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Original Article

Clinical predictors of hypoxemia in pneumonia

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ABSTRACT

Background Pneumonia is one of the main causes of death in infants in developing countries. The device of oxygen saturation measurement for detecting hypoxemia is limited in district hospitals.

Objective The aim of our study was to find the best clinical predictor for hypoxemia that could be used in Indonesia.

Methods Between June 2001 until May 2002, the diagnostic test was performed in 125 infants aged 2–12 month-old who suffered from pneumonia. The oxygen saturation measured by pulse oximetry was used as the gold standard.

Results The samples were divided into two groups, 52 infants with hypoxemia and 73 normal. The base characteristics of both groups were not statistically different. The prevalence of hypoxemia was 41.6%. The best single clinical predictor of hypoxemia was cyanosis (the sensitivity 92%, specificity 86%, likelihood ratio 6.74, post-test probability 83%), as well as the combination of two clinical predictors i.e., cyanosis and nasal flaring. The best combination of three clinical predictors was cyanosis, nasal flaring, and refusal to drink (the sensitivity 92%, specificity 86%, likelihood ratio 6.74, post-test probability 81%).

Conclusion The combination of cyanosis and nasal flaring is good enough as a predictor to detect hypoxemia in area with no facility of oxygen saturation measurement **[Paediatr Indones 2003;43:192-198].**

Keywords: *pneumonia, hypoxemia, oxygen saturation, cyanosis, nasal flaring*

Of 15 millions deaths in children each year (two third of them were less than 1 year-old), 4 millions were due to acute lower respiratory tract infection, mostly caused by untreated pneumonia with hypoxemia,[1] so it is important to detect hypoxemia as early as possible. Unfortunately, there are no facilities for blood gas analysis and pulse oximetry to detect hypoxemia in public health center, therefore, clinical signs and symptoms predictor are used as an alternative. The sensitivity and specificity of clinical predictor for hypoxemia according to WHO i.e., the respiration rate of >70/minute, refusal to drink, and cyanosis were 62% and 82% respectively.[2] In a study performed in Kenya, the respiration rate of >60/minute had a sensitivity of 71% and specificity 67%.[3] In Gambia, the head nodding, cyanosis and no cry had a sensitivity of 59% and specificity of 93%.[1] In a study in Papua New Guinea, the respiration rate of >90/minute, cyanosis, grunting, and unconsciousness had a sensitivity of 67% and specificity 70%.[4]

The clinical predictor of hypoxemia according to WHO based on several studies using African child was not really applicable if it was used in Indonesia which population mostly have brown skin. Ideally, clinical predictor of hypoxemia for Indonesian babies must be based on an experimental study performed in Indonesia using Indonesian population as the study sample. The aim of our study was to find an accurate clinical predictor of hypoxemia for Indonesian babies suffering from pneumonia.

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Methods

We compared several signs and symptoms of hypoxemia with arterial oxygen saturation (SaO_2) using portable pulse oxymetri (Nonin Medical Inc, USA). This study was performed in the Pediatric Pulmonology and Pediatric Emergency Care Unit – Denpasar Public Hospital, from June 2001 until May 2002. The inclusion criteria were babies from 2 to 12 months admitted with pneumonia and the diagnosis was supported by chest x-ray. Subjects were excluded if there was an accompanying disease i.e., anemia, polycythemia, heart disease, moderate or severe malnutrition, asthma bronchial, bronchiolitis, and dehydration. The minimal amount of samples needed for the study was 109 babies by estimating the proportion rate of no hypoxemia in pneumonia was 20%, the confidence interval was 95%, and the wide of standard deviation of sensitivity rate was 15%.

The diagnosis of pneumonia based on WHO criteria (1997) were chief complaint of cough or dyspneu, fever ≥38°C, respiration rate of ≥50/minute, with or without cyanosis, unconsciousness or chest indrawing, with chest x-ray picture of lobar consolidation, fluffy or patchy parenchymal infiltrates, streaky or wedge shaped opacities, parahillar-peribronchial infiltrates, reticular or reticulonodular infiltrates, or hazy to opaque lungs.[1,5] The clinical signs and symptoms of hypoxemia compared in the study were tachycardia (heart rate >140/minute),[6] tachypneu (respiration rate of ≥50/minute),[1] refusal to drink, unconsciousness (Modified Glasgow Coma Scale <11),[7] head nodding, nasal flaring, chest indrawing, central cyanosis, and cold extremities. Hypoxemia was defined as SaO_2 <90% by placing a censor of pulse oximetry on right thumb.[1,8-12]

Babies that fulfilled the inclusion criteria were evaluated by doing early physical examination to observe the clinical manifestation of hypoxemia, simultaneously with pulse oximetry evaluation. Before this physical evaluation, it must be ascertain that 3 L/minute oxygen had been given continuously with face mask for minimal 15 minutes. The oxygen flow was stopped first for five minutes only, for giving a time to perform an early physical examination. If a decrease of SaO_2 <60% occurred in the early physical examination period, the oxygen must be given again immediately. After finishing this early examination, the oxygen was given again in similar flow. This early examination was done by one observer and recorded on form A. The other independent observer asessed the SaO_2 using pulse oximetry and recorded it on form B (the first SaO_2 was asessed when starting the physical examination and the second was at the end of physical examination). The SaO_2 that was analyzed in the study was the mean of both SaO_2 values. The last step was performing a laboratory examination (peripheral blood test) and chest x-ray evaluation, then recorded it on form A to asess whether the sample fulfilled the inclusion criteria or not. Informed consent had been given to the parents.

Samples that fulfilled the inclusion criteria were separated into two groups according to SaO_2 results, the hypoxemic group if the SaO_2 was <90% and normal group if the SaO_2 was ≥90%. Before performing a diagnostic test, the two groups were analyzed with X^2 test and *t*-test for the difference of their demography, clinical, and laboratory characteristics. Data were processed using Statistical Product and Service Solutions 10.0 for Window with the level of significance adopted being $p < 0.05$.

The sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratio of each single dichotomous clinical manifestation of hypoxemia were calculated with 2 x 2 table with using SaO_2 of pulse oximetry as the gold standard. The numerical clinical manifestations were designed as Receiver Operator Characteristic Curve in several cutoff points, to find the best sensitivity and specificity. In the next step, we tried to combine two to four clinical manifestations with good sensitivity and specificity, then calculated the sensitivity, specificity, positive predictive value, negative predictive value, accuracy ,and likelihood ratio of each combination.

Results

Total amount of 125 babies with pneumonia fulfilled the inclusion criteria. Eleven were (8.1% of total 136 babies suffered from pneumonia) excluded from the study, three suffered from congenital heart disease, four with moderate to severe malnutrition, two with anemia, and two suffered from congenital heart disease accompanied with moderate to severe malnutrition.

Of 125 babies, 52 were hypoxemia (SaO_2 <90%), the other 73 babies were classified as normal. The prevalence of hypoxemia of these 125 babies who suffered from pneumonia was 41.6%. Of 52 hypoxemic babies, 30 (58%) babies had SaO_2 of <80%. Except for heart rate and SaO_2, there was no statistically difference at baseline characteristics between the hypoxemic group (N=52) and the normal group (N=73), as shown in **Table 1**.

The sensitivity and specificity of heart rate and respiration rate per minute are seen in **Table 2**, and that both clinical manifestations were not used again as combined clinical manifestations.

In diagnostic test of the other isolated clinical manifestations of hypoxemia, cyanosis had a sensitivity and specificity of 92.3% and 86.3%, respectively (**Table 3**). Chest indrawing was not used anymore in diagnostic test as combined clinical manifestations, because of its specificity of 0.0%.

In the next diagnostic test, cyanosis was used in all of combinations of two clinical manifestations of hypoxemia. The result of diagnostic test showed that the combination of cyanosis and nasal flaring had sensitivity and specificity of 92.3% and 86.3%, respectively (**Table 4**). This result was similar with the isolated clinical predictor of cyanosis, and also similar with the combination of cyanosis and refusal to drink.

Using a combination of three clinical manifestations of hypoxemia, it was found that the combination of cyanosis, nasal flaring and refusal to drink had sensitivity and specificity of 84.6% and 86.3%, respectively; it was similar to the combination of cyanosis

TABLE 1. THE CHARACTERISTICS OF THE HYPOXEMIC GROUP AND THE NORMAL GROUP AT BASELINE

Demographic, clinical, and laboratory characteristics		Hypoxemia (N=52)	Normal SaO_2 (N=73)
Sex, total	Male	36	56
	Female	16	17
Age, month, mean (SD)		4.7 (2.8)	4.4 (2.7)
Body weight, kg, mean (SB)		6.2 (1.7)	5.8 (1.4)
Percent of standard body weight, mean (SD) *		89.7 (11.6)	87.5 (12.4)
Rectal temperature, ^{0}C, mean (SD)		38.5 (0.4)	38.6 (0.4)
Heart rate per minute, mean (SD)		142.9 (7.1)	138.5 (9.1)
Respiration rate per minute, mean (SD)		69.0 (9.7)	68.8 (8.4)
Arterial oxygen saturation, %, mean (SD)		74.3 (12.0)	91.9 (1.7)
Peripheral blood test			
Hemoglobin, g/dL, mean (SD)		10.5 (0.9)	10.81 (1.2)
White blood cell count, K/uL, mean (SD)		17.7 (9.8)	15.02 (6.2)
Packed cell volume, %, mean (SD)		31.7 (3.3)	32.28 (3.3)
Platelet count, K/uL, mean (SD)		327.9 (115.6)	295.08 (116.0)

Note: * Standard body weight of Indonesian Health Department 1988 [13]

TABLE 2. THE SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE (PPP), NEGATIVE PREDICTIVE VALUE (NPR), ACCURACY (ACCUR), AND LIKELIHOOD RATIO (LH) OF HEART RATE AND RESPIRATION RATE PER MINUTE AS AN ISOLATED CLINICAL MANIFESTATION OF HYPOXEMIA

Isolated clinical manifestation	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accur (%)	LH
Heart rate ≥130/minute	100.0	20.6	47.3	100.0	53.6	1.26
Heart rate ≥135/minute	90.4	35.6	50.0	83.9	58.4	1.40
Heart rate ≥140/minute	67.3	60.3	54.7	72.1	63.2	1.69
Heart rate ≥145/minute	38.5	80.8	58.8	64.8	63.2	2.01
Heart rate ≥150/minute	9.6	86.3	33.3	57.3	54.4	0.70
Respiration rate ≥55/minute	96.2	0.0	40.7	0.0	40.0	0.96
Respiration rate ≥60/minute	88.5	11.0	41.4	57.1	43.2	0.99
Respiration rate ≥65/minute	63.5	34.3	40.7	56.8	46.4	0.97
Respiration rate ≥70/minute	32.7	56.2	34.7	54.0	46.4	0.75
Respiration rate ≥75/minute	32.7	79.5	53.1	62.4	60.0	1.59
Respiration rate ≥80/minute	21.2	83.6	47.8	59.8	57.6	1.29

TABLE 3. THE SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE (PPP), NEGATIVE PREDICTIVE VALUE (NPR), ACCURACY (ACCUR), AND LIKELIHOOD RATIO (LH) OF DICHOTOMOUS ISOLATED CLINICAL MANIFESTATION OF HYPOXEMIA

Isolated clinical manifestations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accur (%)	LH
Refusal to drink	92.3	52.1	57.8	90.5	68.8	1.93
Unconsciousness	46.2	100.0	100.0	72.3	77.6	¥
Head nodding	26.9	72.6	41.2	58.2	53.6	0.98
Nasal flaring	100.0	8.2	43.7	100.0	46.4	1.09
Chest indrawing	100.0	0.0	41.6	0.0	41.6	1.00
Cyanosis	92.3	86.3	82.8	94.0	88.8	6.74
Cold extremities	42.3	100.0	100.0	70.9	76.0	¥

Note: ¥ The Likelihood Ratio (LH) could not be calculated

and refusal to drink. Its positive predictive value, negative predictive value, accuracy ,and likelihood ratio were 81.5%, 88.7%, 85.6% and 6.2%, respectively. None of all combinations of four clinical manifestations had a good sensitivity and specificity as a clinical predictor of hypoxemia. The sensitivity and specificity of combination of cyanosis, nasal flaring, and refusal to drink became lower after being combined with one of other single clinical manifestations i.e., head nodding, cold extremities, and unconsciousness.

The pre-test probability had a same value as the prevalence of hypoxemia; it was 41.6%. The post-test probability of the best isolated and combined clinical manifestations as a clinical predictor of hypoxemia was 83% for the best isolated clinical manifestation (i.e. cyanosis), 83% for the best combination of two clinical manifestations (i.e., cyanosis and nasal flaring), and 81% for the best combination of three clinical manifestations (i.e., cyanosis, nasal flaring, refusal to drink).

Discussion

The characteristics of both groups (the hypoxemia and the normal groups) were similar; it was proven as there was no statistical difference between both groups in demographic, clinical and laboratory characteristics, except for SaO_2. It means that no other factors can influence hypoxemia, except for pneumonia. On the other hand, the evidence of significant difference in the mean SaO_2 between both groups showed that both groups were reliable to be used as the sample of diagnostic test study.

The exclusion of five samples with congenital heart disease was aimed to avoid using subjects with central cyanosis that was not only caused by disorders of oxygen diffusion and ventilation process. The central cyanosis in pneumonia accompanied with congenital heart disease may become worse, caused by intracardiac and intrapulmonal shunt as the result of the congenital heart disease.[14] Furthermore, tachycardia and tachypneu may be present, caused by the congenital heart disease before the occurrence of pneumonia.[6] We excluded the moderate and severe malnourished subjects, because the chest indrawing is easy to occur and the head nodding will be rare.[15,16] Subjects with anemia should be excluded because it can mask cyanosis appearance.[17-19]

Other studies about clinical predictors of hypoxemia reported different results[14] and were also different from our study. Some differences in subjects' characteristics and geography may influence the results. The study conducted by Dyke *et al* in Goroka high land in Papua New Guinea found that the best clinical predictor of hypoxemia was the combination of respiration rate >90/minute, cyanosis, grunting, and unconsciousness.[4] The altitude may have an influence, because the inspired oxygen concentration in high altitude is low.[20] Hypoxemia caused by disorders of oxygen diffusion and ventilation process will be worsened by the low inspired oxygen concentration. The age interval of Dyke's samples was wide from 3 months to 3 years. It was different from our study; we used samples that had a narrow age interval from 2 to 12 months, in order to reach the homogeneity of samples in term of respiration physiology. It is known that 0 to 1 month babies do not have many amount of alveoli, the chest cavity is relatively small, the accesorius respiration muscle has not grown perfectly, and the chest wall is still thin.[19,21,22] It is different from a 1 year-old or older child, they have a more capable respiration

TABLE 4. THE SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE (PPV), NEGATIVE PREDICTIVE VALUE (NPV), ACCURACY (ACCUR), AND LIKELIHOOD RATIO (LH) OF SEVERAL COMBINATION OF TWO CLINICAL MANIFESTATIONS OF HYPOXEMIA

Combination of two clinical manifestations of hypoxemia	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accur (%)	LH
Cyanosis, head nodding	26.9	90.4	66.7	63.5	64.0	2.81
Cyanosis, nasal flaring	92.3	86.3	94.0	94.0	88.8	6.74
Cyanosis, cold extremities	42.3	100.0	100.0	70.9	76.0	¥
Cyanosis, unconsciousness	48.1	100.0	100.0	73.0	78.4	¥
Cyanosis, refuse to drink	84.6	86.3	81.5	88.7	85.6	6.18

Note: ¥ The Likelihood Ratio (LH) could not be calculated

physiology.[19,21] Other reason why we recruited the 2–12-month babies was due to the high mortality in babies less than 1 year-old caused by acute lower respiration tract infection, especially pneumonia.[1]

Other study conducted also in Goroka high land found that cyanosis and refusal to drink were risk factors of severe pneumonia.[23] It is known that this burden of pneumonia is caused by the continuing hypoxemia; it results in hypoxia in some vital body organs.[10,22,24-26] It is similar with our study, which showed that cyanosis and refusal to drink was a good combination of two clinical manifestations as a predictor of hypoxemia, but it was not as good as the combination of cyanosis and nasal flaring. Although study conducted by Spooner *et al* had a wide deviation of age from 0 to 5 years,[23] it prooved that the heterogeneity factor of respiration physiology had only a little influence for the outcome.

Margolis *et al* had observed the capability of clinical examination to assess states of hypoxemia, which was done on babies less than 1 year-old in US. They found that single clinical manifestation was not accurate to detect hypoxemia,[27] then the accuracy was improved after being combined with other clinical manifestations. They reported that the combination of unconsciousness, tachypneu, and cyanosis was the most accurate predictor in detecting hypoxemia.

Our study found that cyanosis was the best single clinical predictor of hypoxemia; a combination of three clinical manifestations i.e., cyanosis, nasal flaring, and refusal to drink was a good predictor of hypoxemia. If the study by Margolis was applied to our study, the combination of clinical manifestations should perhaps be the best clinical predictor of hypoxemia. In our study, the value of likelihood ratio of the best single predictor of hypoxemia (LR 6.74) was similar to the best predictor using a combination of two clinical manifestations. However, the best predictor using a combination of three clinical manifestations had a quiet lower likelihood ratio (LR 6.18), but its sensitivity and specificity were still good (84% and 86%, respectively). Based on the value of post-test probability, the combination of cyanosis, nasal flaring, and refusal to drink was still good as a clinical predictor of hypoxemia.

The study conducted by Onyango *et al* in Kenya found that cyanosis was not the best predictor of hypoxemia,[3] in contrast to our study which found that cyanosis was the best single predictor of hypoxemia. We assumed that the difference probably occurs because it is more difficult to observe cyanosis appearance in Kenyan Negro child than in Indonesia child with brown skin. As the study of Weber *et al* in Gambian Negro child, the combination with cyanosis precisely decreased the sensitivity and specificity of combined predictors assessing hypoxemia.[2]

The clinical manifestations of respiration rate and heart rate per minute in our study seemed to be bad predictors of hypoxemia. The increase of respiration rate was not appropriate with linear equation as hypoxemia worsened. In early hypoxemia, the stimulation to peripheral and central chemoreceptor will stimulate the respiration center to do a hyperventilation (tachypneu) in order to get more oxygen.[14-16,28] However, if the hypoxemia worsens and becomes prolonged, the hypoxia of tissues will interfere with the brain function and hyperventilation coordination systems. It will result in the redecrease of respiration rate accompanied with irregular respiration rhythm, then it will finally lead to apnea if the respiration center is damaged.[14,15] As same as the increase of heart rate per minute, hypoxia of adrenal medulla in early hypoxemia will stimulate the secretion of catecholamine. Catecholamine will increase the sensitization of myo-

cardium that results in tachycardia.[10,29,30] However if the hypoxemia worsens and becomes prolonged, the chemoreceptor will stimulate vasomotor and cardioinhibitory center in brain stem, whereas the catecholamine decreases that results in periphery vasoconstriction and bradycardia.[29,30]

We concluded that the prevalence of hypoxemia in 125 babies suffering from pneumonia is 41.6%. The best clinical predictor of hypoxemia is the combination of cyanosis and nasal flaring, as same as single clinical predictor, namely cyanosis. This predictor can be used if there is no pulse oximetry or blood gas analysis available. In order to apply the clinical predictor of hypoxemia in older child, a similar study using older children as the sample population is needed.

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