

Original Article

Association between nutritional status and outcome of childhood acute lymphoblastic leukemia treated with Wijaya Kusuma Protocol

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Abstract

Background Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood. Malnutrition in malignancy patients including ALL is one of major problems. This condition is found at the time of diagnosis as a result of the disease itself or after, chemotherapy or radiation. Many studies have been conducted to determine the relationship between nutritional state and outcome of childhood ALL patients but the result was still controversial.

Objective To determine relative risk of death and relapse in childhood standard-risk ALL who received therapy using Wijaya Kusuma protocol.

Methods This was a retrospective cohort study. Newly-diagnosed patients since May 1999-December 2004 were taken for this study. Body mass index was used to measure nutritional status for >2 years old children, and weight-for-height was used for those of =2 years old. Data was obtained from Yogyakarta Pediatric Cancer Registry Dr. Sardjito Hospital. Chi-squared test was used to analyze the proportion difference and risk relative was used to determine risk for death and relapse.

Results One-hundred and forty five patients included in this study. There was no association between nutritional state and relapse (RR 1.1, 95% CI 0.76;1.61). Logistic regression analysis showed that there was association between nutritional state and death (RR 2.34, 95% CI 1.01;5.45). Sepsis and relapse have contribution to death as well (RR 6.75, 95% CI 2.9;15.4 and RR 3.2, 95% CI 1.3;8.08 respectively).

Conclusion Nutritional status is not associated with relapse but is associated with death of ALL children. [Paediatr Indones 2008;48:28-32].

Keywords: acute lymphoblastic leukemia, nutritional status, relapse, death

Leukemia is the most common pediatric malignancy,^{1,2} approximately 23% among cancers which were diagnosed in children under 15 year of age.³ During 2000-2004, 35% patients were diagnosed as acute lymphoblastic leukemia (ALL) among 486 cancer patients hospitalized in Dr. Sardjito Hospital.⁴ Malnutrition is still a major problem in pediatric malignancy, and it was found in 8% among newly-diagnosed patients up to 50% in advanced disease.⁵ Many studies have been conducted to investigate the association between nutritional status and outcome of therapy in ALL patients, but the results remain controversy. Those studies had differences in methods, treatment protocols, and measurements of nutritional status.⁶⁻¹¹

The objective of this study was to determine the risk of death and relapse among pediatric ALL patients with undernutrition who got therapy using Wijaya Kusuma protocol.

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Methods

This retrospective study was conducted in Department of Child Health, Gadjah Mada University, Dr. Sardjito Hospital on pediatric ALL patients diagnosed between January 2000 – December 2004. Data were obtained from Yogyakarta Pediatric Cancer Registry, Dr. Sardjito Hospital. The inclusion criteria were children 0–15 years old with newly diagnosed ALL, never got chemotherapy before, and got Wijaya Kusuma protocol. Subjects were excluded from the study if they had no complete data or never visited the hospital for routine examinations.

Anthropometric measurement was conducted to assess nutritional status using CDC 2000 chart. Body mass index (BMI) was used for children ≥ 2 –15 years old and weight for height ratio (Wt/Ht) for < 2 year old children. Children ≥ 2 –15 years old were considered as undernourished if BMI below 5 percentile CDC 2000 chart while children < 2 year old if Wt/Ht ratio was 60–79.9%. Children ≥ 2 –15 years old were considered as well-nourished if BMI was between 5–95 percentile CDC 2000 chart. Children < 2 year old were considered as well-nourished if Wt/Ht ratio was 80–120%. The

patients were classified in three groups according to risk factors i.e, < 12 months, ≥ 12 - < 120 months, and ≥ 120 months.

Relapse was defined as presenting blast $> 20\%$ of 200 nucleated cells in bone marrow, and/or presenting blast in peripheral blood smear, and/or presenting blast in liquor cerebrospinal, and/or lymphoblast infiltration to other organs. Death could occur in any phase during therapy.

Chi-squared test was used to determine proportion between two groups, and risk relative was used to determine the risk of death and relapse.

Results

During January 2000 – December 2004, there were 178 newly-diagnosed ALL patients. Five patients were excluded because they were older than 15 years of age, 12 patients diagnosed as L3 or Mixed ALL six patients had chemotherapy (dexamethasone) before, five patients refused to get chemotherapy, one patient had AML, and one patient died before therapy started. The flow chart of study was described as follows.

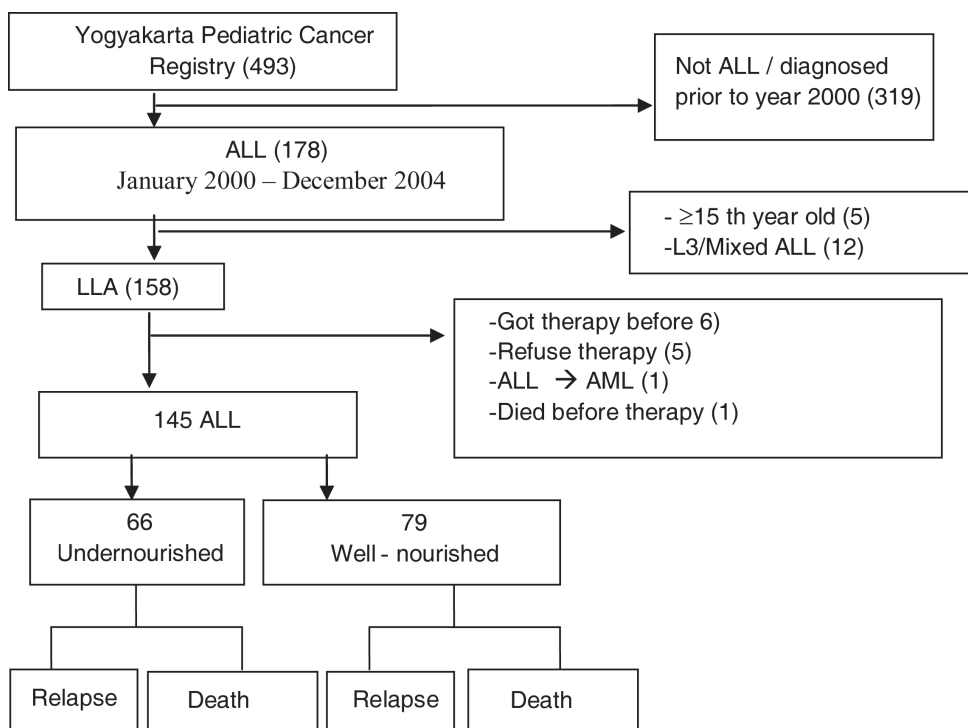


Figure 1. Study Algorithm

In this study, there were 90 (62.1%) boys, and 55 (27.9%) girls. Most of them are $\geq 1-10$ years old. Sixty-six (45.5%) patients were undernourished and 79 (54.5%) were well-nourished. Thirty six percent were included in high risk, and 63.4% in standard risk group. Baseline characteristics are described in the **Table 1**.

During induction phase, 100% got remission but 14 patients (9.6%) drop out and 20 patients (13.8%) died. Five patients were undernourished, and 15 patients were well-nourished. There was no

significant difference (RR 0.57, 95%CI 0.25;1.11). There was no significant difference either in standard and high risk groups (RR 1.27, 95%CI 0.74; 2.19).

Outcome after induction phase is described in **Table 2**. Based on nutritional status, there was no significant difference both in death (RR 0.94, 95% CI 0.64 ;1.38) and relapse (RR 1.1, 95% CI 0.76;1.61). There was no significant difference either in death both in high risk and standard risk groups (RR 1.12, 95% CI 0.72;1.75) and similar results were found in relapse as well (RR 1.1, 95% CI 0.76;1.61).

Overall, the results of this study are described in **Table 3**. It is seen in **Table 3** that there was no association between nutritional status and outcome therapy (death and relapse). We conducted multivariate analysis using logistic regression. The results are described in **Table 4**. **Table 4** shows that sepsis, risks factors and nutritional status had contribution to cause death. Patients with undernourished had risk for death 2.34 compared to well-nourished (95% CI 1.01;5.45).

Table 1. Baseline Characteristics

	Undernourished		Well-nourished	
	n	%	n	%
Gender				
Boys	42	63.6	48	60.7
Girls	24	36.4	31	39.2
Age				
<12 months old	2	0.3	0	0
³ 12-< 120 months	56	84.8	70	88.6
⁼ 120 months old	8	12.1	9	11.4
Risk				
Standard risk	38	57.5	54	68.3
High risk	28	42.5	25	31.7

Table 2. Outcome after induction phase

	Under nourished		Well-nourished		RR	95% CI	P
	n	%	n	%			
Death	21	37.9	27	48.2	0.94	0.64;1.38	0.76
Alive	34	62.1	29	51.8			
Relapse	21	31.8	22	27.8	1.1	0.76;1.61	0.6
No relapse	45	68.3	57	72.2			
Drop out	11	16.7	4	5.7			

Table 3. Outcome during therapy

	Under nourished		Well-nourished		RR	95% CI	P
	n	%	n	%			
High risk							
Death	13	19.6	15	18.9	0.8	0.46;1.28	0.32
Alive	15	22.7	10	12.6			
Relapse	9	13.6	8	10.1	1.00	0.58;1.72	0.9
No relapse	19	28.7	17	21.5			
Remmission	21	39.6	14	26.4			
No remmission	7	13.2	11	20.8			
Drop out	12	22.6	9	17.3			
Standard risk							
Death	13	19.6	27	34.9	0.7	0.39;1.14	0.13
Alive	25	37.8	27	34.9			
Relapse	12	18.1	14	17.7	1.17	0.70;1.95	0.5
No relapse	26	39.3	40	50.6			
Remmission	33	35.9	38	41.3			
No remmission	5	5.4	16	17.4			
Drop out	9	9.8	10	10.9			

Table 4. Logistic regression of cause of death

Variables	Death RR	95% CI P
Sepsis	6.75	2.9;15.4
Relapse	3.2	1.3;8.08
Risks (HR and SR)	1.9	0.84;4.73
Nutritional status	2.34	1.01;5.45

Discussion

High prevalence of undernourish in ALL patients was similar with that of Viana *et al*⁶ study. Other author stated that in some patients who had undernourish at the time of diagnosis, had weight gain during the course of disease.¹² Baseline characteristics showed that most of patients in this study were male and their age were 1–10 year old, and this is similar with that of the previous data.¹³ Even though BMI had sensitivity to assess nutritional status in children with malignancy,⁹ The method of assessing nutritional status can be erroneous because it doesn't consider hepatomegaly and splenomegaly. Children with normal Wt//Ht could have arm circumference less than standard.¹⁴

There is no significant difference in early death between undernourished and well-nourished patients. This is similar with that of previous study.^{7,9} Most of deaths in early phase are due to sepsis and it occur more in well-nourished children. Death after induction is mostly caused by the disease and patient's compliance. Other factors that influence death after induction phase were sepsis, intracranial bleeding, and relapse. All patients who suffered from intracranial bleeding died. Logistic regression analysis showed that sepsis had the largest contribution to cause death (RR 6.75, 95% CI 2.9;15.4), while nutritional status contributed with RR 2.34 (95% CI 1.01;5.45). It is similar with that of previous study.^{6,8} The reason why undernourished children have worse prognosis compared to well-nourished ones is that undernutrition leads to diminished bone marrow reserve that causes suboptimal doses of maintenance chemotherapy. Five year disease free survival of children received low doses MTX was 7% compared to 65% of those who received full doses.⁸

In conclusion nutritional status doesn't have association with relapse, but it has association with death. Other factors that have contribution to death are sepsis and relapse.

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