Paediatrica Indonesiana

VOLUME 50 November • 2010 NUMBER 6

Original Article

# Clinical predictors of hypoxemia in 1-5 year old children with pneumonia

**Made Supartha[1], Putu Siadi Purniti[1], Roni Naning[2], Ida Bagus Subanada[1]**

## Abstract

***Background*** Pneumonia remains a major killer of under five children. Hypoxemia is the most serious manifestation of pneumonia. The most reliable way to detect hypoxemia is an arterial blood analysis or $SpO_2$. However, these tools are not widely available; therefore, a simple clinical manifestation should be used as an alternative.

***Objective*** To determine clinical predictors of hypoxemia in 1-5 year-old children with pneumonia in Indonesia.

***Methods*** This study was conducted between February 2007 to August 2008 at Sanglah Hospital, Denpasar, Bali. Sample was selected using a convenient sampling method. Subjects were divided into group of hypoxemia and normal saturation. We did clinical examination and $SpO_2$ measurement, as the gold standard, simultaneously.

***Results*** From 120 subjects,, the prevalence of hypoxemia was 17.5%. The best single clinical predictors of hypoxemia was cyanosis (sensitivity 43%, specificity 99%, positive predictive value (PPV) 90%, negative predictive value (NPV) 89%). The best combination of clinical predictors of hypoxemia was cyanosis and head nodding (sensitivity 43%, specificity 99%, PPV 90%, NPV 89%.

***Conclusion*** Cyanosis or combination of cyanosis and head nodding is useful clinical predictors of hypoxemia in childhood pneumonia. **[Paediatr Indones. 2010;50:355-60]**.

***Keywords:*** *pneumonia, hypoxemia, predictor*

One of the millennium development goals (MDGs) is to reduce child mortality.[1] World Health Organization (WHO) estimated that in 2002-2003, of the 10.6 million yearly deaths in children under five around the world, 19% died due to pneumonia.[2] In developing countries, pneumonia causes a high morbidity and mortality rates.[2,3] Hypoxemia is the most serious manifestation of pneumonia in children.[4,5] Children who suffer from hypoxemia in lower acute respiratory infection have five-fold increased risk of death compared to children without hypoxemia.[6,7] Because of this impact, early detection of hypoxemia is very important. The most reliable way is by arterial blood gas analysis or determination of arterial oxygen saturation by pulse oximeter ($SpO_2$). However, sometimes those tools are not widely available in all public health facilities, therefore, alternative simple diagnostic tools to detect hypoxemia should be used.[4,5]

Based on several studies in African children, clinical predictors of hypoxemia such as cyanosis,

From the Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Denpasar, Bali Indonesia.[1] From the Department of Child Health, Medical School, Gadjah Mada University, Sardjito Hospital, Yogyakarta, Indonesia.[2]

**Reprint request to**: Made Supartha, MD, Department of Child Health, Medical School, Udayana University, Sanglah Hospital, Jl. Pulau Nias, Denpasar, Bali, Indonesia. Tel. +62-361-244038. Fax. +62-361-244038. E-mail: *partha_bandem@yahoo.com*

inability to drink, severe chest wall retraction, or respiratory rate over 70 breaths per minutes, were not really applicable if used in Indonesia which population mostly have brown skin.[4,5] Skin color differences and environmental conditions such as high altitude may affect the accuracy of clinical predictors of hypoxemia if applied in Indonesia.[8] Although study on the clinical predictors of hypoxemia in pneumonia has been conducted on Indonesian infant, but the accuracy is not known when used in children under five. The aim of our study was to determine the clinical predictors of hypoxemia in 1-5 years old children suffered from pneumonia in Indonesia.

## Methods

This study was conducted between February 2007 and August 2008 at Department of Child Health, Sanglah Hospital, Denpasar, Bali. This study was approved by the Ethics Study Committee of Medical School, Udayana University, Sanglah Hospital. Written informed consent was obtained from the parents. We compared several signs and symptoms of hypoxemia with $SpO_2$ using portable pulse oximeter (Mindray PM 50). The inclusion criteria were children aged 1-5 years admitted with pneumonia and hospitalized in pediatric ward of Sanglah Hospital. We excluded children with any accompanying disease i.e., heart disease, anemia, polycythemia, shock, bronchial asthma, bronchiolitis, severe dehydration, and severe malnutrition.

The minimal number of subjects required in this study was 120 based on the confidence interval of 95% and the range of the standard deviation of the sensitivity and specificity rate of 10%, and the proportion of hypoxemia based on previous studies was 41%.[8] Diagnosis of pneumonia was based on WHO criteria for respiratory rate ≥40/minute, decreased breath sounds, bronchial breath sounds, crackles, abnormal vocal resonance (decreased over a pleural effusion, increased over lobar consolidation), and pleural rub. Severe pneumonia was established if there were cough or dyspnea plus at least one of the following signs: lower chest wall retraction, nasal flaring, in addition, some or all of the other signs of pneumonia may also be present. Diagnosis criteria for very severe pneumonia were cough or dyspnea plus at least one of the following: central cyanosis, inability to breastfeed or drink, or vomits, convulsions, lethargy or unconsciousness, and severe respiratory distress. In addition, some or all of the other signs of pneumonia or severe pneumonia may be present.[9,10] Hypoxemia was defined as $SpO_2 < 90\%$ using Mindray PM 50 pulse oximeter by placing a censor on right toe. The clinical manifestations tested in this study were restlessness, inability to drink, inability to feed, decreased of consciousness, tachycardia, tachypnea, head nodding, nasal flaring, chest wall retraction, and cyanosis.

Upon admission to the hospital, the researcher/ research assistant obtained data about illness history, physical examination and oxygen saturation from study subjects in specific form. If the patient arrived with oxygen supply, we released the oxygen supply for approximately two minutes[11] before clinical manifestations and $SpO_2$ measurement was conducted. Immediately after measurement was completed, the oxygen was reapplied as previously. The clinical manifestations of hypoxemia were obtained by one observer and recorded in form A. Another independent observer assessed the $SpO_2$ using a pulse oximeter, which was recorded in form B. When $SpO2 < 90\%$ occurred during clinical examination, the oxygen was given to the subject immediately. Blood sampling and chest x-ray were performed on all subjects.

We calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), prevalence and post-test probability of each single or combination of clinical manifestations of hypoxemia using the WINPEPI program. PLR of clinical manifestation was considered as an important predictor of hypoxemia if the value ≥ 10. If the PLR of a single predictor was ≥ 10, the predictors were combined with multiple parallel tests.

## Results

A total number of 131 children with pneumonia fulfilled the inclusion criteria. Eleven children were excluded from the study, because of anemia (1), heart disease (4), and severe malnutrition (4). Sixty-nine

subjects (57.5%) were male. The prevalence of hypoxemia in 120 subjects with pneumonia was 17.5%. **Table 1** shows baseline characteristics between the hypoxemic group and the normal saturation group.

The mean SpO2 in this study was 93% (SD 4.6%). The mean SpO2 of the hypoxemic group was 85% (SD 3.4%), while the mean SpO2 of the normal saturation group was 94% (SD 2.6%). SpO2 recorded in this study varied between 78 to 99%. Diagnostic evaluation of 10 single hypoxemia clinical manifestations, i.e., restlessness, inability to drink, inability to eat, unconsciousness, tachycardia, tachypnea, head nodding, nasal flaring, chest wall retraction, and cyanosis found that important single predictors of hypoxemia [PLR ≥ 10] were inability to drink, unconsciousness, head nodding, and cyanosis. Cyanosis is the best single clinical predictor of hypoxemia with a sensitivity of 43% (95% CI 25 to 64), specificity of 99% (95% CI 95 to 100), PPV of 90% (95% CI 63 to 98), NPV of 89% (95% CI 85 to 92), PLR of 42.4 (95% CI 5.7 to 317.1), NLR of 0.6 (95% CI 0.4 to 0.8), and post-test probability of 90% (95% CI 63 to 98). **Table 2** shows the predictive value for each single clinical manifestation of hypoxemia.

**Table 3** showed the predictive value for combinations of two clinical manifestations of hypoxemia. Based on diagnostic testing with a PLR ≥ 10, the combination of cyanosis and head nodding was the best predictors of hypoxemia with a sensitivity of 43% (95% CI 25 to 64), specificity of 99% (95% CI

**Tabel 1.** The characteristics of the hypoxemic group and the normal group at baseline

| Characteristics | Hypoxemia (n = 21) | Normal SpO2 (n = 99) |
|---|---|---|
| Age, month, mean (SD) | 23 (11.5) | 24 (12.2) |
| Percent of standard body weight/height, mean (SD) | 92 (12.4) | 94 (12.8) |
| Axilla temperature, 0C, mean (SD) | 38.1 (1.0) | 38.0 (2.2) |
| Heart rate per minute, mean (SD) | 122 (16.7) | 122 (14.3) |
| Respiration rate per minute, mean (SD) | 60 (11.9) | 55 (10.4) |
| Peripheral blood test | | |
| White blood cell count, K/µL, mean (SD) | 12.1 (5.9) | 12.8 (7.3) |
| Hemoglobin, g/dL, mean (SD) | 12.1 (1.1) | 11.8 (1.1) |
| Packed cell volume, %, mean (SD) | 36.8 (3.8) | 35.6 (3.8) |
| Platelet count, K/µL, mean (SD) | 340 (151.6) | 350 (125.3) |

**Table 2.** The predictive value of each single clinical manifestation of hypoxemia

| Single clinical manifestation | Sensitivity (%) | Spesificity (%) | ROC curve cut-off (%) | PPV (%) | NPV (%) | PLR | NLR | Post-test probability |
|---|---|---|---|---|---|---|---|---|
| Restleness | 33 | 78 | 56 | 24 | 85 | 1.5 | 0.9 | 24 |
| (95% CI) | (17 to 55) | (69 to 85) | (45 to 66) | (14 to 39) | (80 to 88) | (0.7 to 3.1) | (0.6 to 1.2) | (14 to 39) |
| Inability to drink | 33 | 98 | 66 | 70 | 87 | 16.5 | 0.7 | 70 |
| (95% CI) | (17 to 55) | (92 to 99) | (55 to 75) | (41 to 89) | (83 to 90) | (3.1 to 39.1) | (0.5 to 0.9) | (41 to 89) |
| Inability to feed | 24 | 91 | 60 | 36 | 85 | 3.1 | 0.8 | 36 |
| (95% CI) | (11 to 45) | (84 to 95) | (48 to 67) | (18 to 59) | (81 to 88) | (0.9 to 7.0) | (0.7 to 1.1) | (18 to 59) |
| Unconsciousness | 24 | 99 | 61 | 83 | 86 | 23.6 | 0.8 | 63 |
| (95% CI) | (11 to 45) | (92 to 99) | (51 to 70) | (32 to 86) | (82 to 88) | (2.0 to 30.4) | (0.6 to 1.0) | (32 to 86) |
| Tachycardia | 38 | 53 | 50 | 15 | 80 | 0.6 | 1.1 | 0.1 |
| (95% CI) | (21 to 59) | (43 to 62) | (-) | (-) | (-) | (-) | (-) | (-) |
| Tachypnoea | 100 | 7 | 54 | 19 | 100 | 1.1 | 0.0 | 19 |
| (95% CI) | (86 to 100) | (4 to 14) | (51 to 56) | (17 to 20) | (45 to 100) | (1.0 to 1.1) | (-) | (17 to 20) |
| Head nodding | 38 | 99 | 69 | 89 | 88 | 37.7 | 0.6 | 89 |
| (95% CI) | (21 to 59) | (80 to 100) | (58 to 79) | (60 to 98) | (9 to 16) | (4.9 to 285.7) | (0.5 to 0.9) | (60 to 98) |
| Nasal flaring | 91 | 67 | 79 | 37 | 97 | 2.7 | 0.1 | 37 |
| (95% CI) | (71 to 97) | (57 to 75) | (71 to 86) | (30 to 44) | (91 to 99) | (1.9 to 3.7) | (0.0 to 0.5) | (30 to 44) |
| Chest wall retraction | 100 | 0 | 18 | 18 | ∞ | 1.0 | ∞ | 0.2 |
| (95% CI) | (-) | (-) | (-) | (-) | (-) | (-) | (-) | (-) |
| Cyanosis | 43 | 99 | 71 | 90 | 89 | 42.4 | 0.6 | 90 |
| (95% CI) | (25 to 64) | (95 to 100) | (60 to 82) | (63 to 98) | (85 to 92) | (5.7 to 317.2) | (0.4 to 0.8) | (63 to 98) |

(-) could not be calculated.

95 to 100), PPV of 90% (95% CI 63 to 98), NPV of 89% (95% CI 85 to 92), PLR of 42.4 (95% CI 5.7 to 317.1), NLR of 0.6 (95% CI 0.4 to 0.8), and post-test probability of 90% (95% CI 63 to 98).

**Table 4** shows the predictive value for combinations of three clinical manifestations of hypoxemia. Combination of cyanosis, head nodding, and unconsciousness was the best clinical predictor of hypoxemia with a sensitivity of 43% (95% CI 25 to 64), specificity of 98% (95% CI 93 to 99), PPV of 82% (95% CI 55 to 94), NPV of 89% (95% CI 85 to 92), PLR of 21.2 (95% CI 4.9 to 91.2), NLR of 0.6 (95% CI 0.4 to 0.9), and post-test probability of 82% (95% CI 55 to 94).

Diagnostic testing for combination of four clinical manifestations of hypoxemia with an PLR ≥ 10, showed that combination of cyanosis, head nodding, unconsciousness, and inability to drink had a sensitivity of 48% (95% CI 28 to 68), specificity of 97% (95% CI 92 to 99), PPV of 77% (95% CI 52 to 91), NPV of 90% (95% CI 85 to 93), PLR of 15.7 (95% CI 4.7 to 52.2), NLR of 0.5 (95% CI 0.4 to 0.8), and post-test probability of 77% (95% CI 52 to 91).

## Discussion

The study was conducted at a low altitude area in Denpasar, approximately 41 meters above the sea level. During the study period, 21 subjects (17.5%) experienced hypoxemia. The prevalence of hypoxemia

**Tabel 3.** The predictive value of combination of two clinical manifestation of hypoxemia

| Combination of two clinical manifestation | Sensitivity (%) | Spesificity (%) | ROC curve *cut-off* (%) | PPV (%) | NPV (%) | PLR | NLR | *Post-test probability* |
|---|---|---|---|---|---|---|---|---|
| Cyanosis, head nodding (95% CI) | 43 (25 to 64) | 99 (95 to 100) | 71 (60 to 82) | 90 (63 to 98) | 89 (85 to 92) | 42.4 (5.7 to 317.2) | 0.6 (0.4 to 0.8) | 90 (63 to 98) |
| Cyanosis, unconsiousness (95% CI) | 43 (25 to 64) | 98 (93 to 99) | 70 (60 to 81) | 82 (55 to 94) | 89 (85 to 92) | 21,2 (4.9 to 91.2) | 0.6 (0.4 to 0.9) | 82 (55 to 94) |
| Cyanosis, inability to drink (95% CI) | 48 (28 to 68) | 97 (92 to 99) | 72 (62 to 83) | 77 (52 to 91) | 90 (85 to 93) | 15.7 (4.7 to 52.2) | 0.5 (0.4 to 0.8) | 77 (52 to 91) |
| Head nodding, unconsiousness (95% CI) | 43 (25 to 64) | 97 (92 to 99) | 70 (59 to 81) | 75 (49 to 90) | 89 (84 to 92) | 14.1 (4.2 to 47.9) | 0.6 (0.4 to 0.9) | 75 (49 to 90) |
| Head nodding, inability of drink (95% CI) | 48 (28 to 68) | 97 (92 to 99) | 72 (62 to 83) | 77 (52 to 91) | 90 (85 to 93) | 15.7 (4.7 to 52.2) | 0.5 (0.4 to 0.8) | 77 (52 to 91) |
| Unconsiousness, inability to drink (95% CI) | 33 (17 to 55) | 95 (89 to 98) | 64 (54 to 75) | 58 (34 to 79) | 87 (83 to 90) | 6.6 (2.3 to 18.8) | 0.7 (0.5 to 0.9) | 58 (34 to 79) |

**Tabel 4.** The predictive value of combination of three clinical manifestation of hypoxemia

| Combination of three clinical manifestation | Sensitivity (%) | Spesificity (%) | ROC curve *cut-off* (%) | PPV (%) | NPV (%) | PLR | NLR | *Post-test probability* |
|---|---|---|---|---|---|---|---|---|
| Cyanois, head nodding, unconsiousness (95% CI) | 43 (25 to 64) | 98 (93 to 99) | 70 (60 to 81) | 82 (55 to 94) | 89 (85 to 92) | 21.2 (4.9 to 91.2) | 0.6 (0.4 to 0.9) | 82 (55 to 94) |
| Cyanosis, unconsiousness, inability to drink (95% CI) | 48 (28 to 68) | 97 (92 to 99) | 72 (62 to 83) | 77 (52 to 91) | 90 (85 to 93) | 15.7 (4.7 to 52.2) | 0.5 (0.4 to 0.8) | 77 (52 to 91) |
| Cyanosis, unconsiousness, inability to drink (95% CI) | 48 (28 to 68) | 97 (92 to 99) | 72 (62 to 83) | 77 (52 to 91) | 90 (85 to 93) | 15.7 (4.7 to 52.2) | 0.5 (0.4 to 0.8) | 77 (52 to 91) |
| Head nodding, unconsiousness, inability to drink (95% CI) | 48 (28 to 68) | 95 (89 to 98) | 71 (60 to 82) | 67 (44 to 84) | 90 (85 to 93) | 9.4 (3.6 to 24.7) | 0.6 (0.4 to 0.8) | 67 (44 to 84) |

in this study differs from a previous study conducted at Sanglah Hospital in 2003, which have prevalence of hypoxemia of 41.6%.[8] This study used a different age range of study subjects (12-60 months) from the previous study (2-12 months). The prevalence of hypoxemia is 2.4 times higher in infants as reported in the previous study compared to children from this study. This result is similar to a study by Singhi et al[12] and Basnet et al[13], which showed a higher prevalence of hypoxemia in infants aged 2-12 months than children aged 12-60 months as much as 1.9 times and 2.2 times, respectively.

The high prevalence of hypoxemia in infants aged 2-12 months is because infants are vulnerable to acute respiratory infections, not only because their immune systems are immature, but also due to the impairment of mucus and secretion clearance, inhibiting the process of ventilation of these children. Infants are also incapable of verbal communication about breathing distress they might experience, resulting in them being brought in by their parents in a late state of hypoxemia.[13] Prevalence of hypoxemia in children under five with pneumonia are quite varied from one study to another. Based on a systematic literature review, the prevalence varies between 4 to 83%.[11] This variation may be caused by differences in subjectcharacteristics, age range, definition of hypoxemia, the location (whether in the emergency room, inpatient ward, or outpatient clinic) and altitude where the study was conducted. The prevalence of hypoxemia in this study was similar to a previous study which has prevalence of hypoxemia of 11.9%.[12] This study has similar subject characteristics and influencing factors with our study.

Studies in clinical predictors of hypoxemia in pneumonia have shown varied results. This may be caused by different characteristics.[11] In our study, the best single predictor of hypoxemia was cyanosis with PLR 42.4. This results was similar with previous study, which have a high value of PLR, although their sensitivity and specificity are different.[8]

Cyanosis is a specific but less sensitive sign of hypoxemia. Cyanosis is often influenced by a several factors such as the reduced amount of circulating hemoglobin, tissue thickness, blood flow, skin color, and quality of illumination. As a sign of hypoxemia, cyanosis is very useful, but often seen only in the final phase, may not always be found, and is a faint sign that may not be easily recognizable, especially in children who suffer from anemia and subjects with a pigmented skin[14,15] In the study by Duke et al[16], children who suffer from cyanosis have a median $SpO_2$ of 68%, whereas those without cyanosis have a $SpO_2$ of 74%. In the study, cyanosis was detected in only 44% of children with a $SpO_2$ between 70 to 84%. This is in accordance with the results of our study where the sensitivity of cyanosis was 42.9%. Head nodding is a more easily recognizable clinical manifestation. Head nodding was synchronous head and respiratory movement, which is visible due to the use of auxiliary respiratory muscles. Similar to grunting, the sign is more common in younger children, but may be found in all children under five. These symptoms are visible even though the children are still dressed.[14]

Combined clinical manifestations are used to improve the accuracy of clinical predictors of hypoxemia. Combined clinical manifestations are expected to increase the sensitivity, specificity, PPV, NPV, PLR, NLR and post-test probability of the predictor.[17] In this study, the combination of two clinical manifestation or more did not increase PLR if compared to a single predictor. None of the combinations of clinical manifestation had a high sensitivity and specificity. This is also similar to another study, which reported that the combined clinical manifestations do not enhance the predictive ability.[17]

WHO criteria for oxygen therapy are cyanosis, inability to drink, severe chest wall retraction and respiratory rate >70 times/minute with a sensitivity of 62% and specificity of 82%.[4,5] In our study, a combination of two existing clinical manifestations of WHO criteria, cyanosis and the inability to drink, had a high predictive value (PLR 15.7), although it had a low sensitivity 48%, with high specificity 97%. There were limitations in this study. The technique of sampling using convenient sampling method may affect the representativeness of the population covered.

In conclusion, cyanosis or a combination of cyanosis and head nodding are the best predictors of hypoxemia in 1-5 years old childhood pneumonia. The clinical predictors of hypoxemia in 1-5 years old childhood pneumonia should be used when other tests with higher diagnostic values, such as pulse oximeter and blood gas analysis, are not available.

## Acknowledgements

We express the highest gratitude to Prof. I Gde Raka Widiana, MD for his help in constructing the methodology and statistical analysis in this study. Our respect and gratitude to Department of Child Health, Medical School, Udayana University, Sanglah Hospital staffs, Denpasar and all patients who were participated in this study.

## References

1. World Health Organization. The millennium development goals report. 2008 [cited 2010 Mar 4]. Geneva: World Health Organization. Available from: http//www.undp.or.idpubsimdg2004BIIndonesiaMDG_BI_Goal4.pdf.
2. Bryce J, Boschi-Pinto C, Shibuya K, Black RE, WHO Child Health Epidemiology Reference Group. WHO estimation of the causes of death in children. Lancet. 2005;365:1147-52.
3. Unicef/World Health Organization (WHO). Pneumonia: the forgotten killer of children. New York: Unicef/World Health Organization, 2006; p. 1-44.
4. Weber MW, Usen S, Palmer A, Jaffar S, Mulholland EK. Predictors of hospital admissions with acute lower respiratory tract infection in a developing country. Arch Dis Child. 1997;76:310-4.
5. World Health Organization. Informal consultation on clinical use of oxygen. 2004 [cited 2005 Feb 4]. Geneva: World Health Organization. Available from: *http://www.who.int/surgery/collaborations/en/Oxygen_Meeting_Report_Geneva2003.pdf.*
6. Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxemia in young Kenyan children with acute lower respiratory infection. Br Med J. 1993;306:612-5.
7. Usen S, Weber MW, Mulholland K, Jaffar S, Oparaugo A, Omosigho C, et al. Clinical predictors of hypoxemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. Br Med J. 1999;318:86-91.
8. Gunawijaya E, Widia IM. Clinical predictors of hypoxemia in pneumonia. Paediatr Indones. 2003;43:192-8.
9. World Health Organization. Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources. Geneva: World Health Organization; 2005.
10. Said M. Pneumonia. In: Rahayu NN, Supriyatno B, Setyanto DB, editors. Buku ajar respirologi anak. 1st ed. Jakarta: Indonesian Pediatric Society Publishing House, 2008; p. 350-65.
11. Lozano JM. Epidemiology of hypoxemia in children with acute lower respiratory infection. Int J Tuberc Lung Dis. 2001;5:496-504.
12. Singhi S, Deep A, Kaur H. Prevalence and predictors of hypoxemia in acute respiratory infections presenting to pediatric emergency department. Indian J Crit Care Med. 2003;7:118-23.
13. Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its clinical predictors. Indian J Pediatr. 2006;73:777-81.
14. Usen S, Weber MW. Clinical signs of hypoxemia in children with acute lower respiratory infection: indicators of oxygen therapy. Int J Tuberc Lung Dis. 2001;5:505-10.
15. Wilson LM. Fungsi pernapasan normal. In: Wilson LM, Price SA, editors. Fisiologi proses-proses penyakit [terjemahan]. 4th ed. Michigan: Mosby Year Book Inc., 1992; p. 645-59.
16. Duke T, Mgone J, Frank D. Hypoxemia in children with severe pneumonia in Papua New Guinea. Int J Tuberc Lung Dis. 2001;5:511-9.
17. Lodha R, Bhadauria PS, Kuttikat AV, Puranik M, Gupta S, Pandey RM, et al. Can clinical symptoms or signs accurately predict hypoxemia in children with acute lower respiratory tract infections? Indian J Pediatr. 2004;41:129-35.