for Disease Control and Prevention, was published on May 9, 2009, and was applied to direct the surveillance, reporting, diagnosis, and treatment of the disease. A confirmed case was defined by a positive result of RT-PCR assay performed at a laboratory operated under the auspices of the Chinese Center for Disease Control and Prevention. Confirmed cases were admitted to infectious diseases hospitals, where they could be quarantined.

Beijing Ditan Hospital, Capital Medical University had been the designated hospital to receive and treat the critically ill patients in Beijing. All the 30 patients with 2009 influenza A (H1N1) related ARDS receiving treatment with mechanical ventilation were admitted to Beijing Ditan Hospital, among whom 28 cases were from October 2009 to February 2010 and 2 from February 2011 to May 2011.

The study was approved by the Ethics Committee according to the Declaration of Helsinki. And we clearly confirmed that we had all necessary consent from any patients involved in the study, including consent to participate in the study and consent for publication.

Data collection

Data on patient's demographics including age, sex, height, weight, as well as the presence of a number of predefined comorbidities were collected, retrospectively. We assessed whether patients fulfilled criteria during the period before or at the time of presentation to hospital for influenza-like diseases based on typical symptoms (defined as ≥ 3 symptoms of sore throat, cough, myalgia or arthralgia, respiratory distress, vomiting or diarrhea and fever). Patients were followed up until discharged, and the symptoms and signs were recorded daily.

Information on the timing of endotracheal intubation in relation to presumed onset of symptoms and hospital admission, the total duration of mechanical ventilation, and administration of antiviral and antibiotic medications were collected. And the severity of illness before endotracheal intubation by documenting

respiratory rate and measures of oxygenation were assessed. Also, the duration of mechanical ventilation, ICU and hospital stay were recorded. For patients who died during hospital admission, the modes of death from a list of predefined options were collected.

The medical charts, radiologic and laboratory findings were reviewed, retrospectively. All patients enrolled in this study had pneumonia or influenza-like diseases with opacities found on the chest radiograph (revealing pneumonia) and had laboratory-confirmed 2009 pandemic influenza A (H1N1) virus infection.

The details of all investigations and treatments were recorded.

Laboratory confirmation of infection

The 2009 H1N1 virus was detected by real-time RT-PCR assay in accordance with the protocol from the U.S. Centers for Disease Control and Prevention, as recommended by the WHO.⁸

Statistical analysis

Data analysis was described through means $\pm$ SD or medians (with interquartile ranges). The percentages of patients in every category were calculated for categorical variables. Comparisons of proportions were carried out by χ^2 tests for equal proportion or Fisher exact tests for small numbers. Characteristics on admission were compared between patients survived and those died by an unpaired Student's *t*-test, chi-square test, or Fisher's exact test, as appropriate. Multiple logistic-regression analysis was taken to identify independent predictors of outcome among patients. The outcome was predicted with factors such as age, sex, days in ICU and score of APACHE II. All analysis was performed by SPSS software (Inc., Chicago, IL, USA) for Windows (release 13.0). And $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical characteristics of the patients From October 4, 2009 to May 18, 2011, a total of 30 pandemic 2009 influenza A (H1N1) cases with ARDS were admitted to ICU in hospital, among whom, fifteen patients (50%) were male and 3 cases (20%) were children younger than 18 years old. The median age of all cases was 31 years old (range, 11-80 years old). The majority of the patients ($n = 29$, 96.7%) were Han Chinese, and the other ($n = 1$, 3.3%) was white.

All patients resided in the Beijing greater metropolitan area, and 17 cases (56.7%) died, accounting 5% of all 2009 influenza A (H1N1) deaths in mainland China. Case-mortality proportions were the highest in adults aged 20-40 years and lowest in children younger than 18 years old (Table 1).

Table 1. Comparison of demographic characteristics of reported hospitalized cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

	Patients who survived (n = 13)	Patients who died (n=17)	P values
Gender M/F — no. (%)			0.500
Male	6 (46)	9 (53)	
Female	7 (54)	8 (47)	
Age — yr			0.590
Median	34	30	
Range	15 - 80	11 - 75	
Age group — no. (%)			0.639
< 20 yr	1 (8)	1 (6)	
20- 40 yr	8 (61)	12 (70)	
41 - 60 yr	1 (8)	2 (12)	
61 - 80 yr	3 (23)	2 (12)	
Race or ethnic group — no. (%)			1.000
Chinese Han	13 (100)	16 (94)	
White	0 (0)	1 (6)	
BMI (kg/m ²)			0.947
Median	25.5	24.4	
Range	17 - 33	18 - 40	
BMI group — no. (%)			0.541
Underweight (< 18)	1 (8)	0 (0)	
Normal weight (18 - 25)	5 (39)	9 (52)	
Overweight (25 - 30)	4 (31)	4 (24)	
Obesity (> 30)	3 (23)	4 (24)	

Table 2. Comparison of comorbid conditions of reported cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

	Patients who survived (n = 13)	Patients who died (n = 17)
Chronic comorbid illness — no. (%)		
Chronic lung disease		
Chronic obstructive pulmonary disease	1 (8)	1 (6)
Bullae of lung	0 (0)	1 (6)
Chronic cardiac disease		
Coronary heart disease	1 (8)	1 (6)
Pulmonary heart disease	1 (8)	0 (0)
Metabolic disease		
Diabetes	0 (0)	4 (24)
Chronic renal failure	0 (0)	1 (6)
Immunosuppressive conditions		
Pregnancy	3 (23)	3 (18)
Other chronic comorbid illness		
Thoracocyllosis	0 (0)	1 (6)
Dysnoesia	0 (0)	1 (6)
Myelodysplastic syndrome	0 (0)	1 (6)
Decompensation cirrhosis	0 (0)	1 (6)
Chronic hepatitis B	0 (0)	1 (6)
Hyperthyroidism	0 (0)	1 (6)
Hepatolenticular degeneration	0 (0)	1 (6)
Hypertension	2 (15)	3 (18)
Atrophic arthritis	1 (8)	0 (0)
Cerebral thrombosis	1 (8)	0 (0)

Of the 30 patients with preexisting medical conditions: pregnancy (in 6 cases, and 3 died eventually), type 2 diabetes mellitus (in 4, all died eventually), arterial hypertension (in 5, 3 died eventually). None of the patients had a history of pneumococcal vaccination (Table 2).

The time from the onset of symptoms to being admitted in the hospital for ARDS ranged from 3 to 14 days (median, 5.5 days) (Table 3). All patients had fever, with temperatures higher than 38°C, respiratory distress or pneumonia. Almost all patients had cough (n = 29, 96.7%), myalgia or arthralgia (n = 23, 76.7%),

Table 3. Comparison of clinical and management features of reported hospital cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

	Patients who survived (n = 13)	Patients who died (n = 17)	<i>P</i> values
Duration or length of stay— days			
Course of disease			0.000**
Median	34	15	
Range	21- 64	4 - 34	
Days from onset of symptoms to ARDS			0.735
Median	5	6	
Range	3 - 14	3 - 14	
Duration of fever			0.970
Median	8	9	
Range	2 - 22	2 - 28	
Still in ICU			0.028*
Median	14	9	
Range	7 - 35	1 - 25	
Mechanical ventilation			0.709
Median	8	9	
Range	3 - 22	1 - 24	
Still in hospital			0.000**
Median	29	9	
Range	11- 58	1 - 25	
Days from onset of symptoms to oseltamivir therapy			0.355
Median	6	6	
Range	2 - 16	2 - 14	
Period of oseltamivir treatment			0.787
Median	5	5	
Range	5 - 10	1 - 19	
Days from onset of symptoms to glucocorticosteroid therapy			1.000
Median	6	6	
Range	2 - 14	2 - 16	
Period of glucocorticosteroid treatment			0.204
Median	3	3	
Range	3 - 12	1 - 3	
Viral shedding verified with RT-PCR detection			0.361
Median	10	9	
Range	6 - 22	5 - 18	
Therapeutic dose of oseltamivir — mg			0.505
Median	300	300	
Range	150 - 300	75 - 300	
Therapeutic dose of glucocorticosteroid — mg			0.112
Median	120	160	
Range	80 - 240	80 - 320	

Notes: * $P < 0.05$; ** $P < 0.01$.

dyspnea or respiratory distress ($n = 25$, 83.3%), and only one patients (3.3%) reported rhinorrhea and chest pain (Table 4).

The median Acute Physiology and Chronic Health Evaluation II score (APACHE II score) was 19 (range: 8 - 33), which were higher, indicating more severe abnormalities among the patients who died (median 21, range: 14-33) than among those who survived (median 17, range: 8-26) ($P = 0.016$) (Table 5).

Of the 27 adults aged 20 years or older with known body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), 7 cases (3 survived

and 4 died) were obese ($\text{BMI} > 30$) (Table 1).

Laboratory and radiographic findings

At the time of admission, 15 of the 30 patients (50%) were with increased leukocyte levels ($>10^4$ leukocytes per cubic millimeter), and 21 patients had decreased lymphopenia (< 1000 lymphocytes per cubic millimeter). The decreased CD4^+ T lymphocyte ($n = 27$, 90%) and CD8^+ T lymphocyte ($n = 25$, 83.3%) were observed in 30 patients (Table 6).

Total of 19 patients had elevated creatine kinase levels and 27 (90%) patients with elevated creatine kinase MB fraction levels; 15 (50%) patients with

Table 4. Comparison of symptoms and signs of reported hospitalized cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011.

	Patients who survived (n = 13)	Patients who died (n = 17)	P values
Symptom — no. (%)			
Elevated temperature			0.479
38 - 39°C	4 (31)	3 (20)	
39.1 - 40°C	5 (38)	5 (29)	
> 40°C	4 (31)	9 (51)	
Cough	12 (92)	17 (100)	0.464
Blood in sputum	7 (54)	8 (46)	1.000
Rhinorrhea	0 (0)	1 (6)	1.000
Chill	9 (69)	7 (41)	0.276
Headache	5 (39)	7 (41)	0.718
Myalgia or arthralgia	12 (92)	11 (65)	0.333
Dyspnea or respiratory distress	11 (85)	14 (82)	0.583
Diarrhea	3 (23)	3 (18)	1.000
Sore throat	4 (31)	5 (29)	1.000
Nausea, vomiting	4 (31)	2 (12)	0.372
Chest pain	1 (8)	0 (0)	0.464
Sign— no. (%)			
Congestion of throat	4 (31)	6 (36)	0.705
Swelling of tonsils	3 (23.1)	3 (18)	1.000
Enlargement of lymph nodes	2 (15)	1 (6)	0.583

Table 5. Comparison of laboratory, radiographic findings and clinical features on admission of reported hospital cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

Variables	Patients who survived (n = 13)	Patients who died (n = 17)	P values
Laboratory Findings			
C reactive protein ($\bar{x} \pm s$, mg/L)	122.08 $\pm$ 102.58	171.06 $\pm$ 172.81	0.380
Sodium ($\bar{x} \pm s$, mmol/L)	136.85 $\pm$ 5.06	136.93 $\pm$ 5.84	0.970
Chloride ($\bar{x} \pm s$, mmol/L)	104.29 $\pm$ 6.75	100.33 $\pm$ 4.06	0.067
Lactate dehydrogenase ($\bar{x} \pm s$, U/L)	626.71 $\pm$ 349.36	813.17 $\pm$ 644.19	0.361
Hemoglobin ($\bar{x} \pm s$, g/L)	117.88 $\pm$ 25.02	102.37 $\pm$ 28.52	0.141
Platelet count ($\bar{x} \pm s$, /ml)	133.46 $\pm$ 54.56	115.84 $\pm$ 58.49	0.420
Abnormalities on chest radiograph — no. (%)			0.333
Local patchy shadowing	12 (92)	15 (88)	
Ground—glass opacities	1 (8)	2 (12)	
PaO ₂ :FiO ₂ on oxygen or mechanical ventilation			0.912
Median	121	104	
Range	61-187	50 -195	
APACHE II score			0.016*
Median	17	21	
Range	8 - 26	14 - 33	

Note: * $P < 0.05$.

elevated alanine aminotransferase levels; 25 (83.3%) patients with elevated aspartate aminotransferase levels.

Twenty-seven (90%) of the 30 patients had increased blood glucose levels, which were not decreased among 4 patients. Blood potassium levels increased in 4 patients (13.3%), and decreased in 6 patients (21%). Creatinine levels were increased in 10 patients (36%), and blood levels decreased in 7 cases (23.3%) (Table 6).

Findings on chest radiographs were consistent with the acute respiratory distress syndrome in all patients

receiving mechanical ventilation. Twenty-seven (90%) patients had local patchy shadowing, and 3 patients (18%) had ground-glass opacities (Table 5).

All the 30 patients had infectious pneumonia, with the bacterial cultures obtained from blood, sputum, pleural fluid, or catheter, respectively. The cultures were positive in all patients, 17 bacteria or fungi strains and 2 resistant bacteria strains were found, among which *acinetobacter baumannii* and *enterococcus faecalis*, *enterococcus faecalis* were the most common pathogens identified, and the resistant bacteria strains were *moraxella catarrhalis* pandrug-resistant

Table 6. Comparison of laboratory findings on admission of reported hospital cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

Variables	Patients who survived (n = 13)	Patients who died (n = 17)	P values
Leukocyte count — no. (%)			0.001
> 10 /ml	2 (13)	13 (76)	
4 - 10 /ml	11 (87)	2 (12)	
< 4 /ml	0 (0)	2 (12)	
Lymphocyte count — no. (%)			0.084
> 5 /ml	0 (0)	0 (0)	
1 - 5 /ml	1 (7)	6 (35)	
< 1 /ml	12 (93)	11 (65)	
CD4 ⁺ T lymphocyte count — no. (%)			0.464
706 - 1125 /ml	1 (8)	0 (0)	
< 706 /ml	12 (93)	17 (100)	
CD8 ⁺ T lymphocyte count — no. (%)			0.226
323 - 806 /ml	0 (0)	3 (18)	
< 323 /ml	13 (100)	14 (82)	
Creatine kinase — no. (%)			0.700
> 140 U/L	7 (54)	12 (71)	
26 - 140 U/L	6 (46)	5 (29)	
Creatine kinase MB fraction — no. (%)			0.445
≥ 25 U/L	6 (46)	12 (71)	
< 25 U/L	7 (54)	5 (29)	
Alanine aminotransferase — no. (%)			0.476
> 40 U/L	5 (38)	10 (59)	
0 - 40 U/L	8 (62)	7 (41)	
Aspartate aminotransferase — no. (%)			0.639
> 40 U/L	10 (77)	15 (88)	
0 - 40 U/L	3 (23)	2 (12)	
Total bilirubin — no. (%)			0.686
≥ 18.8 μmol/L	3 (23)	5 (29)	
< 18.8 μmol/L	10 (77)	12 (71)	
Glucose — no. (%)			0.583
> 6.44 mmol/L	11 (85)	16 (94)	
3.5 - 5.2 mmol/L	2 (15)	1 (6)	
< 3.5 mmol/L	0 (0)	0 (0)	
Potassium — no. (%)			0.167
> 5.2 mmol/L	1 (8)	3 (18)	
3.5 - 5.2 mmol/L	11 (86)	8 (46)	
< 3.5 mmol/L	1 (8)	6 (36)	
Creatinine — no. (%)			0.385
> 84 mmol/L	3 (25)	8 (47)	
45 - 84 mmol/L	8 (62)	8 (47)	
< 45 mmol/L	2 (13)	1 (6)	

acinetobacter baumannii (Table 7).

Treatment

None of the patients had received oseltamivir before admission; all of them received it in the hospital, with a dose of 75 mg or 150 mg twice a day for a minimum of 5 days (range, 1 - 19 days). Glucocorticosteroid therapy was applied in all patients, with a dose of 1 - 1.5 mg•kg⁻¹•day⁻¹, and the treatment course were from 1 to 12 days (median, 3 days) (Table 3). After admission, all patients received mechanical ventilation and antibiotics to aim directly at the results of bacteric cultures. Five

patients (14%) received ECMO therapy, 2 of whom survived and 3 died (Table 8).

Comorbid illness of H1N1 and the causes of death

Total of 20 complications occurred among the 30 patients, such as alimentary tract hemorrhage (n = 5, 16.7%), kidney failure (n = 7, 23.3%), liver failure (n = 2, 6.7%), and septic shock, septicaemia acute left ventricular failure, hemolytic uremic syndrome, sensitization dermatitis, pneumothorax, bronchopleural fistula, etc.

Total of 17 patients died with the cause as multiple

Table 7. Comparison of bacteria or fungi of pneumonia of reported hospital cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009 - 2011

	Cured (n = 13)	Fatal (n = 17)
Bacteria or fungi — no. (%)		
<i>Stenotrophomonas maltophilia</i>	2	0
<i>Excherichia</i>	2	0
<i>Acinetobacter baumannii</i>	4	2
<i>Staphylococcus aureus</i>	2	1
<i>Moraxella</i>	1	0
<i>Enterococcus faecium</i>	1	0
<i>Klebsiella pneumoniae</i>	1	1
<i>Enterococcus faecalis</i>	5	1
<i>Enterococcus faecalis</i>	5	5
<i>Moraxella catarrhalis</i>	1	2
<i>Enterobacter cloacae</i>	1	0
G ⁺ coccus	1	5
G ⁻ coccus	0	2
G ⁻ bacillus	0	2
<i>Staphylococcus epidermidis</i>	1	2
<i>Staphylococcus capitis</i>	1	0
<i>Staphylococcus haemolyticus</i>	1	0
<i>Enterobacter aerogenes</i>	1	0
Resistant bacteria — no. (%)		
<i>Moraxella catarrhalis</i>	1	2
Pandrug - resistant <i>acinetobacter baumannii</i>	0	2

Table 8. Conditions of EMCO of five reported hospitalized cases with 2009 influenza A (H1N1) ARDS in Beijing, 2009-2011

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Before ECMO					
FiO ₂	100%	80%	100%	100%	70%
Highest PEEP — cm H ₂ O	15	20	18	20	12
PaO ₂ : FiO ₂	55	60	58	48	77
APACHE II score	10	11	12	19	21
SOFA score	9	8	8	8	10
During ECMO					
FiO ₂	60%	45% - 60%	45% - 55%	35% - 50%	40% - 60%
PEEP — cm H ₂ O	12	10 - 12	10 - 14	10 - 16	8 - 14
After ECMO					
PaO ₂ :FiO ₂	122.3	151.2	138.2	254.3	240
APACHE II score	19	4	7	20	19
SOFA score	10	5	9	8	6
Outcome	Death	Death	Death	Cure	Cure

organ dysfunction syndrome (MODS) (n = 7, 41%), intractable respiratory failure (n = 5, 29%), sepsis (n = 3, 18%), intracranial hemorrhage (n = 1, 6%), lung hemorrhage (n = 1, 6%) (Table 9).

One meaningful factor for death in these patients may be the higher APACHE II score (median 2.285; 95% CI, 0.951-5.492; *P* = 0.017). Otherwise, the leukocyte counter (median 1.99; 95% CI, 0.822 - 4.818; *P* = 0.019) may be the risk factor for death, which may be associated with infectious pneumonia (Table 10).

No clinical infection among health care workers

After infection-control measures were strictly enforced—with patients confined and isolated in ICU and N95 respirators used in addition to goggles, gowns, gloves, as well as liberal use of gel-alcohol hand sanitizer, no

more health care workers occurred influenza-like illness.

DISCUSSION

China has reported a large number of persons with mild disease, through the national surveillance system for influenza, the full spectrum of clinical illness have been determined. But more severe infections as the pandemic spreads has not been reported. This case series of the 30 patients hospitalized in Beijing with 2009 influenza A (H1N1) ARDS documented the clinical findings of severe illness or death that were investigated during the beginning of the 2009 influenza A (H1N1) pandemic.

Most of the patients were complicated with other diseases previously, with an influenza-like illness that progressing during a period of 5 to 7 days, eventually

Table 9. Comparison of comorbid illness of H1N1 and cause of death of reported hospital cases with 2009 influenza A (H1N1) ARDS who survived or died in Beijing, 2009-2011

	Patients who survived (n = 13)	Patients who died (n = 17)
Comorbid illness of H1N1 — no.		
Alimentary tract hemorrhage	0	5
Kidney failure	2	7
Liver failure	0	2
Ischemic liver disease	0	1
Drug hepatitis	1	0
Pregnancy-induced myocardiopathy	0	1
Pregnancy-induced hypertension syndrome	0	1
Septic shock	0	2
Septicaemia	2	0
Acute left ventricular failure	0	1
Subcutaneous emphysema and mediastinal emphysema	1	2
Pneumothorax	0	1
Bronchopleural fistula	0	1
Hemolytic uremic syndrome	0	1
Anemia		
Normocytic normochromic anemia	2	0
Hemolytic anemia	0	1
Brain infarction	1	0
Sensitization dermatitis	1	0
CMV infection	0	1
Dead fetus in uterus	1	0
Cause of death — no. (%)		
Multiple organ dysfunction syndrome (MODS)		7 (41)
Intractable respiratory failure		5 (29)
Sepsis		3 (18)
Lung hemorrhage		1 (6)
Intracranial hemorrhage		1 (6)

Table 10. Risk of death in patients with 2009 influenza A (H1N1) ARDS in Beijing, 2009-2011

Variables	Odds ratio (95% CI)	P values
APACHE II score	2.285 (0.951 - 5.492)	0.017
Leukocyte counter	1.99 (0.822 - 4.818)	0.019

pneumonia, and the manifestation during the first day of hospital admission fulfilled the criteria of acute lung injury or the acute respiratory distress syndrome.

In the United States, observations suggested that most H1N1 infections occurred in younger individuals, with 40% aged from 10 to 18 years and 95% younger than 50 years old; high incidence rates (147 per 100 000) have been described in children aged 5 to 14 years.^{4, 9} Persons with risk factors for severe complications from seasonal influenza established by the Advisory Committee on Immunization Practices, such as chronic lung disease, immunosuppression and pregnancy, also appeared to be at risk of severe illness from pandemic 2009 influenza A (H1N1) infection.^{4, 10, 11}

In our review of those hospitalized cases of pandemic 2009 Influenza A (H1N1) infection with ARDS in China, the median age (31 years old) was younger than those who commonly seen with seasonal influenza, and persons aged 50 years or older had the

highest rates of mortality. And these patients often occurred more severe symptoms. But there was no statistical difference between patients who died and survived on BMI, symptoms and signs.

The most consistent laboratory characteristics were decreased CD4⁺T lymphocyte (n = 27, 90%) and CD8⁺T lymphocyte (n = 25, 83.3%) levels, which were observed in all patients and may be immunosuppressed originated from 2009 influenza A (H1N1) virus infection, and may be the possible cause of secondary infection.

Most of the cases presented with clinical features of acute respiratory illness, were confirmed as pneumonia by shaving radiographics. All these patients were identified with infectious pneumonia by culture from blood, sputum, pleural fluid, or catheter. But, the causes of ARDS, pneumonia associated with 2009 influenza A (H1N1) virus or secondary infectious pneumonia were not accurate.

Total of 17 strains bacteria or fungi strains and 2 resistant bacteria strains were found. *Acinetobacter baumannii* and *enterococcus faecalis*, *enterococcus faecalis* were the common pathogens identified. The resistant bacteria strains were *moraxella catarrhalis* pandrug-resistant *acinetobacter baumannii*. Ten patients had double strains infection, and 9 patients had multiple infection. There was no significant difference between patients who died and survived on bacterial strains or numbers ($P = 0.438$).

The leukocyte counter was statistically different between patients who died and survived ($P = 0.001$). The leukocyte counter of patients who died was significantly higher than patients who survived. All these patients had infection, but only 15 patients (50%) had increased leukocyte counter, which was related to immunosuppression originated from 2009 influenza A (H1N1) virus infection.

The causes for the 17 patients who died were multiple organ dysfunction syndrome (MODS) ($n = 7$, 41%), intractable respiratory failure ($n = 5$, 29%), sepsis ($n = 3$, 18%), intracranial hemorrhage ($n = 1$, 6%), lung hemorrhage ($n = 1$, 6%).

Total of 20 complications occurred related to 2009 influenza A (H1N1) virus infection, such as liver failure, septic shock, alimentary tract hemorrhage, kidney failure, septicemia acute left ventricular failure, sensitization dermatitis, bronchopleural fistula, hemolytic uremic syndrome, pneumothorax, sensitization dermatitis, brain infarction, anemia, CMV infection and dead fetus in uterus.

The severity of illness was assessed by means of the acute physiology and chronic health evaluation (APACHE) II score,¹² which was calculated 24 hours after admission to ICU, as well as the $\text{PaO}_2/\text{FIO}_2$ (partial pressure of arterial O_2 to the fraction of inspired O_2), which was calculated on admission to ICU. We adapted a scoring system described by Opravil et al¹³ to grade the severity of pulmonary infiltrates: each lung was divided into four equal quadrants and each quadrant was scored on a scale of 0–3 (0: normal; 1: subtle increased interstitial markings; 2: prominent interstitial opacities; 3: confluent interstitial and acinar opacities), giving a maximum score of 24 for both lungs. Kumar also found that a higher APACHE II score could predict the mortality.¹³ In their study, the mean scores of death and survivors were 26 ± 8 and 18 ± 8 ($P < 0.01$).¹³ Koegelenberg et al considered that APACHE II score > 20 could predict mortality with regards to disease severity. In fact, almost no patient with a score above 20 survived ($P = 0.034$).¹⁴

The median time from the onset of symptoms to hospitalization (days from onset of symptoms to ARDS) was 5.5 days (range, 3–14 days). The most common symptoms include fever, cough, myalgia or

arthralgia and respiratory distress. And the courses of disease, the durations of ICU admission and hospitalizations of patients who survived were longer than those of patients who died. Thus, we consider that the prophase of disease may be related with the outcome.

The mean time from hospital admission to initiation of antiviral treatment was 6 days (range, 2–16 days). While the mean time from hospital admission to initiation of glucocorticosteroid treatment was 6 days (range, 2–16 days). And oseltamivir and glucocorticosteroid treatment were not associated with death.

Among the 5 patients treated with EMCO, 2 were alive and 3 died. One patient died with refractory arrhythmias while the oxygenator was changing. The other two deaths were due to multiple infection and MODS after EMCO.

Risk factors for severe 2009 influenza A (H1N1) illness are still unknown, but most of our patients were young to middle-aged and had previously been complicated with other diseases. The majority of the 2009 influenza A (H1N1) virus infections reported in other countries were mainly mild, influenza-like illnesses.¹⁶ All patients were complicated with chronic foundation diseases, and four cases had type 2 diabetes mellitus in them were all died.

One contributing factor for death in our patients may be the higher APACHE II score (median 2.285; 95% CI, 0.951–5.492; $P = 0.017$). Also, the leukocyte counter (median 1.99; 95% CI, 0.822 – 4.818; $P = 0.019$) may be related to death and associated with infectious pneumonia. Possible mechanisms of damage include direct injury to the respiratory epithelium with a secondary cytokine storm. We are not accurately sure whether our patients, especially those who died, had viremia. We concluded two factors before the onset of illness predicted a worse outcome or death among our patients.^{15–17}

Obesity may be a newly identified risk factor for fatal pandemic 2009 influenza A (H1N1) infection and merits further study.¹⁷ But in our review, these cases of pandemic 2009 influenza A (H1N1) infection with ARDS in China, obesity was not the risk factor for fatal cases.

In our institution highlights, the experience of reinforce precautions from SARS were successful personal protective measures to prevent health care workers from infection.

Our data are subject to several limitations. The cases in this study were not enough. Data were extracted from non-standardized medical records. Case ascertainment was based on passive reporting by clinicians, and may occurred due to poor recognition and general nonspecificity of influenza-like symptoms.

The limited availability of confirmatory laboratory detection may have contributed to diagnose of cases.

CONCLUSIONS

In conclusion, the majorities of patients with respiratory failure secondary to influenza A (H1N1) virus infection were young and with an underlying risk factor for severe disease. Patients with pandemic 2009 influenza A (H1N1) infection had a high mortality, particularly associated with APACHE II score, secondary lung infection or type 2 diabetes mellitus. Future studies should focus on predictive factors of influenza A (H1N1) virus infection for severe disease or death, and especially the effect of oseltamivir and glucocorticosteroid treatment in influenza A (H1N1) virus infection, and the relationship between influenza A (H1N1) virus infection and type 2 diabetes mellitus or metabolism of glucose.

Abbreviations

ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; MODS: multiple organ dysfunction syndrome; RT-PCR: reverse-transcription polymerase-chain-reaction; BMI: body mass index.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The authors (Jin-qian Zhang, Li-cheng Zhang, Na Ren, Ming Zhang, Li-min Guo, Xing-wang Li, Jun Cheng) all contributed equally to the design, acquisition of data, and analysis of data for this study. All the authors have been involved in drafting the manuscript and revising it critically for important intellectual content. They all have given final approval of the version to be published.

All authors have read and approved the final manuscript.

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