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Original Article

Survival and prognostic factors of childhood acute lymphoblastic leukemia

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Abstract

Background The treatment protocols of childhood acute lymphoblastic leukemia (ALL) have been improved. Some factors such as age, sex, and nutritional status could influence therapy outcome.

Objective To study the survival differences among age, sex, and nutritional status groups in childhood ALL.

Methods A retrospective Kaplan-Meier survival analysis of childhood ALL was performed in Cipto Mangunkusumo Hospital since January 1st 1998 until December 31st 2003. We excluded patients aged <1 years, those with L_3 subtype, patients with modified chemotherapy protocol, or with incomplete data.

Results A total of 252 patients were analyzed**.** Overall survival of 1-2 year old, >2-<10 year old, and 10-18 year old subjects were 57% (95% CI 38 to 76%), 47% (95% CI 40 to 54%), and 35% (95% CI 21 to 49%) respectively (P <0.05). Five-year–event-free survival (EFS) of 1-2 year old, >2-<10 year old, and 10-18 year old subjects were 40%, 40%, and 16%, respectively (P <0.05). Overall survival of male and female subjects were 46% and 53% respectively (P >0.05). Five-year-EFS of male and female subjects were 29% and 45% (P >0.05). Overall survival of well-nourished, undernourished, and malnourished patients were 42% 50% and 57% respectively (P >0.05). The five-year-EFS of well-nourished, undernourished, and malnourished subjects were 33%, 38%, and 51%, respectively (P >0.05).

Conclusion Childhood ALL aged 1-2 years had the highest survival rate while those of 10-18 year old had the lowest. There were no survival rate differences between sex and nutritional status groups. **[Paediatr Indones. 2009;49:365-71]**.

Keywords*: lymphoblastic leukemia, acute, childhood, outcome studies, survival*

Although treatment improvement protocols for childhood acute lymphoblast leukemia (ALL) had been published, poor outcomes in the disease are still observed.[1-7] Many factors could influence treatment outcome in childhood ALL such as; age at diagnosis,[1,8-10] sex,[11-13] and nutritional status.[4,6,12] Death and relapse are frequent in malnourished childhood ALL patients.[4,6,14-15] Malnourished childhood ALL patients have lower survival rate (5-year-event free survival (EFS) is 26%) compared to 83% in well-nourished ones due to higher bone marrow relapse rate.[4,6] Poor treatment outcome is also observed in children aged 10-18 years compared to 1-<2 year-old and 2-9 year-old .[8] Boys have lower survival rate compared to girls and this difference was more clearly seen after 24 months of treatment.[11-13] Because there were survival differences between age, sex and nutritional status groups in childhood ALL and only few studies were exist in developing countries, a study to investigate the impacts of age, sex and nutritional status to survival of childhood ALL is needed.

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This study aimed to investigate factors such as age, sex, and nutritional status as prognostic factors in addition to evaluate treatment outcome of the recent ALL protocol used. Survival differences by comparing overall survival and 5-year-EFS among age, sex and nutritional status groups were studied.

Methods

A retrospective Kaplan-Meier survival analysis using secondary data of ALL patients who registered at Division of Hematology and Oncology, Department of Child Health in Cipto Mangunkusomo Hospital (CMH) since January 1st 1998 until December 31st 2003 was performed. We excluded those who aged less than 1-year-old, those with ALL of L_3 subtype, those who had received modified treatment protocol or had or those with incomplete data. Age less than 1-year-old is considered as an infant leukemia of which would have different lymphoblast biological characteristics and responds to different chemotherapy protocol.[15-17] Acute lymphoblastic leukemia of L_3 subtype is a mature B cell leukemia which express the surface of immunoglobulin identically to Burkitt lymphoma. This subtype is considered as Burkitt lymphoma of which infiltrates bone marrow and had high lymphoblast proliferation rate.[17]

We classified the patients according to age into 3 groups; 1-2 years, >2-<10 years, and 10-18 years old in this study.[9] Nutritional status of the subjects were assessed with Waterlow's criteria and classified as well-nourished, undernourished, and malnourished.[18] The sample size in this study was 164 subjects based on single proportion of OS and 5-years of EFS in childhood ALL in previous studies.[7]

The diagnosis of ALL was established when 25% or more of lymphoblasts were present in the bone

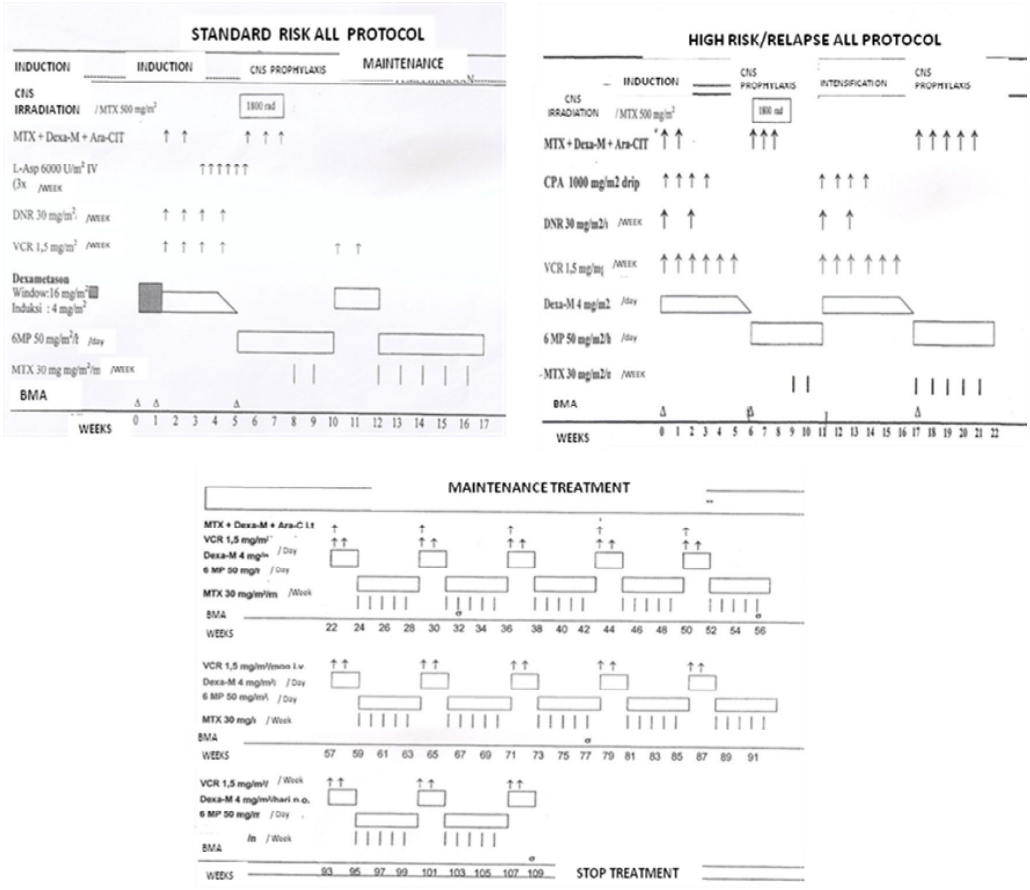

Figure 1. Treatment protocols according to risk.

marrow aspirates and the subtype was determined using French-American-British (FAB) classification.[15] At diagnosis, each subject was stratified into standard risk and high risk groups. The high risk group in our study should meet at least one of these criteria: white blood count was >50.000/µl, central nervous system (CNS) leukemia, mediastinal mass, testicular infiltration, or relapsed.[7]

The regimen of protocols according to risk was illustrated in **Figure 1**. Bone marrow aspiration was done at the end of remission induction therapy and would be performed every six month until the treatment was stopped. When remission was achieved, CNS prophylactic treatment was given.

For patient less than three years old, intravenous infusion of methotrexat (MTX) was given instead of cranial irradiation. After received CNS prophylactic treatment, maintenance treatment was given. The duration of therapy was two years. Complete remission was defined as the absence of lymphoblast in peripheral blood and cerebral spinal fluid (CSF), bone marrow with ≤5% of lymphoblast and no evidence of disease at any other site. Relapse was defined as the recurrence of lymphoblast (≥25%of lymphoblast in bone marrow), or localized leukemia infiltration at any site after remission was achieved. Overall survival was estimated as the duration from the time of diagnosis to the time when death occurred. Event free survival was estimated as the duration from the time of diagnosis to the time when relapse or death occurred. This study had been approved by the ethics committee of Medical School in University of Indonesia. Data was processed with SPSS 15.0 statistical program. The survival rate was analyzed with Kaplan-Meier method and the differences between survivals were analyzed with log-rank test.

Results

Two hundred and fifty two subjects were analyzed, consisted of 162 (64.3%) standard risk-group (SRG) and 90 (35.7%) high risk-group (HRG). The median follow up was 20 months (1 month to 109 months).

Table 1. The characteristics of patients and outcome according to risk

	Standar risk	High risk	P
Age			
1-2 years	17 (10.5%)	7 (7.8%)	
>2-<10 years	128 (79%)	59 (65.6%)	
10-18 years	17 (10.5%)	24 (26.6%)	
Sex			
Male	103 (63.6%)	58 (64.4%)	
Female	59 (36.4%)	32 (35.6%)	
Nutritional status			
Well-nourished	26 (16%)	21 (23.3%)	
Undernourished	122 (75.3%)	65 (72.2%)	
Malnourished	14 (8.7%)		
White blood cell count		4 (4.5%)	
0-50.000/µl	162 (100%)	33 (36.7%)	
50.001-99.999/µl	0	21 (23.3%)	
≥100.000/µl	0	36 (40%)	
Mediastinal mass			
Yes	0	3 (3.3%)	
No	162 (100%)	87 (96.7%)	
CNS infiltration			
Yes	0	9 (10%)	
No	162 (100%)	82 (90%)	
OUTCOME			
Remission induction	142 (87.1%)	55 (61.1%)	<0.0001
Death in induction phase	20 (12.3%)	35 (38.9%)	<0.0001
Death after induction phase	4 (2.5%)	7 (7.8%)	0.007
Relapse	79 (48.7%)	16 (17.8%)	0.87
Loss to follow up	79 (48.7%)	24 (26.7%)	0.001
Overall survival	57% (95% CI 50 to 64%)	26% (95% CI 17 to 35%)	<0.05
5-years of EFS	48% (95% CI 44.1 to 51.9%)	19% (95% CI 15 to 23%)	<0.05

Age ranged from 1 year to 15 year (median was 5 years). Twenty four subjects (9.5%) were 1-2 year old, 187 subjects (74.2%) were between 2 and 10 year old, and 41 subjects (16.3%) were 10-18 year old. One hundred and sixty-one subjects (63.9%) were boys and 91 subjects (36.1%) were girls. Male to female ratio was 1.7:1. Eighteen subjects (7.1%) were malnourished, 187 subjects (77.4%) were undernourished, and 47 subjects (15.5%) were well-nourished.

Complete remission after induction phase was achieved in all subjects (78.2%), 87.1% in SRG and 61.1% in HRG (P <0.001). Death occurred in 66 subjects (26.2%); fifty-five (21.8%) died during induction phase while 11 (4.4%) died after induction phase. The causes of death were septicemia (21), massive bleeding (24), seizure (12), and other infection (9). Relapse occurred in 48 subjects with median time was 13 months. Relapse locations were; bone marrow (39), CNS (4), bone marrow and CNS (3), testicle (1), bone marrow and testicle (1). The duration of continuous complete remission ranged from 2 months to 101 months (median was 25 months). The median of loss to follow up was 28 months. The overall survival and 5-years of EFS were 49% (95% CI 43 to 55%) and 31% (95% CI 28.1 to 33.9%), respectively. Remission induction, OS and 5-years of EFS rate in SRG was higher than HRG. Subjects' characteristics and outcome according to risks were shown in **Table 1**.

Treatment outcome according to prognostic factors was shown in **Table 2**.

According to prognostic factors; remission induction rate, death at induction phase and after induction phase were not different between groups. Subjects aged 1-2 years showed the highest OS and 5-years of EFS rate, while those of 10-18 year old had the lowest OS and 5-years of EFS rate. Overall survival rate among 1-2 year old subjects, >2-<10 years old, and 10-18 year old were 57% (95% CI 36 to 76%), 47% (95% CI 40 to 54%), and 35% (95% CI 21 to 49%), respectively (P<0.05). Five years of EFS rate among 1-2 year old subjects, >2-<10 year old, and 10-18 year old were 40% (95% CI 30 to 50%), 40% (95% CI 37 to 43%), 16% (95% CI 11 to 21%), respectively (P<0.05). There was no significant survival difference between male and female patients. Overall survival rate in male and female were 46% (95% CI 38.3 to 53.7%) and 53% (95% CI 43 to 63%), respectively (P >0.05). Five years of EFS in male and female were 29% (95%CI 26 to 32%) and 45% (95% CI 40 to 50%), respectively (P >0.05). The significant survival difference among male and female was not found. Overall survival rate among well-nourished, undernourished, and malnourished subjects were 42% (95% CI 27.9 to 56%), 50% (95%CI 43 to 57%), and 57% (95% CI 35 to79%), respectively (P >0.05). Five years of EFS rate among well-nourished, undernourished, and malnourished subjects were 33% (95% CI 27 to 39%), 38% (95% CI 35 to 41%), and 51% (95% CI 40 to 62%), respectively (P >0.05). The overall survival and 5-years of EFS according to age, sex, and nutritional status are shown in **Figure 2** and **3**.

Table 2. Treatment outcome according to prognostic factors

	Remission induction rate	P*	Death rate in induction phase	P*	Death rate after induction phase	P*	Relapse rate	P	OS	P**	5-years of EFS	P**
Age												
1-2 years	19(79.2%)	0.45	5(20.8%)	0.45	0	0.08	5(20.8%)	0.52	57%	<0.05	40%	<0.05
>2-<10 years	149(79.3%)		38(20.3%)		7(3.7%)		33(17.7%)		47%		40%	
10-18 years	29(70.7%)		7(3.7%)		4(9.8%)		10(24.4%)		35%		16%	
Sex												
Male	129(80.1%)	0.30	32(19.9%)	0.32	10(6.2%)	0.06	34(21.2%)	0.19	46%	>0.05	29%	>0.05
Female	68 (73.9%)		23(25.3%)		1(1.1%)		14(15.4%)		53%		45%	
Nutritional status												
Well-nourished	36 (76.6%)	0.90	11(23.4%)	0.94	3(6.4%)	0.82	11(23.4%)	0.17	42%	>0.05	33%	>0.05
Undernourished	147(78.2%)		40(21.4%)		7(3.7%)		35(18.7%)		50%		38%	
Malnourished	14(77.8%)		4(22.4%)		1(5.6%)		2(11.1%)		57%		51%	

*chi-square test
** log-rank test

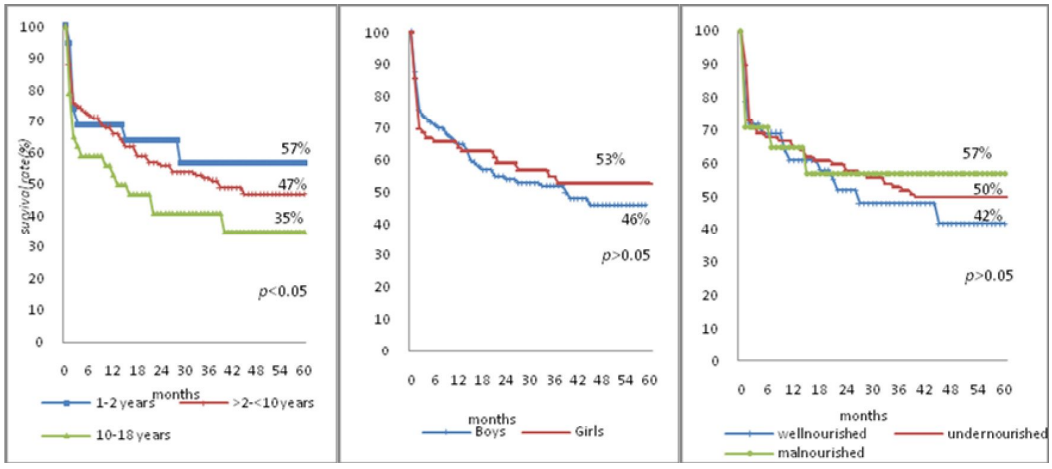

Figure 2. Overall survival according to age, sex, and nutritional status

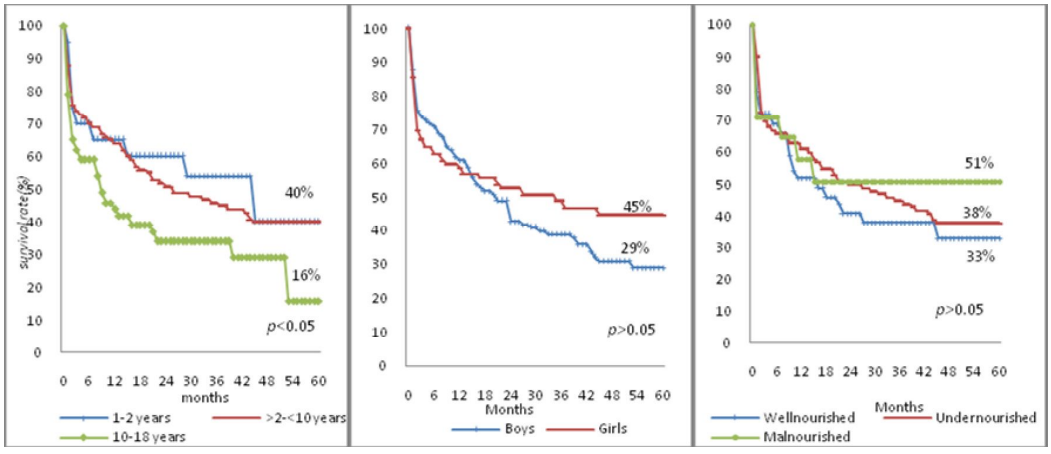

Fig 3. Five-years of EFS according to age, sex, and nutritional status

Discussion

Remission rate in this study was lower than remission rate in other studies which could reach up to 98%.[8,19] Modified treatment protocol of which has become more tolerable, could lead to lower remission rate in this study. High death-rate in induction phase could also be the cause of the low remission rate.[1,4,6,8] The death-rate during induction phase in this study was still high compared to induction phase death-rate in literatures which ranged from 1.2-7%.[1-2,6,8,11,17] It might be due to lack of supportive treatments and isolation room facilities in our study when drug toxicity and neutropenia-related infection were the common cause of death in induction phase.[7,17]

The survival-rate of childhood ALL in this study was lower than in other studies.[1,8,11,20-21] High death-rate during induction phase and high relapse-rate influenced the low survival in this study. The more tolerable chemotherapy protocol during induction phase and during CNS prophylaxis, the higher the relapse-rate. Poor subjects' compliances, dose reduction and poor drug absorption could lead to ineffective treatment and higher relapse-rate. More tolerable treatment protocol was considered in our study regarding to lack of isolation room in health care units, supportive treatment facilities, and high cost of chemotherapy drugs in our country.[7] In this study, the loss to follow-up rate was higher than in other studies which ranged from 0-10%.[7-

[8,16,22] The median loss to follow up was 28 months which was four months after treatment completed. It could be caused by subjects who thought they were cured and did not have to perform further examination.

In our study, survival-rate in 1-2 year group was the highest compared to other age-group. Meanwhile, subjects aged 10-18 years had the lowest survival-rate. Other study also found low survival-rate in older children.[8] Lymphoblast in older children usually were differentiated from more pluripotent lymphoid precursor cells which proliferate progressively and more resistant to chemotherapy.[15-16]

Survival difference among sex group was not shown in our study although more female were in continuous complete remission at the end of follow up compared to boys. Survival difference between male and female usually occurred after the 24th month of treatment and could be due to the differences of maintenance of drugs metabolism.[3,12] In our study, because the median of follow up was only 20 months and there was high rate of loss to follow up, the survival difference between male and female could not be observed.

There was no survival difference between nutritional status groups. However different results found by other studies that stated there was different survival-rate between malnourished and well-nourished in ALL patients, this could be due to different nutritional status classification used.[4,6] In addition, in this study, it was found that successful nutritional support since subject's admission could increase chemotherapy tolerances. As a result, there were no differences in remission-rate, death-rate during induction therapy, overall survival and 5-years of EFS between nutritional status groups. Gomez-Almaguer[23] found that nutritional support and corticosteroid effects during induction phase could improve nutritional status in undernourished and malnourished patients that lead to good chemotherapy tolerance and survival improvements.[23] To monitor nutritional support, nutritional status examination was performed before and after each chemotherapy phase.[23] Unfortunately, there was lack of data about nutritional status examinations before and after each chemotherapy phase.

In conclusion, our study shows that subjects aged 1-2 years had the highest survival-rate while patients aged 10-18 years had the lowest survival-rate. Survival rates among sex group and nutritional status groups were not different significantly due to shorter median follow up time and high loss-to-follow up rate, so further study is needed.

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