EVALUATION OF BIOMARKERS TO PREDICT OUTCOMES AMONG CHILDREN HOSPITALIZED WITH SEVERE COMMUNITY ACQUIRED PNEUMONIA IN WEST NUSA TENGGARA PROVINCE GENERAL HOSPITAL, INDONESIA

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Abstract. Community Acquired Pneumonia (CAP) is a leading cause of respiratory morbidity and mortality among children aged <5 years. In this study, we aimed to evaluate biomarkers associated with outcomes in severe CAP cases in order to guide management of these cases. Study subjects were children aged 1-59 months hospitalized with severe CAP during January to October 2018. The study was performed prospectively at West Nusa Tenggara Province General Hospital in Mataram, Indonesia. Inclusion criteria for study subjects were being of study age hospitalized at the study institution during the study period with severe CAP. The exclusion criterion for study subjects was having one or more comorbidities that could significantly affect the variables studied. We recorded the following on admission: c-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), leukocyte count (LC) and neutrophil-to-lymphocyte ratio (NLR). Patient outcomes (duration of oxygen use, length of hospital stay, death) and demographic characteristics were also recorded. A total of 90 subjects were included in the study, 59% male. The median subject age was 7 months. Our results showed none of the biomarkers were associated with duration of oxygen use or length of hospital stay. Only one factor was significantly associated with outcome: for every log increase in ESR, the age-adjusted log odds of dying due to severe CAP decreased by 3.3 ($p = 0.043$). Children aged <59 months admitted to the study hospital with a diagnosis of severe CAP who have a low ESR should be monitored more carefully and treated more aggressively due to their higher odds of dying from severe CAP.

Keywords: Community Acquired Pneumonia, outcomes, children, biomarkers

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INTRODUCTION

Pneumonia is a leading cause of morbidity and mortality in children aged <5 years (Walker *et al*, 2013). Severe community-acquired pneumonia (CAP)

comprises an estimated 7-13% of these pneumonia cases (Rudan *et al*, 2013; Walker *et al*, 2013). Severe CAP is defined as a previously healthy child with a community source of infection who presents with difficulty in breathing and any of the following: oxygen saturation <90% on room air or central cyanosis; severe respiratory distress; the presence of danger signs, such as inability to drink or breastfeed, altered consciousness or convulsions; and chest radiography showing an infiltrate or consolidation (Cherian *et al*, 2005; Principi and Esposito, 2011; WHO, 2013; Agweyu *et al*, 2018). It would be useful for patient management to know if there are any factors significantly associated with poor outcomes in these patients in order to inform the monitoring and management of these subjects. There is little consistent published data regarding outcomes and associated biomarkers among children aged <59 months hospitalized with severe CAP and most of these studies are retrospective (Porter Moore *et al*, 2013; Bekdas *et al*, 2014; Williams *et al*, 2015; Ning *et al*, 2016). Therefore, in this study we aimed to determine if there were any biomarkers associated with outcomes among children aged <5 years hospitalized with severe CAP in the study hospital during the study period in order to inform management strategies.

MATERIALS AND METHODS

Ethical approval for this study was obtained from the West Nusa Tenggara Province General Hospital Ethics Committee (070.1/23/KEP/2017). Written informed consent to participate in the study was obtained from the parents of all subjects prior to inclusion in this study.

The study institution was the Pediatrics Department, West Nusa Tenggara Province General Hospital, Indonesia. The study was conducted prospectively during January-October 2018. All subjects meeting inclusion criteria during the study period at the study hospital were invited to participate in the study.

Inclusion criteria for study subjects were: being aged 1-59 months, admitted to the study hospital during study, having a diagnosis of severe CAP and having a parent willing to give consent to participate in the study. A case of severe CAP was defined as a previously healthy child with a source of infection in the community who presented with difficulty in breathing and having any of the following: an oxygen saturation <90% on room air or central cyanosis; having severe respiratory distress (*eg* tachypnea for age, grunting, severe chest retractions); the presence of danger sign, such as inability to drink milk, having altered consciousness, having convulsions; and having a chest radiograph showing an infiltrate or consolidation (Cherian *et al*, 2005; WHO, 2005; Principi and Esposito, 2011; WHO, 2013; Agweyu *et al*, 2018). Tachypnea for age was defined as: >60 breaths/minute in a child aged <2 months; >50 breaths/minute in a child aged 2-11 months; >40 breaths/minute in a child aged 1-5 years (WHO, 2005; WHO, 2013).

The exclusion criterion for study subjects was having a comorbid condition on hospital admission that could significantly affect the results of the studied factors, such as acute leukemia with leukocytosis, aplastic anemia, severe anemia, sepsis, cyanotic congenital heart disease (CHD), human immunodeficiency virus (HIV) infection, or an autoimmune disease, such as systemic lupus erythematosus or rheumatoid arthritis.

Demographic characteristics, socio-economic factors (including parental education level and occupation, household crowding, and family income), passive cigarette smoke exposure, immunization status, nutritional status, breastfeeding, prematurity, birth order, significant medical history, clinical features on admission, danger signs and symptoms and outcomes were also recorded for each subject. Danger signs and symptoms were defined as an inability to breastfeed or drink, persistent vomiting, lethargy, loss of consciousness, convulsions and severe malnutrition (WHO, 2014). A low family income was defined as a family income < IDR 1,000,000 per month. Overcrowding was defined as living with >3 persons per room (WHO, 2018). The 2006 World Health Organization Child Growth Standards were used to classify subjects as being normal, wasted, severely wasted, or overweight for age (WHO, 2006). Outcomes recorded were duration of oxygen use, length of hospital stay, and death.

Chest radiography was conducted on all subjects within 24 hours of admission and the films were read by a radiologist and the results recorded. The following laboratory tests were performed within 24 hours of admission: complete blood count (CBC), c-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), leukocyte count (LC) and neutrophil-to-lymphocyte ratio (NLR). The CBC was performed using a *Sysmex-XT*™ (Sysmex Corporation, Kobe, Japan). The CRP level was measured using the immunometric method with a *NycoCard*™ CRP (Alere Technologies AS, Oslo, Norway). The ESR was measured by the Westergren method.

Statistical analyses were done using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM, Chicago, IL). CRP and ESR levels and leukocyte counts were log transformed prior to analysis. We used simple linear regression analysis to evaluate the potential association between biomarkers and duration of oxygen use as well as length of hospital stay. Multiple linear regression was used to analyze these associations adjusting for age, sex, nutritional status, chest radiography results, and oxygen saturation on admission. We used simple logistic regression analysis to evaluate potential associations between individual biomarkers and mortality. Multiple logistic regression analysis was used to evaluate these associations adjusting for age and oxygen saturation on admission. The associations were reported as regression coefficients (SE) and odds ratios with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

RESULTS

A total of 90 subjects were included in this study (Fig 1), 59% male. The median age of subjects was 7 months; 68% were aged <1 year. Eighty-seven percent of subjects had been exposed to passive cigarette smoke, 56% lived in a crowded environment, 62% came from a family with a low income and 90% were exclusively breastfed (Table 1).

Clinical danger signs were found in 42% of subjects on admission, 81% had a comorbid condition, and 10% had more than 1 comorbid condition (Table 2). These comorbidities did not affect studied factors. Iron deficiency anemia was the most common comorbid condition (64%). Seventy-two percent of subjects had a normal nutritional status. Twenty-six percent of subjects were stunted and 19% were severely stunted. The

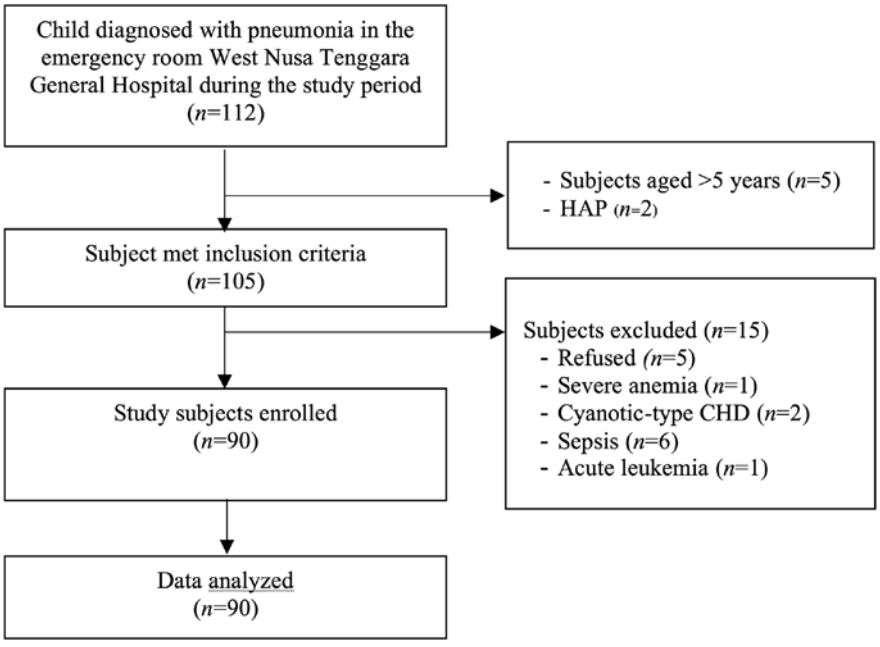

Fig 1-Study subject recruitment

HAP: hospital acquired pneumonia, defined as pneumonia occurred 48 hours or more after being hospitalized.

Table 1
Demographic characteristics of study subjects.

Characteristics	*n* = 90
Median (min, max) age in months	7 (1, 59)
Subject age groups in months, number (%)	
1 - 11	61 (68)
12 - 23	21 (23)
24 - 35	5 (6)
36 - 47	1 (1)
48 - 59	2 (2)
Gender, number (%)	
Male	53 (59)
Female	37 (41)
Subjects born with a low birth weight, number (%)	18 (20)
Subjects born prematurely, number (%)	11 (12)
Subject breastfed, number (%)	
Exclusively	81(90)
Not exclusively	6 (7)
Not breastfeeding	3 (3)

Table 1 (Continued)

Characteristics	$n = 90$
Completed immunizations for age, number (%)	48 (53)
Birth order in family, number (%)	
First	32 (36)
Second or more	58 (64)
Passive cigarette smoke exposure, number (%)	78 (87)
Living in a crowded environment, number (%)	50 (56)
Maternal education, number (%)	
None	2 (2)
Elementary school	15 (17)
Junior high school	29 (32)
Senior high school	29 (32)
University	15 (17)
Paternal education, number (%)	
None	3 (3)
Elementary school	18 (20)
Junior high school	19 (21)
Senior high school	38 (42)
University	12 (13)
Maternal occupation, number (%)	
None	72 (80)
Government employee	1 (1)
Private employee	5 (6)
Entrepreneur	8 (9)
Education worker	3 (3)
Health worker	1 (1)
Paternal occupation, number (%)	
None	1 (1)
Government employee	4 (4)
Private employee	20 (22)
Farmer/laborer	39 (43)
Entrepreneur	23 (26)
Education worker	3 (3)
Family monthly income in IDR, number (%)	
< 500,000	18 (20)
500,000 - 999,999	38 (42)
1,000,000 - 2,999,999	25 (28)
3,000,000 - 5,000,000	5 (6)
> 5,000,000	4 (4)

Low birth weight was defined as birth weight < 2,500 g; premature was defined as gestational age < 37 weeks; IDR: Indonesian Rupiahs

Table 2
Clinical characteristics of study subjects.

Clinical characteristics	$n = 90$
History of: number (%)	
Previous CAP	14 (16)
Atopy in family	18 (20)
Comorbidity, number (%)	
Iron deficiency anemia	58 (64)
Congenital heart disease	8 (9)
Global developmental delay	7 (8)
Febrile seizures	4 (4)
Measles	4 (4)
Tuberculosis	3 (3)
Diarrhea	3 (3)
Others[a])	9 (10)
Number of comorbid conditions, number (%)	
None	17 (19)
1 or 2	64 (71)
>2	9 (10)
Clinical features on admission	
Mean (SD) respiratory rate per minute	53.2 (11.8)
Mean (SD) pulse rate per minute	145.4 (23.3)
Median (min, max) axillary temperature in °C	37.4 (36, 41.2)
Median (min, max) oxygen saturation	90 (60, 98)
Retractions, number (%)	90 (100)
Crackles, number (%)	90 (100)
Wheezing, number (%)	36 (40)
Danger signs, number (%)	38 (42)
Nutritional status defined as weight-for-length/height, number (%)	
Normal	65 (72)
Wasted	10 (11)
Severely wasted	8 (9)
Overweight	7 (8)
Nutritional status defined as length/height-for-age, number (%)	
Normal	50 (55)
Stunted	23 (26)
Severely stunted	17 (19)
Outcomes	
Median (min, max) duration of fever in days	3 (0, 18)
Median (min, max) time in hours requiring oxygen	133 (9, 465)
Median (min, max) length of hospitalization in hours	133 (9, 467)
CAP complications[b], number (%)	7 (8)
Requiring admission to the intensive care unit, number (%)	7 (8)
Deaths, number (%)	4 (4)

Danger signs were defined as inability to breastfeed or drink, persistent vomiting, lethargy, loss of consciousness, convulsions and severe malnutrition; wasted: body weight was between -2 and -3 SD of weight for length/height 2006 WHO Child Growth Standard; severely wasted: body weight was <-3 SD of weight for length/height 2006 WHO Child Growth Standard; overweight: body weight was >2 of weight for length/height 2006 WHO Child Growth Standard; stunted: body height was between -2 and -3 SD of height for age 2006 WHO Child Growth Standard; severely stunted: body height was <-3 SD of height for age 2006 WHO Child Growth Standard.

[a]Others: Down syndrome, congenital hypothyroid, thalassemia, epilepsy; [b]CAP Complication: respiratory failure, pleural effusion, pneumothorax, sepsis, meningoencephalitis; CAP: community acquired pneumonia; SD: standard deviation.

shortest duration of oxygen use during hospitalization and the shortest length of hospital stay occurred in one subject who died in the emergency room before being transferred to the intensive care unit (ICU). The longest duration of oxygen use during hospitalization (465 hours) and the longest length of hospital stay (685 hours) occurred in one subject with epilepsy and recurrent seizures. Ninety-two percent of subjects recovered completely, 4% were discharged against medical advice, and 4% died; one in the emergency room, one in the intensive care unit and two on the intermediate ward. Seven subjects required intensive care but only 4 of them were actually transferred to the ICU, 2 of whom required mechanical ventilation. The other 3 subjects were hospitalized in the regular pediatric ward due to lack of available ICU beds. Complications occurred in seven subjects: 2 developed respiratory failure, 2 developed sepsis, 1 developed a pleural effusion, 1 developed a pneumothorax and 1 developed meningoencephalitis.

Chest radiography and laboratory results are shown in Table 3. On chest radiography, 59% had an infiltrate only, 1% had consolidation only, 38% had both an infiltrate and consolidation, 1% had an infiltrate combined with a pleural effusion, and 1% had an infiltrate combined with a pneumothorax.

There was no association between CRP, ESR, LC, NLR and duration of oxygen use or length of hospital stay (p>0.05) (Tables 4 and 5). Because these two outcomes reflected the duration needed for hospital care, subjects who died or were discharged against medical advice were not included in these analyses.

There was no significant association between CRP, LC, NLR, and mortality. After adjusting for age, we found ESR was inversely associated with mortality: for every one log increase in ESR, the log odds of dying due to severe CAP decreased by 3.3 (p=0.043) (Table 6).

DISCUSSION

The majority of hospitalized CAP patients in our study were aged < 2 years. These results are similar to a study conducted in Bandung, Indonesia, in which 90% of subjects hospitalized with severe pneumonia were aged 2-24 months (Nataprawira *et al*, 2010).

Most of our study subjects were male, similar to several previous studies which reported most children hospitalized with severe CAP were male (Jroundi *et al*, 2014; Ansari *et al*, 2017).

Eighty-seven percent of the subjects in our study had been exposed to passive cigarette smoke, similar to the findings of a study from Bandung, Indonesia that

Table 3
Chest radiography and laboratory results of study subjects.

Results	$n = 90$
Chest radiography results, number (%)	
Infiltration	53 (59)
Consolidation	1 (1)
Infiltration and consolidation	34 (38)
Infiltration with pleural effusion	1 (1)
Infiltration with pneumothorax	1 (1)
Laboratory results	
Median (min, max) hemoglobin level in g/dl	10 (6.3, 18.0)
Median (min, max) leukocyte count in cells/mm^3	11.570 (3.610, 52.630)
Median (min, max) neutrophile:lymphocyte ratio	1.11 (0.08, 13.84)
Median (min, max) CRP level in mg/L	15 (4, 310)
Median (min, max) ESR in mm/hr	14 (2,95)

CRP: c-reactive protein; ESR: erythrocyte sedimentation rate.

Table 4
Association between CRP, ESR, leukocyte count, neutrophil/lymphocyte ratio and duration of oxygen use.

Variable	Unadjusted B[a](SE)	*p*-value	Adjusted B[b](SE)	*p*-value
Log CRP	0.048 (0.053)	0.375	-0.041 (0.062)	0.510
Log ESR	0.050 (0.087)	0.568	0.126 (0.093)	0.184
Log leukocyte count	0.031 (0.119)	0.796	-0.102 (0.130)	0.438
Neutrophil/ lymphocyte ratio	-0.016 (0.030)	0.603	0.074 (0.045)	0.110

[a]Regression coefficient by simple linear regression analysis; [b]regression coefficient by multiple linear regression analysis adjusted for age, gender, nutritional status, abnormal chest radiography result, oxygen saturation on admission; SE: standard error; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate.

reported 75.8% of children hospitalized with severe CAP had a history of exposure to passive cigarette smoke (Wulandari *et al*, 2013). Most subjects in our study lived in a crowded environment. A study from India also reported 81.7% of children hospitalized with severe CAP had been living in a crowded environment (Ansari *et al*, 2017).

Our study hospital is a provincial referral hospital, so many study subjects had comorbid conditions, experienced complications, and were sicker on presentation. Iron deficiency anemia was the most common comorbid condition found, similar to a previous study from Lombok, Indonesia among children hospitalized with severe CAP children that found most of their subjects had iron deficiency anemia (Indriyani and Krisna, 2018).

Table 5
Association between CRP, ESR, leukocyte count, neutrophil/lymphocyte ratio and length of hospital stay.

Variable	Unadjusted B[a](SE)	*p*-value	Adjusted B[b](SE)	*p*-value
Log CRP	0.022 (0.040)	0.577	-0.055 (0.041)	0.189
Log ESR	-0.001 (0.065)	0.982	0.073 (0.062)	0.248
Log leukocyte count	0.094 (0.088)	0.289	-0.016 (0.087)	0.858
Neutrophil:lymphocyte ratio	-0.022 (0.022)	0.325	0.016 (0.030)	0.602

[a]Regression coefficient by simple linear regression analysis; [b]regression coefficient by multiple linear regression analysis adjusted by age, gender, nutritional status, abnormal chest radiography, oxygen saturation at admission; SE: standard error. CRP: c-reactive protein; ESR: erythrocyte sedimentation rate.

Four of the 90 subjects in our study (4%) died. This number is similar to the mortality rates reported among children with severe CAP at our hospital in 2015 (4.3%) and 2016 (Indriyani and Krisna, 2018). Variable mortalities rates of been reported from Kenya (5%) (Agweyu *et al*, 2018), India (10.3%) (Ansari *et al*, 2017) and Bandung, Indonesia (2.6%, 7.2%) (Nataprawira *et al*, 2010; Wulandari *et al*, 2013).

In our study, we found no associations between CRP and duration of oxygen use or length of hospital stay. In contrast to our study results, a study from USA among children aged 2 months to 18 years reported that for every increase in CRP level of 1 mg/dl, the length of hospital stay increased by 1 hour (Williams *et al*, 2015) and a study from India found shorter duration of oxygen use and length of hospital stay in children with severe CAP with lower CRP levels (Yadav *et al*, 2015).

In our study, CRP was not associated with mortality similar to previous studies from Bandung, Indonesia (Wulandari *et al*, 2013) and Egypt (Atwa, 2015) but in contrast to a study from Sudan (Salih *et al*, 2015).

In our study, we found no association between LC and duration of oxygen use or length of hospital stay similar to the findings of several previous studies (Porter Moore *et al*, 2013; Bekdas *et al*, 2014; Williams *et al*, 2015).

In our study, we also found no association between LC and mortality. in contrast to a previous similar study (Atwa, 2015).

In our study, we found no association between NLR and mortality, also in contrast to a previous study (Mathews *et al*, 2019).

In our study, we found no association between ESR and duration of oxygen use or length of hospital stay but did find a significant association between ESR and mortality: the higher ESR the lower the chance of dying due to severe CAP. One study from USA reported subjects with a higher ESR were less likely to be admitted to the ICU (Porter Moore *et al*, 2013) but another study did not find this association (Bekdas *et al*, 2014). The ESR begins to increase 48 hours after the onset of inflammation, later than other acute phase reactants. The ESR peaks at about 120 hours after the onset of inflammation and

Table 6
Association between CRP, ESR, leukocyte count, neutrophil/lymphocyte ratio and mortality.

Variable	Unadjusted B[a](SE)	OR (95% CI)	*p*-value	Adjusted B[b](SE)	OR (95% CI)	*p*-value	Adjusted B[c](SE)	OR (95% CI)	*p*-value
Log CRP	-0.058 (0.412)	0.94 (0.42; 2.12)	0.887	0.395 (0.549)	1.49 (0.51; 4.36)	0.472	0.125 (0.555)	1.13 (0.38; 3.37)	0.821
Log ESR	-2.017 (0.986)	0.13 (0.02; 0.92)	0.041	-3.324 (1.642)	0.04 (0.00; 0.90)	0.043	-2.279 (1.230)	0.10 (0.01; 1.14)	0.064
Log leukocyte count	1.162 (0.952)	3.20 (0.50; 20.63)	0.222	0.997 (1.382)	2.71 (0.18; 40.71)	0.471	1.381 (1.324)	3.98 (0.30; 53.34)	0.297
Neutrophil/ lymphocyte ratio	0.064 (0.193)	1.07 (0.73; 1.56)	0.741	1.264 (0.673)	3.54 (0.95; 13.24)	0.060	0.217 (0.240)	1.24 (0.78; 1.99)	0.365

[a]Regression coefficient by simple logistic regression analysis; [b]regression coefficient by multiple logistic regression analysis adjusted by age; [c]regression coefficient by multiple logistic regression analysis adjusted by oxygen saturation at admission; CI: confidence interval; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; SE: standard error; OR: odds ratio.

persists beyond the inflammatory process. A poor increase in the ESR may reflect a suboptimal inflammatory response by the immune system, which could be associated with greater mortality risk (Kjelgaard-Hansen and Jacobsen, 2011).

There were some limitations in our study. First, because 4 of the 90 subjects died, the mortality rate was too small to make conclusions. Second, we only measured biomarkers once on admission and repeated them only if there was no improvement, so we do not know if the biomarkers changed over time. We also did not measure procalcitonin (PCT) levels due to the expense and lack of facilities. Third, for referral patients with an oxygen saturation >90% but with dyspnea, we do not know what their oxygen saturation was on room air before admission. Fourth, because our hospital is a referral center, our patients tended to be sicker and some patients with severe CAP may have died before being referred to our hospital. This means our numbers do not reflect mortality rates due to severe CAP at other hospitals and in the community in general. Further studies with a larger number of subjects, longer enrolment period, and conducted at multiple centers are needed to have a better understanding of the outcomes of and factors associated with them among severe CAP patients. Serial measurements of biomarkers, including PCT levels, and diagnostics to identify the microbial etiology of the CAP would be helpful to get a clearer picture of the epidemiology of severe CAP among children in the study area.

In conclusion, our study found that a higher ESR was associated with a lower risk of death. Our study suggests that ESR as a low-cost biomarker should be considered by clinicians to identify children at higher risk of death from CAP.

Care should be taken in interpreting the results, as they should be combined with other clinical features, radiological and laboratory findings.

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