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Original Article

The outcomes of childhood acute lymphoblastic leukemia with hyperleukocytosis

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Abstract

Background Hyperleukocytosis in childhood acute lymphoblastic leukemia (ALL) is an emergency in oncology. This condition showed high mortality and relapse rates, as well as low survival rate. The outcomes of this group of patients are not yet well studied.

Objective To evaluate the characteristics and outcomes of childhood acute lymphoblastic leukemia (ALL) with hyperleukocytosis.

Methods This was a retrospective cohort study. The patients were children less than 18 year of age who were diagnosed as ALL in Dr. Sardjito Hospital, Yogyakarta, from January 1, 2010 to November 30, 2016. Event-free survival rate and overall survival rate were estimated for group of patients with the white blood cell (WBC) groups 50-200 x 10^9/L and >200 x 10^9/L using the Kaplan-Meier method.

Results There were 705 children diagnosed as ALL during the study period, 129 (18%) with hyperleukocytosis and 111 of them met the inclusion criteria, consisted of 76 children in a group of WBC 50-200 x 10^9/L and 35 children in a group of WBC >200 x 10^9/L. Presentation at diagnosis: median age were 7 years (range 1 month-18 years), male was 1.5 higher than female, 92% of cases with lymphoid infiltration, 5% with CNS involvement, 40% had bleeding tendency, and 10% had clinical tumor lysis syndrome (TLS). Median WBC was 122 (range 53.4-876) x 109/L; mean Hb was 8 (SD 3) g/dL; median platelet count was 30 (range 1-221) x 10^9/L. Immunophenotyping was done in 23 patients, 5/23 (8%) was T cell. The patients in lower WBC group showed lower death (26% *vs.* 34%, P=0,389), higher two-year event-free survival (EFS) 68% *vs.* 45%, P=0.003, and overall survival (77% *vs.* 68%, P= 0.16), compared to patients in higher WBC group. Univariate and multivariate Cox regression analyses revealed that none of the variables was a significant prognostic factor for 2 years EFS or overall survival.

Conclusion The group of children with ALL and hyperleukocytosis with lower WBC at diagnoses showed better outcomes than the higher WBC. **[Paediatr Indones. 2018;58:186-91; doi: http://dx.doi.org/10.14238/pi58.4.2018.186-91]**.

Keywords: *hyperleukocytosis; white blood cell; survival rate; childhood acute lymphoblastic leukemia; ALL*

Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children. This is a condition were hematopoietic cells proliferate and accumulate excessively.[1] The epidemiological data of childhood ALL differs among countries, this may due to genetic predisposing factors, exposure to infectious diseases, and other environmental factors.[2] The incidence of childhood ALL is 3.6 cases out of 100,000 children, and 1.4 cases out of the entire population per year.[3] The incidence of childhood ALL is higher in North and West Europe, North America, and Oceania, compared to Asia and Africa.[1] In Europe, there were 46.7 new cases per one million population in 2009.[4] However, in Asian countries new cases were estimated to be 54,000 new cases per year.[5] A study in Dr. Sardjito Hospital, Yogyakarta, found that childhood ALL comprised 68.9% of all leukemia cases in children who were diagnosed during 1998-2009.[6]

Hyperleukocytosis was defined as WBC more than 50-100 x 10^9/L.[7,8] This presentation is related to

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poor outcomes.[9] The most common complications are metabolic, such as hyperphosphatemia, hypocalcemia, hyperkalemia, hyperuricemia, and hemodialysis (33.3%), as well as neurological effects, such as seizures, bleeding, and respiratory complications in 8.3%.[10] Hyperleukocytosis complications lead to a high mortality rate of 20% and a low event-free survival rate of 63.3% vs. 100% for >100 x 10^9/L *vs.* < 100 x 109/L.[11,12] The prognosis of childhood ALL with hyperleukocytosis worse than those without hyperleukocytosis. Some studies revealed that hyperleukocytosis increased the risk of poor outcomes by 12 times, including high relapse and mortality rates and low survival rate.[10,13] The poor outcome such as relapse rate was significantly correlated with high leukocyte count. The WBC of > 300 x 10^9/L resulted in shorter survival, highest relapse rate, and highest mortality rate caused by chemotherapy. In contrast, WBC of 200-300 x 10^9/L had the highest survival rate and lowest relapse rate for unknown reasons.10 In comparison, WBC < 100 x10^9/L *vs.* >100 x 10^9/L resulted in a 4 year survival rate of 79 (SD 4) % *vs.* 52 (SD 8) %, respectively (P=0.0001), while WBC 100-200 x 10^9/L *vs.* > 200 x 10^9/L resulted in a survival rate of 4 years [64 (SD 10) % *vs.* 34 (SD 14)%, respectively (P=0.04)].[12]

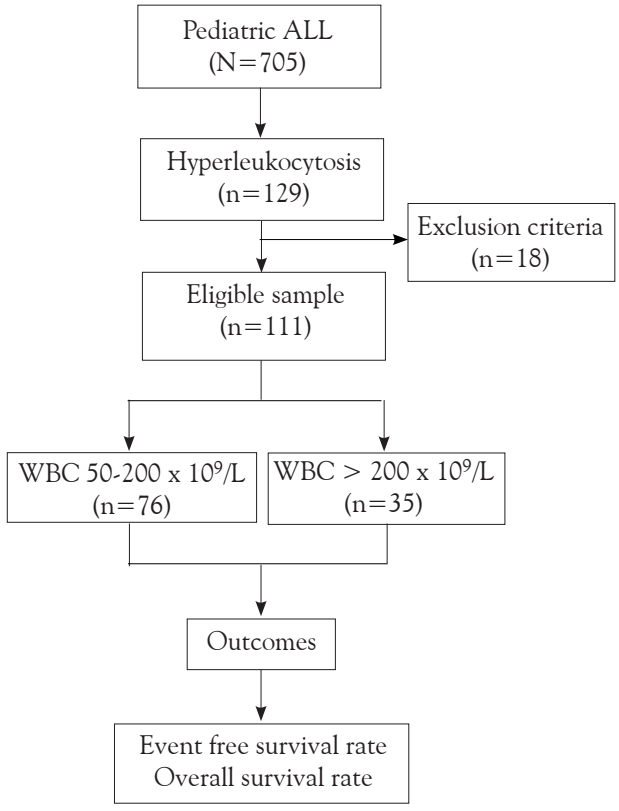

Figure 1. Study flow diagram

Methods

This retrospective cohort study was conducted in Dr. Sardjito Hospital, Yogyakarta. Subjects were pediatric ALL patients, aged 1 month-18 years with hyperleukocytosis (WBC > 50 x10^9/L) at the time of diagnosis, and treated in the Oncology Ward during the periode of January 1, 2010 to November 30, 2016. The diagnosis of ALL was based on leukemic cell morphology identification under light microscope, cytochemistry, and immunophenotyping of marrow aspirates. Patients with incomplete medical record were excluded from this study. Flow of the study is shown in **Figure 1**.

The event free survival (EFS) and overall survival (OS) were analyzed using Kaplan-Meier log-rank test utilized *SPSS version 20* program. The events in this study were death (all systemic organs stopped functioning and marked by brain stem death); abandonment (discontinuation of treatment more than 2 weeks or refused treatment); relapse, defined as (1) isolated bone marrow relapse: blast cells > 25% in bone marrow puncture or biopsy without central nervous system (CNS) and testicular involvement after remission already reached, (2) isolated CNS relapse: positive cytomorphology and WBC > 5/μL and CNS signs and symptoms, (3) isolated testicular relapse: leukemic infiltration in the testicle confirmed by biopsy, and (4) combined relapse: M2 or M3 after remission, with CNS or testicular involvement and disease resistance (blast > 5% from bone marrow aspiration at the end of induction phase). Bone marrow remission status was classified as M2 or M3 if the blast in bone marrow was 5-25% or > 25%, respectively.[13]

The survival analysis was conducted for two WBC groups: those with 50-200 x 10^9/L and those with > 200 x 10^9/L, following the studies already done.[10,12] Potential prognostic factors were analyzed by bivariate with Cox regression model; variables with P values < 0.25 at univariate analysis were included

in the multivariate analysis. A P value of < 0.05 was considered to be statistically significant. Age and immunophenotype stratification in bivariate and multivariate analyses were compared to the group with good prognosis, namely, patients aged 1-10 years and B cell immunophenotype.

Results

During the study period, there were 705 childhood ALL patients, 129 (18.3%) had hyperleukocytosis, however, 18 were excluded due to incomplete medical records. Subjects were divided into two groups, based on WBC of 50-200 x 109/L or >200 x 109/L. The characteristics of subjects are described in **Table 1** and case mortality by WBC group is shown in **Table 2**. The two-year EFS for the WBC 50-200 x 10^9/L and > 200 x 10^9/L groups were 68% and 45%, respectively (HR 2.3; 95%CI 1.30 to 4.12; P=0.003). The OS rates of the WBC groups were 77% and 68%, respectively (HR 1.6; 95%CI 0.81 to 3.41; P=0.16).

Kaplan-Meier analysis for EFS and OS are presented in **Figures 2** and **3**. Bivariate analysis was performed using Cox regression method to see the effect of independent variables on EFS

Table 1. Subjects' characteristics (N= 111)

Characteristics	WBC, x 10^9/L		Total	P value
	50-200 (n= 76)	>200 (n= 35)		
Age at the time of diagnosis, n (%)	76 (68.47)	35 (31.53)	111	0.082
<1 year	2 (2)	3 (3)	5 (4.50)	
1-10 year[a]	46 (41)	15 (14)	61 (54.95)	
>10 year	28 (25)	17 (15)	45 (40.54)	
Median age (range), year	7.35 (0.13-18.07)			
Sex, n (%)	76 (68.47)	35 (31.53)	111	0.136
Male	43 (39)	25 (22)	68 (61.27)	
Female	33 (30)	10 (9)	43 (38.73)	
Infiltration of lymphoid tissue, n (%)	76 (68.47)	35 (31.53)	111	0.229
No, n (%)	7 (6)	1 (1)	8 (7.20)	
Yes, n (%)	69 (62)	34 (31)	103 (92.80)	
Immunophenotype, n (%)	13 (56.52)	10 (43.48)	23	0.008
T cell	1 (4)	4 (18)	5 (8.30)	
B cell[b]	11 (48)	3 (13)	7 (58.30)	
Mixed	1 (4)	3 (13)	4 (33.30)	
Median leukocyte count (range), 10^9/L	122 (53.4-876)			
Hb, n (%)	76 (68.47)	35 (31.53)	111	0.123
>6 g/dL	55 (50)	30 (27)	85 (76.58)	
<6 g/dL	21 (19)	5 (4)	26 (23.42)	
Mean Hb (SD), g/dL	8.04 (2.58)			
Platelet count, n (%)	76 (68.47)	35 (31.53)	111	0.012
> 20 x 10^9/L	50 (45)	31 (28)	81 (72.97)	
< 20 x 10^9/L	26 (23)	4 (4)	30 (27.03)	
Median (range), 10^9/L	30 (1-221)			
CNS involvement, n (%)	45 (61.64)	28 (38,36)	73	0.572
No	42 (58)	27 (37)	69 (94.52)	
Yes	3 (4)	1 (1)	4 (5.48)	
Bleeding evidence, n (%)	76 (68.47)	35 (31.53)	111	0.434
No	44 (40)	23 (20)	67 (60.36)	
Yes	32 (29)	12 (11)	44 (39.64)	
Clinical TLS, n (%)	76 (68.47)	35 (31.53)	111	0.002
No	73 (66)	27 (24)	100 (90.09)	
Yes	3 (3)	8 (7)	11 (9.91)	

[a]Good prognosis for age stratification, [b]Good prognosis for immunophenotype stratification

Table 2. Outcomes for two-year EFS by WBC group

WBC (x 10^9/L)	Outcomes						
	Survived					Died	Total
	Without event	Disease resistance	Relapse	Drop out	Total		
50-200, n (%)	49 (64.47)	3 (3.95)	1 (1.31)	3 (3.95)	56	20 (26.31)	76
>200, n (%)	14 (40)	5 (14.28)	2 (5.71)	2 (5.71)	23	12 (34.28)	35
Total	63	8	3	5	79	32	111
P value							0.389

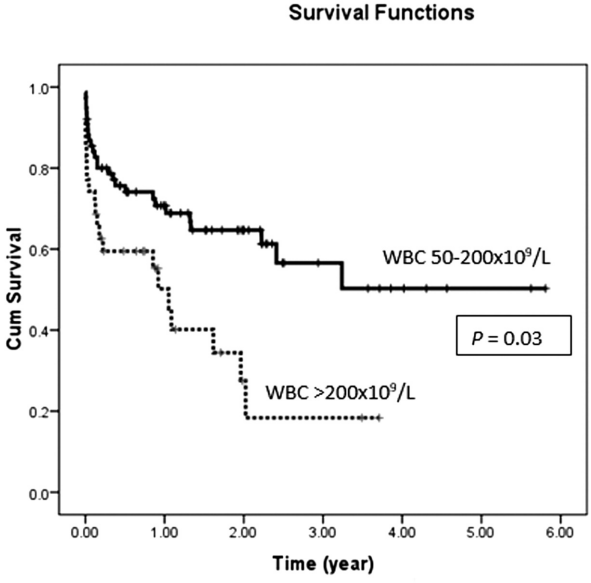

Figure 2. Event-free survival rate

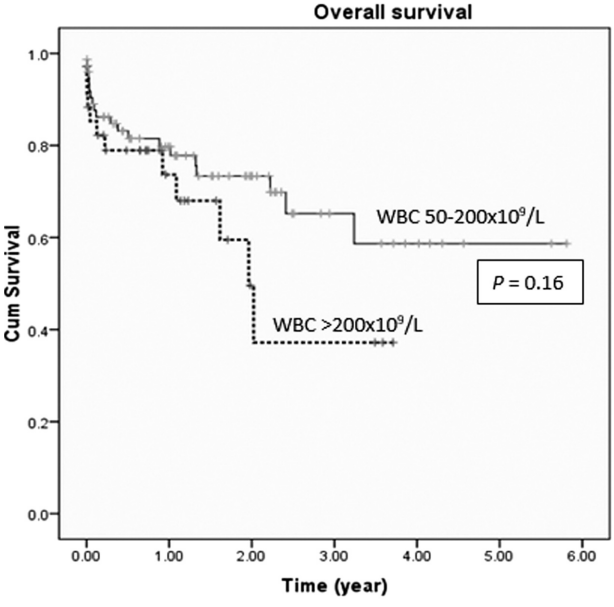

Figure 3. Kaplan-Meier curve for overall survival rate

Table 3. Multivariate analysis for prognostic factors of EFS

Variables	EFS		
	P	HR	95%CI
Age stratification	0.073	14.72	0.78 to 277.04
Hb stratification	0.98	0,0004	-
Leukocyte stratification	0.058	18.64	0.91 to 383.29
Platelet stratification	0.98	0.0001	-
Immunophenotype	0.37	0.29	0.02 to 4.20
CNS Involvement	0.99	0.00023	-

was shown to not be a significant prognostic factor for OS. The multivariate analysis results are shown in **Table 3**.

Discussion

The incidence of hyperleukocytosis and subject characteristics in this study were similar to others, in terms of sex, mean age, and presence of lymphoid infiltration.[10,12,14] Male sex and lymphoid infiltration had significant associations with hyperleukocytosis.[10,15,16] In addition, the age group of 1-10 years had a significant association with the incidence of WBC count > 200 x 10^9/L.[10]

The differences in our study from other studies were imunophenotype B-cell as the most common immunophenotype and only a few patients had symptoms of TLS. But only 23/111 (21%) patients underwent immunophenotyping. Only 10% of patients had TLS symptoms, but objective parameter such as laboratory findings were not explored in our study. In this study, there was significant differences between group of WBC count 50-200 x 10^9/L and > 200 x 10^9/L in term of platelet stratification (P=0.012), immunophenotype (P=0.008) and

clinical TLS (P=0.002) but after continuing with multivariate analysis, there was no significant prognostic factor for EFS. However, previous studies reported that hyperleukocytosis had significant relationships with T cell ALL and CNS leukemia.[12,14] Because of our small sample sizes, we cannot conclude that T cell phenotype or TLS were associated with hyperleukocytosis. Nor can we suggest that race or geography may play a role in our findings. In previous studies, geographic area were suggested to differ in genetics and environmental exposure that may lead to cancer risk.[2,15] As such, ALL is likely to be caused by multiple factors.

We found that the two-year EFS was significantly different between the WBC 50-200 x 10^9/L and >200x109/L groups [68% *vs.* 45%, respectively, (HR 2.3; 95%CI 0.88 to 3.56; P=0.003)]. However, the two-year OS was not significantly different between the two leukocyte groups [77% *vs.* 68%, respectively (HR 1.69; 95%CI 1.49 to 2.43; P=0.16)]. The EFS and OS results were similar to those of previous studies.[10,12,13] The four-year EFS in another studi was 52 (SD 8) % for patients with WBC > 100 x 10^9/L *vs.* 79 (SD 4) % for patients with WBC < 100 x 10^9/L (P< 0.0001). In addition, high leukocyte count and massive splenomegaly were poor prognostic factors for EFS.[12] Another study showed that the three-year EFS and OS for childhood ALL with hyperleukocytosis were 75% and 81.2%, respectively.[10] Furthermore, Yang et al. in 2016 reported a difference in EFS, with the shortest EFS in the WBC >300 x 10^9/L group (P=0.006).[14] We suspected that higher WBC count may lead to poor EFS, because we observed a higher mortality rate in the WBC > 200 x 10^9/L group (34%) than in the WBC 50-200 x 10^9/L group (26%), but the P value shows not significant (P= 0.389).

We found that 4.5% of our subjects abandoned treatment and 29% died. The mortality rate of the WBC 50-200 x 10^9/L was 26% (20/76), while that of patients with WBC > 200 x 10^9/L group was 34% (12/35). Similarly, other studies showed that the higher the WBC at the time of diagnosis, the poorer the prognosis.[8,14] A previous study in Indonesia in 1997-2002 reported that 35% of children drop out from ALL treatment, 23% experienced treatment-related death and 20% had an overall event-free survival rate.[17] Our findings may differ, as most of our patients had insurance for treatment. A lack of financial resources, medical facilities, or social support services in the previous study may have contributed to discontinued treatment.[18]

In conclusion, higher WBC count at the time of diagnosis may lead to poorer prognosis in pediatric ALL patients with hyperleukocytosis. However, a longer study period is needed as this study was undertaken to obtain primary data on hyperlukocytosis in childhood ALL in developing countries, like Indonesia.

Conflict of Interest

None declared.

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