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Epidemiological analysis of critically ill adult patients with pandemic influenza A(H1N1) in South Korea

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SUMMARY

A total of 245 patients with confirmed 2009 H1N1 influenza were admitted to the intensive-care units of 28 hospitals (South Korea). Their mean age was 55·3 years with 68·6% aged >50 years, and 54·7% male. Nine were obese and three were pregnant. One or more comorbidities were present in 83·7%, and nosocomial acquisition occurred in 14·3%. In total, 107 (43·7%) patients received corticosteroids and 66·1% required mechanical ventilation. Eighty (32·7%) patients died within 30 days after onset of symptoms and 99 (40·4%) within 90 days. Multivariate logistic regression analysis showed that the clinician's decision to prescribe corticosteroids, older age, Sequential Organ Failure Assessment score and nosocomial bacterial pneumonia were independent risk factors for 90-day mortality. In contrast with Western countries, critical illness in Korea in relation to 2009 H1N1 was most common in older patients with chronic comorbidities; nosocomial acquisition occurred occasionally but disease in obese or pregnant patients was uncommon.

Key words: Critical illness, H1N1 subtype, influenza A virus, Korea.

INTRODUCTION

The first reports of human infection with influenza A(H1N1) 2009 (2009 H1N1) occurred in early April 2009 in southern California and Mexico. By late April, the virus had spread to other regions of the world [1]. On 11 June 2009, the World Health Organization declared the first Phase 6 global influenza pandemic of the century [2].

In Korea, the first case of 2009 H1N1 was documented on 2 May 2009. Subsequently, confirmed cases in Korea were reported mainly in overseas travellers or in those who had come into direct contact with infected people. By October 2009, the

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incidence of 2009 H1N1 had significantly increased and by 17 April 2010, about 750 000 Korean patients were confirmed as having 2009 H1N1 infection and 252 had died [3]. The clinical features and disease course of critically ill patients have been described for several countries in the northern and southern hemispheres that were affected by 2009 H1N1 [4–7]. The characteristics of 2009 H1N1 compared with seasonal influenza were younger age and higher rates of obesity and pregnancy in critically ill patients. However, little information was available concerning Korean patients who became critically ill after infection with 2009 H1N1. Here, the characteristics, clinical features, treatments and outcomes of adult Korean patients who became critically ill after being infected with 2009 H1N1 influenza are described.

METHODS

We retrospectively reviewed the medical records of all adult patients with confirmed 2009 H1N1-related critical illness who were treated at the 28 participating hospitals in South Korea between 1 September 2009 and 28 February 2010. This study was approved by the local institutional review board. Informed consent was not required because this was not an interventional study.

Eligible patients were aged $\geqslant$15 years, were critically ill and had been admitted to one of the 28 study hospitals with confirmed 2009 H1N1 infection. Infection with 2009 H1N1 was confirmed by testing a sample acquired via nasopharyngeal swab or bronchoalveolar lavage (BAL), and obtaining a positive result in a probe-based reverse transcriptase–polymerase chain reaction (RT–PCR) for the 2009 H1N1 virus. Critically ill patients were defined as those who (i) were admitted to the intensive-care unit (ICU) or required mechanical ventilation (i.e. invasive or non-invasive); (ii) had a ratio of partial pressure of oxygen in arterial blood (PaO_2) to inspired fraction of oxygen (FiO_2) $<$300 mmHg; or (iii) required intravenous infusion of an inotropic or vasopressor medication. First, the patients were identified by searching the databases of the microbiology laboratory. Patients were then included on the basis of critical illness criteria. Eligibility criteria were confirmed by site investigators at each centre and data were recorded by trained research nurses or site investigators at each centre.

We reviewed the medical records of the patients and recorded the following data: date of admission to hospital and the ICU, age, sex, weight and height [for calculation of body mass index (BMI)], date of first symptoms, laboratory data, radiographic findings and comorbidities. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA) scores on the day of admission. Nosocomial influenza acquisition was defined as the onset of influenza-like symptoms at least 72 h after hospital admission. Nosocomial bacterial pneumonia was defined as microbiological evidence for bacterial infection that was acquired more than 48 h after hospital admission, with clinical features compatible with bacterial pneumonia and with one or more of the following signs and symptoms: production of purulent sputum or a worsening in sputum character; fever or hypothermia (oral temperature $\geqslant$38 °C or $\leqslant$35·5 °C); systolic blood pressure (BP) $<$90 mmHg; and total leukocyte count $>$10 000/μl, leukopenia (total leukocyte count $<$4500/μl) or $>$15% immature neutrophils regardless of total leukocyte count. In addition, a patient was required to have a chest radiograph consistent with the diagnosis of pneumonia (new or progressive infiltrates, consolidation, with or without pleural effusion). The primary outcome measures consisted of mortality at 30 days and 90 days after onset of symptoms. Secondary outcomes included frequency and duration of mechanical ventilation and duration of ICU and hospital stay.

Statistical analysis

Categorical variables were presented as numbers and percentages and were compared using the χ^2 test or Fisher's exact test. Continuous variables were expressed as means [standard deviation (S.D.)] or medians [interquartile range (IQR)] and were compared using Student's t test or Mann–Whitney test. To evaluate 90-day mortality, logistic regression analysis was performed. Variables with a P value $<$0·15 in univariate analyses were candidates for the multivariate logistic model. A backward elimination process was used to develop the final multivariate model, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A P value $<$0·05 was considered statistically significant. All analyses were performed using SPSS for Windows release 18.0 (SPSS Inc., USA).

Table 1. *Baseline characteristics of critically ill patients with confirmed pandemic influenza A(H1N1) 2009*

	All patients ($n=245$)	Survivors ($n=146$)	Non-survivors ($n=99$)	P value
Age, mean (±S.D.), years	55·3 (±18·4)	51·8 (±19·9)	60·5 (±14·5)	<0·001
Male sex	134 (54·7)	84 (57·5)	50 (50·5)	0·278
BMI, mean (±S.D.), kg/m²	22·9 (±4·3)	22·5 (±4·0)	23·5 (±4·8)	0·183
Nosocomial acquisition	33 (13·5)	9 (6·2)	24 (24·2)	<0·001
APACHE II score, mean (±S.D.)	19·1 (±8·4)	15·9 (±7·4)	23·7 (±7·4)	<0·001
SOFA score, mean (±S.D.)	7·7 (±3·7)	6·3 (±3·1)	9·9 (±3·5)	<0·001
No. of comorbidities, median (IQR)	2 (1–3)	1 (1–3)	2 (1–3)	<0·001
Malignancy				
Solid cancer	49 (20·0)	19 (13·0)	30 (30·3)	0·001
Haematological malignancy	19 (7·8)	8 (5·5)	11 (11·1)	0·106
Chronic lung disease				
COPD	20 (8·2)	10 (6·8)	10 (10·1)	0·362
Asthma	19 (7·8)	12 (8·2)	7 (7·1)	0·812
Other respiratory disorder	24 (9·8)	13 (8·9)	11 (11·1)	0·568
Hypertension	88 (35·9)	42 (28·8)	46 (46·5)	0·005
Smoking	70 (28·6)	46 (31·5)	24 (24·2)	0·217
Type 1 or 2 diabetes	60 (24·5)	30 (20·5)	30 (30·3)	0·081
Neurological disease				
Cerebrovascular disease	31 (12·7)	17 (11·6)	14 (14·1)	0·564
Seizures	3 (1·2)	0 (0)	3 (3·0)	0·065
Cardiac disease				
Ischaemic heart disease	16 (6·5)	10 (6·8)	6 (6·1)	0·806
Congestive heart failure	20 (8·2)	12 (8·2)	8 (8·1)	0·969
Arrhythmia	3 (1·2)	2 (1·4)	1 (1·0)	1·00
Hypercholesterolaemia	6 (2·4)	3 (2·1)	3 (3·0)	0·688
Chronic renal insufficiency	30 (12·2)	13 (8·9)	17 (17·2)	0·053
Chronic alcoholism	16 (6·5)	7 (4·8)	9 (9·1)	0·182
Liver cirrhosis	9 (3·7)	0 (0)	9 (9·1)	<0·001
Obesity (BMI >30 kg/m²)	9 (3·7)	5 (4·3)	4 (6·0)	0·726
Autoimmune disease	5 (2·0)	3 (2·1)	2 (2·0)	1·000
Immune suppression state	5 (2·0)	1 (0·7)	4 (4·0)	0·161
Pregnancy	3 (1·2)	2 (1·4)	1 (1·0)	1·000
No known comorbidity	40 (16·3)	33 (22·6)	7 (7·1)	0·001
Concurrent bacterial pneumonia	18 (7·3)	11 (7·5)	7 (7·1)	1·000
Streptococcus pneumoniae	7 (2·9)	4 (2·7)	3 (3·0)	1·000
MSSA	7 (2·9)	3 (2·1)	4 (4·0)	0·445
Mycoplasma pneumoniae	4 (1·6)	4 (2·7)	0	0·150

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MSSA, methicillin-susceptible *Staphylococcus aureus*; SOFA, Sequential Organ Failure Assessment.
Values given are *n* (%) unless stated otherwise.

RESULTS

Characteristics of study hospitals and patients

A total of 245 critically ill patients infected with H1N1 were admitted to the ICUs of 28 participating hospitals [ICU beds (median 20, IQR 15–24); total hospital beds (median 965, IQR 908–1200)] between 1 September 2009 and 28 February 2010. Twenty-two hospitals (78·6%) were university or university-affiliated hospitals.

The mean (±S.D.) age of the 245 critically ill patients was 55·3±18·4 years (range 15–93 years) and 68·6% of the patients were aged >50 years. Table 1 provides additional characteristics of the 245 patients. Upon initial presentation, the mean (±S.D.) APACHE II score was 19·1±8·4. A total of 205 (83·7%)

Table 2. *Clinical features upon intensive care unit admission*

	All patients ($n=245$)	Survivors ($n=146$)	Non-survivors ($n=99$)	P value
ARDS, *n* (%)	136 (55·5)	73 (50·0)	63 (63·6)	0·035
PaO_2/FiO_2, mean (±S.D.), mmHg	154·7 (±87·5)	175·5 (±90·0)	124·6 (±74·3)	<0·001
PaO_2/FiO_2 ⩽200 mmHg, *n* (%)	172 (70·2)	89 (61·0)	83 (83·8)	<0·001
Shock, *n* (%)	88 (35·9)	34 (23·3)	54 (54·5)	<0·001
Initial mean arterial pressure, mean (±S.D.), mmHg	75·1 (±17·2)	77·8 (±16·9)	70·9 (±17·1)	0·002
Lowest SBP, mean (±S.D.), mmHg	100·2 (±21·2)	104·4 (±20·3)	93·9 (±20·9)	<0·001
Heart rate, mean (±S.D.), /min	118·3 (±30·9)	112·0 (±31·6)	127·6 (±27·4)	<0·001
Creatinine, mean (±S.D.), mg/dl	1·8 (±2·3)	1·6 (±2·2)	2·1 (±2·4)	0·127
Platelet count, mean (±S.D.), $\times 10^3/\mu$l	174·6 (±119·7)	197·7 (±125·1)	140·6 (±102·6)	<0·001
Bilirubin, mean (±S.D.), mg/dl	1·6 (±8·7)	0·9 (±0·7)	2·6 (±13·6)	0·133
White blood cell count, mean (±S.D.), $\times 10^3/mm^3$	10·9 (±8·6)	11·1 (±6·1)	10·7 (±11·4)	0·715
Lymphocyte, mean (±S.D.), /mm^3	980·7 (±1246·4)	1147·0 (±1480·1)	733·8 (±719·8)	0·005
Lymphocyte count <1500/mm^3, *n* (%)	202 (82·4)	118 (80·8)	84 (84·8)	0·495
AST, mean (±S.D.), U/l	105·3 (±392·6)	97·1 (±421·4)	117·2 (±348·0)	0·690
ALT, mean (±S.D.), U/l	54·3 (±150·6)	50·4 (±129·8)	60·1 (±177·4)	0·649
PT(INR), mean (±S.D.)	1·5 (±2·8)	1·3 (±1·2)	1·8 (±4·2)	0·357
Lung infiltrates on CXR, *n* (%)				
⩽1 lobe or peribronchial infiltration	81 (33·1)	48 (32·9)	33 (33·3)	0·941
⩾1 bilateral infiltrates	164 (66·9)	98 (67·1)	66 (66·7)	0·941

ALT, Alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CXR, chest X ray; ICU, intensive care unit; PT(INR), prothrombin time (international normalized ratio); SBP, systolic blood pressure.

patients had one or more comorbidities. The most common comorbidities were hypertension (35·9%), smoking (28·6%), malignancy (27·8%), chronic lung disease (25·8%) and diabetes (24·5%). The BMI data were available for 184 patients. The mean (±S.D.) BMI was 22·9±4·3 kg/m^2 and only nine (3·7%) patients were obese (BMI >30 kg/m^2). Three of the patients were pregnant. Of these, two were in the third trimester and one in the first trimester. Thirty-five (14·3%) patients had been infected via nosocomial transmission, none of whom were healthcare workers. Nosocomial acquisition predominantly affected older subjects (mean age±S.D. = 60·4±13·4 years) who had several comorbidities [malignancy ($n=22$, 62·8%), cerebrovascular disease ($n=9$, 25·7%), chronic lung disease ($n=8$, 22·9%), liver cirrhosis ($n=5$, 14·3%)].

Coexistent bacterial pneumonia on admission was diagnosed in 18 (7·3%) patients. The most common presenting symptoms were respiratory symptoms such as shortness of breath (74·3%), cough (60·4%), sputum production (52·7%) and fever (65·3%). Leucocytosis was present in 48·2% of the patients and lymphopenia in 82·4%. Based on chest radiography at presentation, 164 (66·9%) patients had bilateral infiltrates (Table 2). Patients who died were more likely to have higher APACHE II and SOFA scores (Table 1) and lower mean arterial pressure, PaO_2/FiO_2 ratio, platelet count and lymphocyte count at admission (Table 2).

Course of illness and treatments received

The median time from symptom onset to presentation was 3 days (IQR 1–4 days) and the median time from presentation to ICU admission was 1 day (IQR 0–2 days) (Table 3). All patients received antiviral treatment. Of these, 112 (45·7%) patients received high-dose oseltamivir (300 mg/day). Twenty (8·2%) and 39 (15·9%) patients received double (i.e. oseltamivir and amantadine or ribavirin) or triple (i.e. oseltamivir, amantadine, ribavirin) combination regimens, respectively. Only 42·9% received antiviral therapy within 48 h of symptom onset. The duration from symptom onset to initiation of antiviral agents was not significantly different between survivors and non-survivors [3 days (IQR 1–5 days) and 3·5 days (IQR 2–6 days), respectively, $P=0·078$]. There were also no significant differences in antiviral regimen or dose between survivors and non-survivors. Fourteen of the 17 patients who received rescue therapy died. Other medical treatments included antibiotics (243 patients, 99·2%), corticosteroids (107 patients, 43·7%) and diuretics (153 patients, 62·4%).

Table 3. *Clinical course and treatment of critically ill patients with confirmed pandemic influenza A(H1N1) 2009*

	All patients ($n=245$)	Survivors ($n=146$)	Non-survivors ($n=99$)	P value
Days from symptom onset to hospitalization, median (IQR)	3 (1–4)	3 (1–4)	2 (1–4)	0·513
Days from hospitalization to ICU admission, median (IQR)	1 (0–2)	0 (0–1)	1 (0–3)	0·003
Days from symptom onset to antiviral agent, median (IQR)	3 (2–5)	3 (1–5)	3·5 (2–6)	0·078
Antiviral treatment				
Oseltamivir ($\leqslant$150 mg/day)	125 (51·0)	73 (50·0)	52 (52·5)	0·698
High dose oseltamivir (300 mg/day)	112 (45·7)	70 (47·9)	42 (42·4)	0·395
Double combination regimen*	20 (8·2)	12 (8·2)	8 (8·1)	1·000
Triple combination regimen†	39 (15·9)	24 (16·4)	15 (15·2)	0·860
Zanamivir	13 (5·3)	10 (6·8)	3 (3·0)	0·251
Peramivir	17 (6·9)	3 (2·1)	14 (14·1)	<0·001
Received $\leqslant$24 h after symptom onset	54 (22·0)	37 (25·3)	17 (17·2)	0·158
Received $\leqslant$48 h after symptom onset	105 (42·9)	65 (44·5)	40 (40·4)	0·559
Received $\leqslant$72 h after symptom onset	134 (54·7)	84 (57·5)	50 (50·5)	0·278
Corticosteroid	107 (43·7)	45 (30·8)	62 (62·6)	<0·001
Dose equivalent (prednisolone), mg/day, median (IQR)	75 (50–81)	75 (47–137)	75 (50–79·7)	1·000
Diuretics	153 (62·4)	75 (51·4)	78 (78·8)	<0·001
Antibiotics	243 (99·2)	144 (98·6)	99 (100)	0·516
Vasopressors	88 (35·9)	34 (23·3)	54 (54·5)	<0·001
Mechanical ventilation				
NIV	13 (5·3)	7 (4·8)	6 (6·1)	0·664
Invasive MV	162 (66·1)	67 (45·9)	95 (96·0)	<0·001
FiO_2, mean ($\pm$S.D.), mmHg	73·2 ($\pm$22·2)	67·1 ($\pm$23·0)	78·2 ($\pm$20·3)	0·003
PEEP, mean ($\pm$S.D.), cmH_2O	9·1 ($\pm$4·0)	8·7 ($\pm$3·7)	9·3 ($\pm$4·1)	0·373
Neuromuscular blocking agent	106 (43·3)	40 (59·7)	66 (68·8)	0·233
Prone position	21 (8·6)	4 (6·0)	17 (17·7)	0·033
NO	13 (5·3)	2 (3·0)	11 (11·5)	0·075
ECMO	12 (4·9)	2 (3·0)	10 (10·4)	0·125
Renal replacement therapy	55 (22·4)	17 (11·6)	38 (38·4)	<0·001
Length of MV, days, median (IQR)	7 (3–16·5)	8 (3–14)	7 (3–17)	0·406
Length of ICU stay, days, median (IQR)	7 (3–14)	6 (3–13)	8 (4–20)	0·015
Length of hospital stay, days, median (IQR)	14 (7–29)	13 (7–27·5)	19 (6·5–30)	0·938

ECMO, Extracorporeal membrane oxygenation; ICU, intensive-care unit; IQR, interquartile range; MV, mechanical ventilation; NIV, non-invasive ventilation; NO, nitric oxide; PEEP, positive end-expiratory pressure.
Values given are n (%) unless stated otherwise.
* Oseltamivir and amantadine or ribavirin.
† Oseltamivir and amantadine and ribavirin.

A total of 164 (66·9%) patients underwent mechanical ventilation for a median of 7 days (IQR 3–16·5 days). Initially, 151 (61·6%) of these procedures were invasive and 13 (5·3%) were non-invasive. Ultimately, 11/13 patients who received non-invasive ventilation required invasive ventilation. On the first day of ICU admission, the mean ($\pm$S.D.) PaO_2/FiO_2 ratio was 154·7$\pm$87·5 mmHg, the mean ($\pm$S.D.) FiO_2 value was 73·2$\pm$22·2% and the mean ($\pm$S.D.) positive end-expiratory pressure (PEEP) was 9·1$\pm$4·0 cmH_2O. Rescue therapies for oxygenation failure required neuromuscular blockade in 106 (43·3%) patients, prone positioning ventilation in 21 (8·6%) patients, inhaled nitric oxide in 13 (5·3%) patients and extracorporeal membrane oxygenation in 12 (4·9%) patients. Fifty-five (22·4%) patients became dependent on haemodialysis during their stay in the ICU. The median length of ICU stay was 7 days (IQR 3–14 days) for all patients, 6 days (IQR 3–13 days) for survivors and 8 days (IQR 4–20 days) for non-survivors ($P=0·015$). The median duration of ventilation was 7 days (IQR 3–16·5 days) for all patients, 8 days (IQR 3–14 days) for survivors and 7 days (IQR 3–17 days) for non-survivors ($P=0·406$).

Table 4. *Complications during treatment*

	All patients ($n=245$)	Survivors ($n=146$)	Non-survivors ($n=99$)	P value
Barotrauma	14 (5·7)	5 (3·4)	9 (9·1)	0·090
Nosocomial pneumonia	78 (31·8)	32 (21·9)	46 (46·5)	<0·001
CRAB	37 (15·1)	10 (6·8)	27 (27·3)	<0·001
MRSA	32 (13·1)	22 (15·1)	10 (10·1)	0·335
Klebsiella pneumonia	14 (5·7)	8 (5·5)	6 (6·1)	0·848
Pseudomonas aeruginosa	11 (4·5)	3 (2·1)	8 (8·1)	0·031
Others	4 (1·6)	1 (0·7)	3 (3·0)	0·306
Fungaemia				
Candida species	7 (2·9)	2 (1·4)	5 (5·1)	0·122
Aspergillus species	4 (1·6)	0 (0)	4 (4·0)	0·026

CRAB, Carbapenem-resistant *Acinetobacter baumannii*; MRSA, methicillin-resistant *Staphylococcus aureus*.
Values given are *n* (%).

Patients who died had more severe hypoxaemia, multisystem organ failure, a requirement for frequent and prolonged mechanical ventilation or haemodialysis, and delayed ICU admission (Table 3).

Barotrauma occurred in 14 (5·7%) patients during mechanical ventilation. Nosocomial bacterial pneumonia developed in 78 (31·8%) patients during the course of treatment. Eleven (4·5%) patients became infected with fungus. The frequency of nosocomial pneumonia caused by carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* was particularly high in non-survivors (Table 4).

Outcomes

Ninety-nine (40·4%) of the 245 patients died within 90 days of symptom onset, 131 recovered and were discharged from hospital within 60 days and 15 remained in hospital for longer than 60 days. Fifty-four (54·6%) of those 99 patients died within the first 14 days of symptom onset and 80 (80·8%) died within 30 days of symptom onset. Seventy-six (76·8%) of the 99 patients who died were aged >50 years. Twenty-five (71·4%) of the 35 patients who were infected by nosocomial transmission died. Of the three pregnant women, one experienced a miscarriage and one died.

Risk factor analysis

Univariate and multivariate analyses of risk factors associated with 90-day mortality are given in Table 5. Multivariate logistic regression analysis revealed that old age, SOFA score, clinician's decision to prescribe corticosteroids and nosocomial bacterial pneumonia caused by CRAB were independent risk factors for 90-day mortality. In addition, in order to explore the potential for a mortality time bias (patients need to survive long enough to receive a treatment, therefore, such treatment-related variables may be more likely to show an association with survival), we restricted our analysis of 90-day mortality to patients ($n=230$) who survived longer than the first 3 days. The associations and significance were attenuated only mildly.

DISCUSSION

In South Korea, critically ill adult patients infected with 2009 H1N1 were most commonly in older age groups. Hypertension, malignancy and chronic lung disease were common comorbidities, but in contrast with other studies [4, 5, 7, 8], obesity was rare and only three patients were pregnant. The frequency of nosocomial acquisition was high and was associated with high mortality. Respiratory failure progressed rapidly in some patients, necessitating prolonged mechanical ventilation or frequent use of rescue therapies. Although some patients were given high-dose oseltamivir or triple combination antiviral therapy, there was no significant difference in the survival rates with these treatment regimens. Multivariate logistic regression analysis revealed that the clinician's decision to prescribe corticosteroids, older age, SOFA score and nosocomial bacterial pneumonia caused by CRAB were independent risk factors for 90-day mortality.

In this study, in contrast with data from other countries [4, 5, 7, 9, 10], 68·6% of the infected patients

Table 5. *Risk factors associated with 90-day mortality*

	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years	1·028	1·013–1·044	<0·001	1·038	1·013–1·064	0·003
BMI, kg/m²	1·051	0·980–1·128	0·165			
Nosocomial acquisition	4·871	2·154–11·018	<0·001	2·954	0·952–9·168	0·061
APACHE II	1·143	1·098–1·190	<0·001	0·996	0·933–1·064	0·906
SOFA score	1·378	1·257–1·511	<0·001	1·427	1·223–1·665	<0·001
Solid cancer	2·906	1·525–5·540	0·001	1·502	0·618–3·648	0·369
Hypertension	2·149	1·261–3·663	0·005	0·872	0·412–1·844	0·719
Day from hospitalization to ICU admission	1·160	1·046–1·286	0·005	1·112	0·956–1·294	0·168
Day from symptom onset to antiviral agent	1·053	0·983–1·127	0·139	1·051	0·956–1·156	0·301
High dose oseltamivir	0·800	0·478–1·338	0·395			
Triple combination regimen	0·908	0·450–1·832	0·787			
Clinician's decision that corticosteroids should be prescribed	3·761	2·197–6·439	<0·001	3·700	1·739–7·873	0·001
Nosocomial bacterial pneumonia	3·092	1·772–5·394	<0·001	3·381	1·162–9·836	0·025
Nosocomial bacterial pneumonia by CRAB	5·100	2·338–11·123	<0·001	5·594	1·538–20·354	0·009
Clinician's decision that RRT should be prescribed	4·727	2·473–9·036	<0·001	1·215	0·466–3·164	0·691

APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CI, confidence interval; CRAB carbapenem-resistant *Acinetobacter baumannii*; ICU, intensive-care unit; OR, odds ratio; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

who developed severe disease were aged >50 years, which is higher than the percentages reported in Canada (25%) [5], France (48%) [11] and Spain (28–31%) [7, 12]. In Korea, as in other countries, 2009 H1N1 affected mostly younger people, but critical illness occurred mainly in older patients [13, 14]. Thus, we believe that not only is this study not biased but also that it is representative of the Korean adult acutely critically ill patients with 2009 H1N1. This study showed that the age-related mortality rate had a J-shaped curve, as did the studies of Kim *et al.* [15] and Echevarria-Zuno *et al.* [16]. However, Sundar *et al.* reported that in the USA, 87% of deaths occurred in those aged <65 years [17]. Our study supports the perspective that great heterogeneity among regions in terms of the incidence and mortality of infection is a characteristic of pandemics [18].

Compared with a previous study, the frequency of nosocomial acquisition observed in our population was high. Most cases of nosocomial acquisition occurred in older subjects with chronic comorbidities. Several reports have shown nosocomial influenza acquisition in patients with haematological malignancy [19–21]. In our study, 62·8% of patients with nosocomial acquisition had haematological or other malignancies. The presence of an immunocompromised state such as malignancy might be a risk factor for nosocomial influenza acquisition. Although there are insufficient data about nosocomial influenza acquisition, it is necessary to establish guidelines for prevention of nosocomial transmission of 2009 H1N1 and reinforce surveillance because of the high mortality resulting from an immunocompromised state, delayed treatment and transmission of resistant organisms [19, 22].

The 2009 H1N1 virus is associated with many of the same comorbidities as seasonal influenza, except for obesity and pregnancy [4–7, 23]. Obesity and pregnancy in patients were rare in this study. Louie *et al.* [24] reported obesity as a novel risk factor for 2009 H1N1 and Kim *et al.* [13] published a report of mortality in 115 Korean cases with a frequency of BMI >25 for 23% and no pregnancy. However, two multicentre studies from Canada and Mexico also showed that obesity was not a risk factor for 2009 H1N1 [4, 5]. Additionally, Yu *et al.* showed that pregnancy was rare in critically ill patients in China [25]. We suggest

that these risk factors might be subject to regional or racial differences, and that further study of this issue is needed. In this study, more than 80% of our patients had a comorbidity such as malignancy (solid cancer and/or haematological malignancy) or chronic lung disease. The high incidence of malignancy in our patients may reflect the fact that this study was mainly conducted at tertiary referral hospitals. Patients with malignant diseases are immunocompromised, and death from influenza-related infections is more common in cancer patients [26].

Only 42·9% of our patients received antiviral agents within 48 h of symptom onset. There was no significant difference between survivors and non-survivors in the period of time from symptom onset to initiation of treatment with antiviral agents. Some studies showed that severe 2009 H1N1 infection that required admission to an ICU was associated with a longer period of time between symptom onset and initiation of antiviral therapy [27–29], but a recent meta-analysis showed that early antiviral therapy did not decrease lower respiratory tract complications [30]. Thus, it is possible that the initial antiviral treatment seldom, if ever, influences the fate of rapidly fatal outcomes of 2009 H1N1. The hypothesis that there is a physiological 'point of no return' prior to antibiotic therapy has been confirmed in sepsis of critically ill patients [31]. Some reports have found that high-dose oseltamivir (300 mg/day) may be more effective for H5N1 (avian influenza) in patients with severe pulmonary disease [32]. Nguyen *et al*. [33] reported that the components of the triple combination treatment (i.e. oseltamivir, amantadine, ribavirin) act synergistically against influenza A. At present, there are insufficient clinical data on the efficacy of high-dose oseltamivir or triple combination regimens in the treatment of 2009 H1N1. Some of our 2009 H1N1 patients received high-dose oseltamivir or triple combination therapy, but there was no significant difference between survivors and non-survivors in the use of antiviral regimens. In Taiwan and Argentina, some patients received oseltamivir at a dose of 150 mg b.i.d., but the dosage of oseltamivir was not significantly associated with death [8, 28]. Although 17 patients in our study received peramivir as rescue therapy, only three survived. Thus, critically ill patients with 2009 H1N1 infection have a grave outcome despite rescue therapy with peramivir. The efficacy of peramivir as an early treatment in such patients, rather than as rescue therapy, should be further evaluated. Also lacking are clear data on the potential efficacy of corticosteroids in the treatment of severe acute respiratory distress syndrome (ARDS) resulting from 2009 H1N1 infection [34]. Our multivariate logistic regression analysis revealed that the clinician's decision to prescribe corticosteroids was a potent independent risk factor for 90-day mortality. The use of dexamethasone did not reduce mortality in a murine model of ARDS infected with H5N1 [35], and a study of H5N1 influenza cases revealed a higher mortality rate in those treated with steroids than in the non-steroid-treated group [32]. Lee *et al*. [36] reported that major comorbidities and systemic use of corticosteroids were associated with slower influenza clearance. A small number of studies have reported a rate of nosocomial bacterial pneumonia in patients with 2009 H1N1 of around 25% [7, 8]. In our study, the rate of nosocomial bacterial pneumonia was 32%. Use of corticosteroids could cause immunosuppression and secondary infection [37–39]. Although corticosteroid dose, timing of corticosteroid commencement and duration of corticosteroid treatment were not standardized between centres, these studies suggest that caution is necessary when administering corticosteroids to patients with influenza. Future studies are needed to assess the effects of different antiviral regimens and corticosteroids on 2009 H1N1-related critical illness.

In our study population, the 90-day mortality rate for critical illness relating to 2009 H1N1 was 40·4%, which was higher than in previous reports [4–6, 8, 9]. A couple of explanations may be advanced. First, some studies reported that the case-fatality rate was high in older patients (age $\geqslant 50$ years) [6]. Most of the patients in our study population were aged >50 years and 76·8% of the patients who died were aged >50 years. The high incidence of malignancy in our patients may also have contributed to the high mortality. Second, nosocomial bacterial pneumonia and fungal infection could have contributed to the mortality in this study.

This study has some limitations. As previously mentioned, the retrospective design may have resulted in selection bias. Furthermore, in some cases, we were unable to collect relevant patient data such as history of influenza vaccination and transmission route of nosocomial influenza infection, and the dose, timing and duration of corticosteroid treatment were not standardized among centres. In addition, the design of this study meant that causality could not be assessed and despite use of a multivariate regression model, confounders might still exist. This study

was conducted mainly at tertiary referral hospitals and only included patients who were aged $\geqslant$15 years – paediatric ICUs were not included in this study. Thus, it is possible that we underestimated the number of young and healthy patients infected with 2009 H1N1 influenza. All 28 hospitals that are members of the Korean Study Group for Respiratory Failure participated in this study voluntarily. The 28 hospitals were evenly distributed across the country. All of them were referral hospitals (22 of them were university or university-affiliated hospitals) so that most severely ill patients diagnosed in primary clinics might have been transferred to these hospitals. It could be possible that this group of patients received more specialized intensive care in these hospitals. However, when the national data for Korea were reviewed, we had included 99/252 (39·3%) patients in Korea who died with a diagnosis of H1N1 pneumonia [3].

CONCLUSION

In our Korean population, older patients with chronic comorbidities (especially hypertension, malignancy or chronic lung disease) were more likely to become critically ill with 2009 H1N1 influenza, but obesity and pregnancy were rare in infected patients. The frequency of nosocomial acquisition was high and associated with a high rate of mortality. Many of the study subjects received high-dose oseltamivir or a triple combination antiviral regimen after hospital admission. Nonetheless, the death rate was 40·4% in patients who became critically ill as a result of infection with 2009 H1N1.

APPENDIX. Korean Society of Critical Care Medicine H1N1 Collaborative

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DECLARATION OF INTEREST

None.

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