

SENSITIVITY AND SPECIFICITY OF CLINICAL FEATURES OF INFLUENZA LIKE ILLNESS AND LABORATORICAL FINDINGS FOR DIAGNOSED INFLUENZA A (H1N1) IN CHILDREN

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ABSTRAK

Departemen Kesehatan RI berdasarkan pedoman Pusat Pengendalian dan Pencegahan Penyakit WHO telah menerbitkan pedoman untuk diagnosis infeksi influenza A (H1N1) virus, dengan standart emas spesimen PCR. Diagnosis yang tepat dan terapi intensif dikaitkan dengan hasil yang menguntungkan. Alat sederhana diperlukan pada awal diagnosis untuk konfirmasi hasil PCR. Penelitian ini bertujuan mengeksplorasi kekuatan gambaran klinis penyakit mirip influenza dan temuan laboratorium sebagai prediktor influenza A (H1N1) pada anak. Penelitian ini merupakan studi kasus-kontrol retrospektif, dilakukan pada anak dengan kasus dugaan influenza A H1N1 yang dirawat di RSUD Dr. Soetomo dari Juli hingga September 2009. Dikonfirmasi seorang pasien influenza H1N1 berdasarkan rt RT-PCR H1N1 dari spesimen usap nasofaring. Dicatat gejala penyakit mirip influenza dan temuan laboratoris. Data dianalisis menggunakan uji X2. Kami menemukan bahwa pada 83 pasien yang dirawat dengan dugaan influenza A H1N1, dikonfirmasi 52 kasus (67,2%). Batuk ditemukan pada 81 kasus (97,6%), demam pada 50 kasus (60,2%) dan dari temuan laboratorium ada 40 kasus (48,2%) dengan limfopenia. Batuk dengan demam memiliki hubungan yang signifikan dengan kasus influenza A H1N1 ($p = 0,047$; LR 3,92, CI 95%, 1,002-6,238), dengan sensitivitas dan spesifisitas 71% dan 50% (PPV = 67%, NPV = 55%). Batuk dengan demam dan limfopenia dikaitkan dengan kasus dikonfirmasi influenza A H1N1 ($p = 0,009$, LR = 7.21, CI 95%, 1,359-10,089), dengan sensitivitas 79% dan spesifisitas 49% (PPV = 52%, NPV = 77%). Sebagai kesimpulan, tanda klinis batuk dengan demam dan temuan limfopenia terkait dengan hasil positif dari rt RT-PCR. Batuk dengan demam dan limfopenia lebih baik dalam memprediksi kasus konfirmasi influenza A H1N1.

ABSTRACT

Indonesian Health Department based on guidelines of WHO-Centers for Disease Control and Prevention had published a guidelines for diagnosed influenza A (H1N1) virus infection, with a gold standart of PCR specimen. Prompt diagnosis and intensive therapy was associated with favourable outcomes. A simple tools was need for early diagnosed to confirmed the PCR result. This study was to explore the strength of clinical features of influenza like illness and laboratorical findings as a predictor of influenza A (H1N1) in children. This was a retrospective case-control study was carried out among children with suspected case of influenza A H1N1 admitted to Soetomo hospital from July to September 2009. Confirmed influenza A H1N1 patient define based on rt RT-PCR H1N1 of specimen from nasopharyngeal swab. Symptoms of influenza like illness and laboratorical findings were noted. The data was analyzed using X2 test. We found that within 83 patients admitted with suspected influenza A H1N1, 52 cases (67.2%) were confirmed. Cough was found at 81 cases (97.6%), with fever at 50 cases (60.2%) and from laboratorical findings there were 40 cases (48.2%) with lymphopenia. Cough with fever had significant association with confirmed case of influenza A H1N1 ($p=0.047$; LR 3.92; CI 95%; 1.002-6.238), with sensitivity and spesificity 71% and 50% (PPV=67%;NPV=55%). Cough with fever and lymphopenia was associated with confirmed case of influenza A H1N1 ($p=0.009$;LR=7.21;CI 95%; 1.359-10.089), with sensitivity 79% and spesificity 49% (PPV=52%; NPV=77%). In conclusion, clinical sign of cough with fever and laboratorical findings of lymphopenia related with positive results of rt RT-PCR. Cough with fever and lymphopenia is better to predict confirmed case of influenza A H1N1.

Keywords: children, clinical features, laboratorical findings, influenza A H1N1

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INTRODUCTION

The outbreak of pandemic influenza H1N1 2009 in Mexico and the United States from late March to mid-April 2009 caused the World Health Organization on 11 June 2009 to raise the warning level for the virus to the highest available—Phase Six—indicating that this episode of influenza had entered a pandemic stage (WHO, 2009a) Different from strains in the past and

containing a unique combination of gene segments from swine, avian and human lineages, this new virus is able to spread among human beings, leading to influenza-like symptoms and progressing in a few cases to viral pneumonia, respiratory failure, multiple organ failure and death (Trifonov V, 2009). As of 13 December 2009, more than 208 countries and overseas territories or communities have reported laboratory-confirmed cases of pandemic influenza H1N1 2009, resulting in at least

10,582 deaths (WHO, 2009b). In June 28, 2009, Indonesia Ministri of Health declared first two cases confirmed with influenza A (H1N1) were found in Indonesia (Depkes, 2009a)

Unlike severe influenza A, which has characteristic findings, mild or moderate influenza A is clinically indistinguishable from influenza-like illness. Guidelines for the diagnosis of swine H1N1 influenza A virus have been released by the United States Centers for Disease Control and Prevention (CDC) (CDC, 2009). In September 2009, Indonesian Health Department issued guidelines on the diagnosis of influenza A (H1N1). Diagnosis is confirmed by clinical criteria symptoms of Influenza Like Illness (ILI) consisted of a fever with temperature $> 38^{\circ}\text{C}$, cough, runny nose, muscle aches and sore throat. Other possible symptoms accompanies the headache, shortness of breath, joint pain, nausea, vomiting and diarrhea. In children, clinical symptoms may occur fatigue. Diagnosis of a influenza A (H1N1) by rt RT-PCR performed only for treated patients, clusters and cases of influenza are not uncommon (unusual). Investigations are needed in patients treated (moderate and severe criteria) such as laboratory examination (a complete peripheral blood, liver function tests, renal function tests, blood sugar) and chest X-ray examination. Other tests depending on the indication. If leukopenia and thrombocytopenia were found, its will be confirmed the diagnosis, but if not found leukopenia and thrombocytopenia did not rule out the diagnosis (Depkes, 2009b).

The rt RT-PCR H1N1 as a gold standard diagnosis of influenza A (H1N1) is relatively takes time. Criteria for diagnosis of influenza A (H1N1) based on clinical criteria and a simple laboratory examinations are needed to provide immediate therapy. It is most needed, especially in peripheral health facilities. The aim of our study is to explore the strength of clinical features of influenza like illness and laboratorial findings as a predictor of influenza A (H1N1) in children.

MATERIALS AND METHODS

A retrospective case-control study was carried out among children with ILI suspected case of influenza A (H1N1) admitted to dr. Soetomo hospital from July to September 2009. Confirmed influenza A H1N1 patient define based on rt RT-PCR H1N1 of specimen from nasopharyngeal swab. Clinical diagnosis is confirmed by clinical criteria symptoms of ILI consisted of a fever with temperature $> 38^{\circ}\text{C}$, cough, runny nose, muscle aches and sore throat. Other possible symptoms accompanies the headache, shortness of breath, joint pain, nausea, vomiting and diarrhea. Blood routine

count were drawn to all of patients. Normal leukocyte count was 4,000-12,000/cm³. Leukopenia was leukocyte count less than 4,000/cm³. Normal thrombocyte count was 150,000-350,000/cm³, thrombocytopenia was thrombocyte count less than 150,000/cm³. Normal lymphocyte count was lymphocyte percentage 20-40%, lymphopenia was lymphocyte percentage less than 20%. Based on predominant symptoms at presentation were cough and fever, its used as clinical criteria. The data was analyzed using X2 test.

RESULTS

During a pandemic phase (July-September 2009), there were 83 patients admitted with symptoms of Influenza Like illness suspected influenza A (H1N1), 52 cases confirmed as influenza A (H1N1) based on the positive results of rt RT-PCR H1N1. Symptoms at presentation included cough, fever, dyspneu, diarrhea dan seizure. The most common clinical manifestation in the both group was cough and fever. Cough was found at 81 cases (97.6%), with fever at 50 cases (60.2%) and from laboratorial findings there were 40 cases (48.2%) with lymphopenia. (table 1)

Table 1. Clinical features of Influenzae like illness and laboratory findings based on rt RT-PCR H1N1 results

	rt RT-PCR H1N1		p value
	positive	Negative	
Symptoms of influenza like illness	35	14	0.030*
Leucocyte			NS
Decreased	5	2	
Normal	41	25	
Increased	6	4	
Thrombocyte count			NS
Decreased	15	11	
Normal	37	20	
Lymphocyte count			0.01*
Decreased	34	9	
Normal	18	22	

NS, not significant

* $p \leq 0.05$ using Chi-Square test

Table 1 shows the clinical criteria of cough and heat have significant differences ($p < 0.05$) between groups with positive rt RT-PCR results and others. Based on laboratory results, lymphopenia showed significant differences ($p < 0.05$) between the two groups. Cough with fever had significant association with confirmed case of influenza A H1N1 ($p = 0.047$; LR 3.92; CI 95%; 1.002-6.238), with sensitivity and specificity 71% and 50% (PPV=67%; NPV=55%). Cough with fever and lymphopenia was associated with confirmed case of

influenza A H1N1 ($p=0.009$; LR=7.21; CI 95%; 1.359-10.089), with sensitivity 79% and specificity 49% (PPV=52%; NPV=77%).

DISCUSSION

We described the 83 patients with influenza like illness suspected Influenza A H1N1 in Soetomo Hospital Surabaya at July-September 2011. Confirmed case based on rt RT-PCR result in our study was 62.5%, compared with patients in India (Sriram P, 2010) 24% of the total cases screen with symptoms influenza like illness was confirmed cases. The study in Korea (Park SI, 2010), confirmed cases was 52.6% of total cases screen with symptoms influenza like illness. Similar to the others studies (Sriram P, 2010; Park SI, 2010), the most clinical symptoms was cough and fever.

Clinical criteria and routine blood count, a simple laboratory examination was analyzed to get a predictor diagnostic confirmed cases influenza A (H1N1). It was the strength of our study because early identification of patients with influenza A H1N1 may enable the early administration of antiviral agents with possible improved outcome. We didn't use the chest-X ray because the facilities of chest X-ray examination is not always available in peripheral health service.

In this study, the most symptoms, cough with fever had significant association with confirmed case of influenza A H1N1 ($p=0.047$; LR 3.92; CI 95%; 1.002-6.238), with sensitivity and specificity 71% and 50% (PPV=67%; NPV=55%). Thrombocyte and leukocyte count is not helpful in diagnosis confirmed cases influenza A (H1N1). If clinical criteria combined with lymphopenia is better to predict confirmed case of

influenza A H1N1 ($p=0.009$; LR=7.21; CI 95%; 1.359-10.089), with sensitivity 79% and specificity 49% (PPV=52%; NPV=77%).

Study in Singapore on adults patient (Ong AK, 2009), among ARI cases, fever, cough, headache, rhinorrhea, the absence of leukocytosis, and a normal chest radiograph positively predict for both PCR-confirmed H1N1-2009 and seasonal influenza infection. The sensitivity and specificity of current WHO and CDC influenza-like illness (ILI) criteria were modest in predicting influenza infection. However, the combination of WHO ILI criteria with the absence of leukocytosis greatly improved the accuracy of diagnosing H1N1(2009) and seasonal influenza (positive LR of 7.8 (95%CI 3.5–17.5) and 9.2 (95%CI 4.1–20.3) respectively).

Study by Bewick A want (1) to compare and contrast the clinical features of adult patients admitted with CAP versus H1N1 influenza-related pneumonia and (2) to develop a model that identifies H1N1 influenza-related pneumonia using simple clinical criteria. This study showed that diagnostic prediction model was derived from five simple clinical criteria (age ≥ 65 years, presence of bilateral radiographic consolidation, absence of confusion as measured by orientation in time, place or person, leucocyte count $\geq 12 \times 10^9/l$ and temperature $\geq 38.0^\circ C$). Conclusion of this study was there are substantial clinical differences between H1N1 influenza-related pneumonia and inter-pandemic CAP. A model based on five simple clinical criteria enables the early identification of adults admitted with H1N1 influenza-related pneumonia (Bewick, 2010)

Table 2. Diagnostic test for influenza like illness and laboratory findings for diagnosing influenza A (H1N1) in children.

		rt RT-PCR H1N1		p value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR
		Positive	Negative						
Cough with fever	Yes	35	14	0.047*	71	50	67	55	3.92
	No	17	17						
Cough with fever and lymphopenia	Yes	27	7	0.009*	79	49	52	77	7.21
	No	25	24						

* $p \leq 0.05$ using Chi-Square test

CONCLUSION

Clinical sign of cough with fever and laboratorical findings of lymphopenia related with positive results of rt RT-PCR. Cough with fever and lymphopenia is better to predict confirmed case of influenza A H1N1.

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