A Prediction Rule to Identify Severe Cases among Adult Patients Hospitalized with Pandemic Influenza A (H1N1) 2009

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Received: 3 December 2010
Accepted: 17 February 2011

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This study was supported by a 2010 Research Grant from Kangwon National University (Grant number: C1007258-01-01 (120100335)).

The purpose of this study was to establish a prediction rule for severe illness in adult patients hospitalized with pandemic influenza A (H1N1) 2009. At the time of initial presentation, the baseline characteristics of those with severe illness (i.e., admission to intensive care unit, mechanical ventilation, or death) were compared to those of patients with non-severe illnesses. A total of 709 adults hospitalized with pandemic influenza A (H1N1) 2009 were included: 75 severe and 634 non-severe cases. The multivariate analysis demonstrated that altered mental status, hypoxia (PaO_2/FiO_2 ≤ 250), bilateral lung infiltration, and old age (≥ 65 yr) were independent risk factors for severe cases (all $P < 0.001$). The area under the ROC curve (0.834 [95% CI, 0.778–0.890]) of the number of risk factors were not significantly different with that of APACHE II score (0.840 [95% CI, 0.790-0.891]) ($P = 0.496$). The presence of ≥ 2 risk factors had a higher sensitivity, specificity, positive predictive value and negative predictive value than an APACHE II score of ≥ 13. As a prediction rule, the presence of ≥ 2 these risk factors is a powerful and easy-to-use predictor of the severity in adult patients hospitalized with pandemic influenza A (H1N1) 2009.

Key Words: pandemic influenza A (H1N1) 2009; Severity; Risk Factors; Prediction Rule

INTRODUCTION

While most pandemic influenza A (H1N1) 2009 infections were mild or subclinical, early reports suggested that clinical courses of pandemic influenza A (H1N1) 2009 were somewhat different from that of seasonal influenza (1, 2). Although individuals with comorbid conditions were at high risk, small subsets of previously healthy people developed rapidly progressive disease. In severe cases, patients generally began to deteriorate 3-5 days after the onset of symptom, with rapid progression to respiratory failure within 24 hr. Most of these required immediate life support with mechanical ventilation, renal replacement therapy, or extracorporeal membrane oxygenation.

Although most studies have evaluated risk factors for mortality (3-5), a few have focused on those associated with severe pandemic influenza A (H1N1) 2009 (6, 7). From the viewpoint of clinical practice, knowledge on risk factors for the severity including the mortality and the prediction of severe cases is more crucial for decisions regarding hospitalization, treatment, or intensive care of these patients. Therefore, we evaluated the baseline characteristics of adult patients hospitalized with pandemic influenza A (H1N1) 2009 to identify risk factors associated with severity. Eventually, a rule comprising these risk factors was established to predict the severity of illness in adult patients hospitalized with pandemic influenza A (H1N1) 2009.

MATERIALS AND METHODS

Patients

This study was conducted at 17 teaching hospitals in Korea: Kangwon National University Hospital, Chuncheon; Gyeongsang National University Hospital, Jinju; Kwandong University Myongji Hospital, Goyang; Dongguk University Ilsan Hospital, Goyang; Boramae Medical Center, Seoul; Seoul National University Bundang Hospital, Seongnam; Seoul National University Hospital, Seoul; Pusan National University Yangsan Hospital, Yangsan; Wonju Christian Hospital, Wonju; Yeungnam University Medical Center, Daegu; Wonkwang University Hospital, Iksan; Inje University Sanggye-Paik Hospital, Seoul; Inje University Ilsan-Paik Hospital, Goyang; National Health Insurance Corporation Ilsan Hospital, Goyang; Chunbuk National University Hospital, Jeonju; Cheongju St. Mary's Hospital, Cheongju; and Kangbuk Samsung Hospital, Seoul.

All adult patients hospitalized with the laboratory-confirmed, pandemic influenza A (H1N1) 2009 from September 1, 2009 to February 28, 2010 were included in the study. Laboratory-confirmed cases were defined as the presence of influenza-like illness with pandemic influenza A (H1N1) virus infection confirmed by real-time or multiplex reverse-transcriptase polymerase chain reaction assays. Patients younger than 18 yr were excluded.

Data collection and definitions

Demographic, clinical, laboratory and radiographic data were collected from all patients. Obesity was defined as a body mass index (BMI) of more than 25 kg/m². Comorbid conditions included chronic lung diseases (chronic obstructive pulmonary disease, asthma, pneumoconiosis, or bronchopulmonary dysplasia), cardiovascular diseases (congestive heart failure, ischemic heart disease, or cyanotic congenital heart disease), cerebrovascular diseases (stroke or cerebral hemorrhage), malignancy, immunosuppression (HIV infection, asplenia or hyposplenia, transplantation, anticancer chemotherapy, corticosteroid, or other immunosuppressants), diabetes mellitus, chronic renal diseases (nephrotic syndrome or chronic renal failure), chronic liver diseases (liver cirrhosis or chronic active hepatitis), and neurocognitive diseases (mental retardation, dementia, or seizure).

To identify risk factor(s) associated with severe pandemic influenza A (H1N1) 2009 at the time of initial presentation, we compared the baseline characteristics of patients with severe illness to those of patients with non-severe illness. Severe cases were defined as those who had been admitted to intensive care unit (ICU), mechanically ventilated, or died of influenza itself or related complications; other cases were considered to have a non-severe illness. Clinical or laboratory parameters derived from Pneumonia Severity Index (PSI) for community-acquired pneumonia or the diagnostic criteria for sepsis or severe sepsis were used in part to evaluate the baseline characteristics of patients (8, 9). The presence of the following complications due to infection was also determined: pneumonia (defined as new or progressive infiltrate(s) on chest radiography), acute respiratory distress syndrome ($PaO_2/FiO_2 \leq 200$ in the presence of bilateral alveolar infiltrates in chest radiography), septic shock (systolic blood pressure < 90 mm Hg despite adequate fluid resuscitation), acute renal failure (serum creatinine ≥ 2.0 mg/dL without previous renal disease), rhabdomyolysis (profound muscle weakness and tenderness, brown-colored urine, and CPK ≥ 5 times the upper normal limit), and exacerbation of underlying diseases (worsening of the patient's condition such that additional treatment is required).

Statistical analysis

A Pearson's chi-square or Fisher's exact test was used for categorical variables, and the Student's t-test was used for continuous variables. A multivariate logistic regression analysis using baseline characteristics seen only at the time of initial presentation was performed to identify risk factors associated with severe pandemic influenza A (H1N1). A level of significance of less than 0.10 was required for inclusion and greater than 0.05 meant exclusion. The goodness-of-fit for this regression model was verified by the Hosmer-Lemeshow test (10).

As a prediction rule for severe pandemic influenza A (H1N1),

both the number of risk factors, derived from the logistic regression model, and the Acute Physiology and Chronic Health Evaluation (APACHE) II score were calculated for each patient. To validate their discriminatory power, the sensitivity and specificity of the risk factors were compared to those of the APACHE II score by means of the receiver operating characteristic (ROC) curves (11). We also determined their cut-points defining severe pandemic influenza A (H1N1) to maximize the sum of sensitivity and specificity.

A two-tailed $P < 0.05$ was considered to be statistically significant for all analyses. IBM SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA) and dBSTAT for Windows version 5.0 (dBSTAT, Seoul, Korea) were used.

Ethics statement

This study protocol was approved by the institutional review board (IRB) of Kangwon National University Hospital (IRB approval number: 09-22). Informed consent was waived in this study by the board.

RESULTS

A total of 709 adult patients hospitalized with the laboratory-confirmed, pandemic influenza A (H1N1) 2009 were included in the study. There were 280 (39.5%) males and 429 (60.5%) females, and the median age was 50 yr (interquartile range [IQR], 31-66 yr). A total of 75 (10.6%) patients had severe illness: 23 were admitted to ICU but not ventilated, 35 were mechanically ventilated in the ICU, 5 were mechanically ventilated in emergency departments or general wards, and 12 died without either admission to ICU or mechanical ventilation.

Baseline characteristics of severe pandemic influenza A (H1N1)

The demographic, clinical, laboratory and radiographic findings of patients at the time of initial presentation are summarized in Table 1. The median age of severe cases was higher than that of non-severe cases (65 yr [IQR, 50-75 yr] vs 49 yr [IQR, 30-63 yr]; $P < 0.001$). The proportions of males and nursing home residents were also higher in severe cases ($P = 0.01$ and 0.002, respectively). Of the total, 367 (52.1%) had one or more comorbidities: 62 (82.7%) severe cases vs 305 (48.1%) non-severe cases ($P < 0.001$). Chronic lung disease (21.7%) was the most common comorbidity, followed by diabetes mellitus (13.6%), cardiovascular disease (9.4%), malignancy (9.4%), immunosuppression (8.4%), chronic liver disease (5.5%), and chronic renal diseases (5.0%). Of these, chronic lung disease, cardiovascular disease, and immunosuppression were more frequently observed in severe cases than in non-severe cases ($P < 0.001$, < 0.001, and 0.011, respectively). However, there were no significant differences in the proportions of pregnancy and obesity between severe and

non-severe cases ($P = 0.11$ and 0.499, respectively).

While fever was the most common symptom (78.3%) at initial presentation, it was less frequent in severe than in non-severe cases (65.3% vs 79.8%; $P = 0.004$). On the contrary, dyspnea, purulent sputum, altered mental status, and cyanosis were more frequent in severe than in non-severe cases ($P < 0.001$, 0.018, < 0.001, and < 0.001, respectively). However, the median interval from symptom onset to initial presentation in severe cases was not significantly different than that in non-severe cases (2 days [IQR, 1-4 days] vs 2 days [IQR, 1-4 days]; $P = 0.619$). With respect to initial laboratory findings, anemia (hematocrit < 30%), azotemia (BUN ≥ 30 mg/dL), hyperglycemia (serum glucose ≥ 250 mg/dL), hyponatremia (serum sodium < 130 mEq/L), acidosis

Table 1. Baseline characteristics of adults hospitalized with pandemic influenza A (H1N1) 2009 (N = 709)

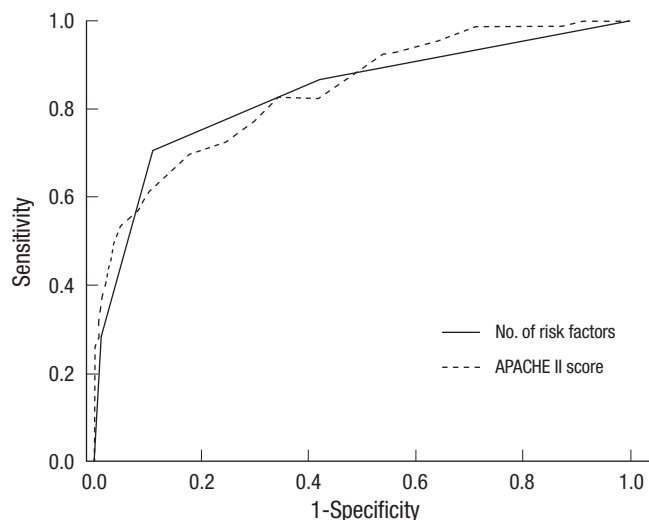| Baseline characteristics	No. (%) of pandemic influenza A (H1N1)		P value
	Severe cases (n = 75)	Non-severe cases (n = 634)	
Demography			
Age ≥ 65 yr	38 (50.7)	150 (23.7)	< 0.001
Male	40 (53.3)	240 (37.9)	0.010
Nursing home resident	7 (9.3)	16 (2.5)	0.002
Pregnancy	0	21 (3.3)	0.110
Obesity (body mass index ≥ 25 kg/m²)	15 (20.0)	36 (5.8)	0.499
Comorbid conditions			
Chronic lung disease	31 (41.3)	122 (19.2)	< 0.001
Cardiovascular disease	17 (22.7)	49 (7.7)	< 0.001
Malignancy	10 (13.3)	56 (8.8)	0.205
Immunosuppression	12 (16.0)	47 (7.4)	0.011
Diabetes mellitus	10 (13.3)	86 (13.6)	0.956
Chronic liver disease	3 (4.0)	36 (5.7)	0.547
Chronic renal disease	4 (5.3)	31 (4.9)	0.867
Symptoms			
Fever (oral temperature ≥ 37.8°C)	49 (65.3)	506 (79.8)	0.004
Duration of fever > 48 hr	19 (25.3)	198 (19.0)	0.295
Cough	49 (66.2)	473 (74.6)	0.085
Purulent sputum	42 (56.0)	264 (41.6)	0.018
Dyspnea	51 (68.0)	178 (28.1)	< 0.001
Sore throat	11 (14.9)	216 (34.1)	0.001
Rhinorrhea	14 (18.9)	175 (27.6)	0.098
Signs			
Systolic blood pressure < 90 mmHg	11 (14.7)	8 (1.3)	< 0.001
Heart rate ≥ 125 beats/min	11 (14.7)	25 (3.9)	< 0.001
Respiratory rate ≥ 30 breaths/min	7 (9.3)	15 (2.4)	0.001
Temperature < 35°C or ≥ 40°C	2 (2.7)	3 (0.5)	0.032
Altered mental status	23 (30.7)	17 (2.7)	< 0.001
Cyanosis	9 (12.0)	5 (0.8)	< 0.001
Laboratory findings			
WBC < 4,000 cell/μL	11 (14.7)	91 (14.4)	0.942
Hematocrit < 30%	20 (26.7)	72 (11.4)	< 0.001
BUN ≥ 30 mg/dL	20 (26.7)	48 (7.6)	< 0.001
Serum glucose ≥ 250 mg/dL	9 (12.0)	22 (3.5)	0.001
Serum sodium < 130 mEq/L	13 (17.3)	30 (4.7)	< 0.001
Arterial pH < 7.35	22 (29.3)	18 (2.8)	< 0.001
PaO₂/FiO₂ ≤ 250	34 (45.3)	45 (7.1)	< 0.001
Radiographic findings			
Presence of pneumonic infiltration	53 (70.7)	209 (33.0)	< 0.001
Bilateral lung infiltration	46 (61.3)	135 (21.3)	< 0.001

Fig. 1. Receiver operating characteristic (ROC) curves for the number of risk factors and APACHE II score. The areas under the ROC curves are 0.834 (95% confidence interval [CI], 0.778-0.890) for the number of risk factors and 0.840 (95% CI, 0.790-0.891) for the APACHE II score (P = 0.496 for each pairwise comparison).

Risk factors and the prediction of severe pandemic influenza A (H1N1) 2009

In the multivariate logistic regression model using baseline characteristics seen only at the time of initial presentation, altered mental status, hypoxia ($PaO_2/FiO_2 \leq 250$), bilateral lung infiltration, and old age (≥ 65 yr) were independent risk factors associated with severe pandemic influenza A (H1N1) (all $P < 0.001$; Table 3). The Hosmer-Lemeshow test did not show statistical significance (P = 0.88), indicating the goodness of fit of this logistic regression model.

The median number of risk factors in severe cases was higher than that in non-severe cases (2, IQR 1-3, vs 0, IQR 0-1) ($P < 0.001$). The median APACHE II score was also higher in severe cases than in non-severe cases (17, IQR 10-22, vs 6, 3-11) ($P < 0.001$). Both the number of risk factors and APACHE II scores were significantly correlated with patient age (Pearson's correlation coefficients > 0.5; all $P < 0.001$). The ROC curve for the number of risk factors, which were derived from the logistic regression model, was compared to that for the APACHE II scores (Fig. 1). The areas under the ROC curves were 0.834 (95% confidence interval [CI], 0.778-0.890) for the number of risk factors and 0.840 (95% CI, 0.790-0.891) for APACHE II score, but there was no significant difference between both areas under the ROC curves (P = 0.496). When the cut-points were determined to maximize the sum of the sensitivity and specificity by means of the ROC curves, they were 2 for the number of risk factors and 13 for the APACHE II score (Table 4). As a prediction rule for severe pandemic influenza A (H1N1) 2009, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the number of risk factors ≥ 2 were all higher than those of the APACHE II score ≥ 13.

DISCUSSION

During an influenza A (H1N1) 2009 pandemic, the determination of the severity of illness played an important role in early detection and proper management of severe cases and, eventually, improvement of clinical outcome. Although many studies about risk factors for death in patients with pandemic influenza A (H1N1) 2009 has been published, no prediction rule for the severe case has yet been established. In this study, the number of risk factors (i.e., altered mental status, hypoxia, bilateral lung infiltration, and old age) as a prediction rule seems to be adequate for the detection of severe cases among adult patients hospitalized with pandemic influenza A (H1N1) 2009. While APACHE II has been widely used to measure the severity of illness in critically ill patients, its application to all patients with pandemic influenza A (H1N1) can be limited in clinical practice because of the complexity of its parameters. When the cut-points were determined to maximize the sum of the sensitivity and specificity, the area under the ROC curve of the number of risk factors was comparable with that of the APACHE II score. More precisely, the presence of ≥ 2 risk factors had a higher sensitivity, specificity, PPV, and NPV than an APACHE II score ≥ 13. Therefore, we think that the presence of ≥ 2 risk factors is a more useful predictor for severe pandemic influenza A (H1N1) 2009, especially during a pandemic when the burden of care for the patients is too heavy for the physicians.

This study also highlights several clinical features observed in adult patients hospitalized with severe pandemic influenza A (H1N1) 2009 infection. Early case reports indicated that the infection in previously healthy young individuals might often be associated with serious complications or death (4, 12). Most of the serious illnesses occurred among children and young adults, and approximately 90% of deaths were observed in those < 65 yr of age. However, the overall case fatality rate among hospitalized patients appeared to be highest among those ≥ 50 yr of age. In this study, which included only adult patients hospitalized with pandemic influenza A (H1N1) 2009, there was a tendency for the severity of illness to increase with patient age. Most deaths occurred in patients who were ≥ 65 yr of age or had one or more comorbidities, but the only death attributed directly to influenza occurred in a previously healthy young individual. Although determination of the true case-fatality rate of pandemic influenza A (H1N1) 2009 is particularly challenging, it is thought to be less than 0.5%, with a broad range of estimates (13, 14). In a surveillance data (15), a total of 740,835 patients were reported to be infected with pandemic influenza A (H1N1) 2009 and 225 of them were reported to have died during 2009-2010 influenza season. The incidence was calculated as 1,493 per 100,000 population and the case fatality rate was 30 per 100,000 cases. In an early report (16) that included 272 patients hospitalized with pandemic influenza A (H1N1) 2009, the in-hospital case-fatali-

ty rate was -7%; it was -5% in the present study.

Previous studies have suggested that pregnant women are at increased risk for complication and death from pandemic influenza A (H1N1) infection, and that this risk is highest in the third trimester (17-19). In a cohort study (20), however, there was no death among 211 pregnant women, suggesting that the prevention of disease progression with early treatment might account for the cohort of mild cases. In the present study, pregnancy itself was not significantly associated with complications (spontaneous abortion, preterm labor, or fetal distress), the severity of illness, or death. This may be attributable to the small number of pregnant women as well as the early treatment with antiviral agent(s) in this study.

Several studies have suggested that fever is one of the most common symptoms (> 80%) at initial presentation (12, 21). In this study, approximately 80% of all hospitalized patients presented initially with fever; however, more than one-third of patients with severe illness had no fever at initial presentation, regardless of use of antipyretic agent(s). This finding suggests that pandemic influenza A (H1N1) 2009 should not be excluded in patients with severe influenza-like illness, even if they have neither fever nor a history of fever. Furthermore, a confirmatory test for pandemic influenza A (H1N1) 2009 may be necessary in such patients.

In recent studies (6, 7, 21), the presence of one or more comorbidities was found to be associated with both admission to ICU and death in patients with pandemic influenza A (H1N1) 2009. Comorbidities associated with complications of seasonal influenza are also risk factors for complications related to this virus. Although chronic lung disease, cardiovascular disease, and immunosuppression were more frequently detected in severe than in non-severe cases in the bivariate analysis of this study, they were not found to be independent risk factors for severe illness in the multivariate logistic regression analysis. Instead, the multivariate logistic regression analysis demonstrated that altered mental status, hypoxia, bilateral lung infiltration, and old age were independent risk factors for severe illness in adult patients hospitalized with pandemic influenza A (H1N1) 2009.

The use of neuraminidase inhibitor within 48 hr of symptom onset may reduce the risk of progression to severe illness or death (16, 21, 22). In an early report (23), the use of neuraminidase inhibitor even 48 hr after symptom onset was associated with reduced rates of death. In this study, however, more than 70% of infected patients received neuraminidase inhibitor within 48 hr after symptom onset, so that their clinical outcome was not related with the timing of antiviral administration.

The strengths of this study include it being a nationwide multicenter study with a large number of laboratory-confirmed cases, relatively little missing data, careful control of confounding factors in the analyses, and the establishment of a prediction rule for severe pandemic influenza A (H1N1) 2009 with large sample size (e.g., the number of events per each variable ≥ 40). This study has several limitations. Because only adult patients hospitalized with pandemic influenza A (H1N1) 2009 were included in this study, the derived prediction rule cannot be applied to estimate the severity of illness in children or adult outpatients. In addition, final outcome was measured as in-hospital mortality because many of the patients were lost to follow-up. Finally, a prediction rule derived from this study need be externally validated in other larger-scaled studies for testing accuracy and generalizability and studying the clinical impact of a rule on physician's behavior and patient's outcome (24).

In summary, although clinical features of adult patients hospitalized with pandemic influenza A (H1N1) 2009 can be diverse, altered mental status, hypoxia, bilateral lung infiltration, and old age are independent risk factors for severe illness. As a prediction rule, furthermore, the presence of ≥ 2 of these risk factors can be used to determine the likely severity of illness.

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AUTHOR SUMMARY

A Prediction Rule to Identify Severe Cases among Adult Patients Hospitalized with Pandemic Influenza A (H1N1) 2009

Won Sup Oh, Seung-Joon Lee, Chang-Seop Lee, Ji-An Hur, Ae-Chung Hur, Yoon Seon Park, Sang-Taek Heo, In-Gyu Pai, Sang Won Park, Eu Suk Kim, Hong Bin Kim, Kyoung-Ho Song, Kkot Sil Lee, Sang-Rok Lee, Joon Sup Yeom, Su Jin Lee, Baek-Nam Kim, Yee Gyun g Kwak, Jae Hoon Lee, Yong Keun Kim, Hyo Youl Kim, Nam Joong Kim, and Myoung-don Oh

During a pandemic, it is important to establish a prediction rule for detecting severe cases among patients with pandemic influenza A (H1N1) 2009. Data from this study showed that altered mental status, hypoxia ($PaO_2/FiO_2 \leq 250$), bilateral lung infiltration, and old age (≥ 65 yr) were independent risk factors for severe cases among patients with pandemic influenza A (H1N1) 2009. For detecting severe cases, the presence of ≥ 2 risk factors had a higher sensitivity, specificity, positive predictive value and negative predictive value than an APACHE II score of ≥ 13. As a prediction rule, the presence of ≥ 2 these risk factors can be easily used to determine the severity in adult patients hospitalized with pandemic influenza A (H1N1) 2009.