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Clinical Factors Predictive of Pneumonia Caused by Pandemic 2009 H1N1 Influenza Virus

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Abstract. Pneumonia was the most common cause of death during the 2009 pandemic H1N1 influenza virus infection. Clinical risk factors for pneumonia caused by this virus are limited. We enrolled consecutive patients treated at the H1N1 Clinic in Thungsong Hospital in Nakhon Si Thammarat, Thailand, during June–December 2009 who had positive polymerase chain reaction results for H1N1 virus. Clinical features for patients given a diagnosis with and without pneumonia were studied. There were 441 patients with positive polymerase chain reaction results for H1N1 virus. Of these patients, 51 (11.56%) had pneumonia. Three independent clinical factors for H1N1 pneumonia were myalgia, dyspnea, and an absolute neutrophil count > 7,700 cells/μL. Adjusted odds ratios (95% confidence intervals) for these three variables were 0.413 (0.173–0.988), 2.625 (1.230–5.604), and 4.475 (1.882–10.644), respectively. Clinical features may be a useful tool for predicting risk for pneumonia caused by H1N1 virus.

INTRODUCTION

Pneumonia was the most common cause of death during the 2009 pandemic H1N1 influenza virus infection. Clinical features of pneumonia caused by this virus are not different from those caused by seasonal influenza. A study from South Korea showed that clinical predictors of pneumonia are dyspnea, wheezing, vomiting, and diarrhea.[1] In Thailand, the first case report of pandemic 2009 H1N1 influenza virus infection was documented on May 12, 2009.[2] Clinical characteristics of patients infected with this virus might vary in different countries.[3,4] Data on predictors of pneumonia from pandemic 2009 H1N1 influenza virus are limited. In addition, the results of confirmatory tests for infection with pandemic 2009 H1N1 influenza virus may take up to several days in Thailand. Knowing clinical predictors for pneumonia caused by this virus might be helpful in early treatment. We report clinical predictors for pneumonia caused by this virus during the influenza outbreak in southern Thailand.

MATERIALS AND METHODS

Thungsong Hospital is a primary care hospital for a population of 150,169 persons in Thungsong District in Southern Thailand. Recently after the influenza outbreak in Thailand, we conducted an epidemiologic study of pandemic 2009 H1N1 influenza virus for the Thai government. The H1N1 clinic was established to monitor and treat H1N1 patients. All suspected patients were prospectively enrolled. All data were recorded by one study nurse and verified by the principle investigator (Sawan Kanchana).

We consecutively enrolled patients in the H1N1 clinic who had a positive result for H1N1 by real-time reverse transcription–polymerase chain reaction (rRT-PCR) during June–December 2009. The rRT-PCR has been used in a previous study.[5] Clinical presentations and laboratory results were recorded. A diagnosis of pneumonia was made if the patients had any one of the following signs or symptoms: tachypnea (respiratory rate > 60 breaths/minute if the person was less than 2 months of age, 50 breaths/minute if 2–12 months of age, 40 breaths/minutes if 1–5 years of age, 30 breaths/minute if 5–10 years of age, and 24 breaths/minute if > 10 years of age), dyspnea/chest pain, lung crepitation or consolidation signs upon physical examination, oxygen saturation at room air > 95% plus abnormal chest radiographic finding compatible with pneumonia. The study protocol was approved by the ethics committee for human research at Thungsong Hospital.

Descriptive statistics were used to compare clinical factors between persons with or without pneumonia caused by H1N1 influenza. All variables with $P < 0.20$ in univariate analysis were included in subsequent multivariate logistic regression analyses. All variables with $P > 0.20$ in the multivariate model were excluded, and variables with $P < 0.05$ were retained in the final model. The adjusted odd ratio (OR) was the risk of having pneumonia caused by H1N1 influenza compared with the risk of not having pneumonia caused by H1N1 influenza. Analytical results were presented as adjusted ORs and 95% confidence intervals. Goodness of fit of the final model was evaluated by using Hosmer-Lemeshow statistics. All data analyses were performed with STATA software version 10 (StataCorp LP, College Station, TX).

RESULTS

During the study, 5,651 patients were treated at the Thungsong H1N1 clinic. Of these patients, 441 had positive PCR test results for H1N1 virus. The diagnosis of pneumonia was made for 51 (11.56%) patients. Baseline clinical features and laboratory results for H1N1 patients without and with pneumonia are shown in Table 1. Most clinical variables were comparable between both groups. Patients without pneumonia had a higher frequency of headache and myalgia, and patients with pneumonia had a higher frequency of seasonal influenza vaccination, any underlying disease, body temperature > 39°C, a leukocyte count > 12,000 cells/mm^3,

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TABLE 1

Baseline characteristics of patients infected with pandemic 2009 H1N1 influenza virus with and without pneumonia*

Variable	No pneumonia, n = 390, no. (%)	Pneumonia, n = 51, no. (%)	*P*
Age, years	17.84 (3.24)	18.62 (0.76)	0.750
Males	176 (45.13)	28 (54.90)	0.188
Coryza	246 (63.08)	26 (50.98)	0.095
Nasal congestion	177 (45.38)	22 (43.17)	0.762
Headache	216 (55.38)	14 (27.45)	< 0.001
Myalgia	200 (51.28)	13 (25.49)	0.001
Fatigue	158 (40.51)	25 (49.02)	0.246
Vomiting	80 (20.51)	12 (23.53)	0.618
Diarrhea	41 (10.51)	6 (3.06)	0.785
Cough	364 (93.33)	45 (88.24)	0.187
Dyspnea	55 (14.10)	18 (35.29)	< 0.001
Sore throat	245 (62.82)	27 (52.94)	0.172
Contact with H1N1 virus–infected patients	95 (24.36)	12 (23.53)	0.897
Travel to outbreak area	31 (7.95)	3 (5.88)	0.603
Seasonal influenza vaccination	7 (1.79)	5 (9.80)	0.001
Underlying disease	59 (15.13)	16 (31.37)	0.004
Body temperature ≥ 39°C	78 (20.00)	18 (35.29)	0.013
Laboratory tests			
Leukocyte count > 12,000 cells/mm^3	25 (6.89)	13 (26.00)	< 0.001
Leukocyte count < 4,000 cells/mm^3	29 (7.99)	3 (6.00)	0.622
Absolute neutrophil count > 7,700 cells/μL	33 (8.99)	14 (27.45)	< 0.001
Absolute lymphocyte count < 1,500 cells/μL	123 (33.42)	22 (43.14)	0.172
Platelet count < 140,000/mm^3	24 (6.56)	3 (5.88)	0.854
Serum CPK > 200 U/L	68 (19.10)	13 (28.26)	0.145
Serum LDH > 500 U/L	143 (40.06)	30 (65.22)	0.001
Oseltamivir treatment after 48 hours	205 (52.56)	30 (58.82)	0.383

*CPK = creatine phosphokinase; LDH = lactate dehydrogenase.

an absolute neutrophil count > 7,700 cells/μL, and serum creatine phosphokinase and lactate dehydrogenase (LDH) levels > 500 U/L. The three most common underlying diseases were asthma (31 patients), hypertension/coronary artery disease (14 patients), and diabetes (8 patients). Other underlying diseases were chronic obstructive airway disease (5 patients), thalassemia (5 patients), and infection with human immunodeficiency virus (3 patients).

There were three significant factors in the final model predictive for pneumonia by multiple logistic regression analysis: myalgia, dyspnea, and an absolute neutrophil count > 7,700 cells (Table 2). The adjusted OR (95% confidence interval) for all three variables were 0.413 (0.173–0.988), 2.625 (1.230–5.604), and 4.475 (1.882–10.644), respectively (Table 2). The Hosmer-Lemeshow value was 5.47 ($P = 0.706$).

TABLE 2

Multiple logistic regression analysis of factors predictive of pneumonia caused by pandemic 2009 H1N1 influenza virus

Variable	Adjusted odd ratio	95% confidence interval
Myalgia	0.413	0.173–0.988
Dyspnea	2.625	1.230–5.604
Absolute neutrophil count > 7,700 cells/μL	4.475	1.882–10.644

DISCUSSION

There were three significant clinical factors predictive of pneumonia for persons infected with pandemic 2009 H1N1 influenza virus. One of them showed a negative correlation with pneumonia, and the others showed a positive correlation with pneumonia. Clinical factors may be helpful in facilities in which the results of laboratory tests for confirmation of H1N1 influenza are not rapidly obtained.

A history of myalgia may indicate risk for influenza but not a risk for pneumonia. Myalgia showed a negative correlation with pneumonia caused by H1N1 virus infection. This finding may be explained by the fact that having pneumonia may be associated with severe disease, and patients tended to have more severe clinical features such as dyspnea, body temperature > 39°C, and high levels of serum creatine phosphokinase or LDH. A previous study also showed that high body temperature is associated with a positive test result for H1N1 virus infection.[4]

Dyspnea and high levels of serum LDH were reported to be associated with the severe form of H1N1 influenza.[1,6] Having dyspnea increased the risk of having pneumonia caused by H1N1 influenza by a factor of 2.625. Dyspnea suggests a lower respiratory tract infection or pneumonia. Hypoxia catalyzes pyruvate to lactate and results in a high level of LDH. Persons with pneumonia caused by H1N1 virus infection were shown to have dramatically high levels of LDH, particularly in persons who died.[6] In our study, serum LDH levels > 500 U/L were significantly more common in patients with pneumonia, as analyzed by univariate analysis (Table 1). However, these levels were not an independent factor for H1N1 pneumonia. High levels of LDH may be associated with critically ill H1N1 patients but are not a predictor for H1N1 pneumonia.[1,6]

In an animal model, excessive neutrophils cause acute lung injury by forming neutrophil extracellular traps during H1N1 influenza pneumonitis.[7] Our clinical study showed similar results in which neutrophil levels are associated with pneumonia (adjusted OR = 4.475). The role of neutrophils in H1N1 virus infection is still unclear and can be protective or detrimental.[8] More than half (70%) of H1N1 virus–infected patients in China had high neutrophil levels.[9] These findings may imply that neutrophils may be the main responder cells during H1N1 virus infection and are significantly related to severity of the disease.

Previous reports showed that lymphopenia and thrombocytopenia were related to severity of H1N1 virus infection.[10,11] In our study, both factors were not associated with pneumonia. Compared with results of a previous study,[1] we found positive and negative independent predictors for pneumonia caused by H1N1 virus. In addition, laboratory tests and oseltamivir treatment were included in the analysis. We also confirmed that oseltamivir treatment after 48 hours of symptoms was not an independent factor for development of pneumonia. Thus, clinical features may be a useful tool for clinicians in predicting risk of pneumonia caused by H1N1 virus infection.

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