Differences in induction phase outcomes of acute lymphoblastic leukemia between well-nourished and malnourished pediatric patients

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Abstract

Leukemia is the most common malignancy in childhood, involving uncontrollable proliferation of abnormal leukocytes. The prevalence of acute leukemia is 30-40% of all childhood cancers; 82% are acute lymphoblastic leukemia (ALL) and 17% are acute myeloblastic leukemia (AML). The proliferation of lymphoid precursor cells originate from B lymphocytes in 80% of cases, and from T lymphocytes in the remainder. Out of 486 cancer cases in children in 2000-2004 in Dr. Sardjito Hospital, Yogyakarta, 35% were ALL cases. In 2018, there were 72 newly-diagnosed ALL patients in Haji Adam Malik General Hospital, accounting for 48% of childhood cancer cases.

Malnutrition, a deficiency of energy, protein, and other nutrients, is the main nutritional disorder occurring in children with cancer. Malnutrition in cancer can be caused by the disease, inherent patient condition, and therapeutic factors. These factors may affect metabolism, leading to decrease in appetite, which further promotes weight loss. The prevalence of malnutrition in childhood cancer was 50-60%.

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Keywords: acute lymphoblastic leukemia; malnutrition; induction phase outcomes

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Malnutrition is one of several prognostic factors in ALL. Children with malnutrition are more prone to infection and less able to tolerate the given treatment. During the continuation phase of chemotherapy, an undernourished child is at higher risk for relapse and death. One study found that the chance of dying during the initial phase of ALL treatment was 2.6 times lower in well-nourished children than in undernourished children. In industrialized countries, malnutrition occurred in <10% of standard-risk ALL children, but studies from developing countries are lacking.

Nutritional supportive care is a medical modality associated with improved tolerance to chemotherapy, increased survival rate and quality of life, as well as decreased risk of infection in children undergoing anticancer therapy. Induction is an important chemotherapy phase, in which maximum destruction of leukemic cells occurs. Therefore, nutritional status evaluation at the initial diagnosis and its possible association with induction phase outcome is needed. This study aims to examine differences in induction phase outcomes between well-nourished and malnourished pediatric ALL patients.

Methods
This study was conducted in newly-diagnosed ALL patients at Haji Adam Malik General Hospital from December 2019 to December 2020. Inclusion criteria were children aged 1 to 18 years with ALL confirmed by bone marrow aspiration who underwent induction phase chemotherapy. Children with overweight/obesity or those who refused to participate were excluded. Based on their leukocyte count at the time of initial diagnosis, patients were classified into standard risk (leukocytes <50,000/µL) and high risk (leukocytes >50,000/µL). Mid-upper arm circumference (MUAC) was used to determine nutritional status. Patients were considered well-nourished if their MUAC was between the 5th to 95th percentile in the Frisancho table and malnourished if it was ≤5th percentile.

Data collection was done for complete blood count (CBC) at the time of diagnosis, occurrence of febrile neutropenia, duration of induction, length of hospital stay, and remission status. Febrile neutropenia was defined as an axillary temperature of ≥38.0°C with a neutrophil count of <1,000/mm³. Duration of induction was defined as the time in days required for the completion of induction. Length of hospital stay was defined as the time in days required from initial presentation to discharge. Remission status was obtained from the results of bone marrow aspirate microscopy after the induction phase.

Statistical analysis was done using SPSS version 23.0 for Windows (IBM, Armonk, New York). Descriptive statistics are expressed in the form of mean (standard deviation/SD) for normally distributed data and median (range) for abnormally distributed data; categorical data are presented in the form of frequency. We analyzed differences in CBC parameters, frequency of febrile neutropenia, duration of induction, and length of hospital stay between the malnourished and well-nourished groups using the independent t-test and the Mann-Whitney test. The difference in the proportion of remission between the two groups was analyzed by using the chi-square test. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik General Hospital Medan.

Results
Subjects were divided into well-nourished and malnourished groups. There were 21 subjects in each group, which consisted of 14 male subjects (66.7%) and 7 female subjects (33.3%). The mean age of subjects was 7.5 years in the well-nourished group and 6.9 years in the malnourished group. The malnourished group had more high-risk patients than the well-nourished group (28.6% vs. 23.8%, respectively). One subject in each group underwent a 25%-to -50% reduction in chemotherapy dose due to granulocytopenia and/or thrombocytopenia. The baseline characteristics of subjects are described in Table 1.

Differences in hematologic outcomes, occurrence of febrile neutropenia, length of hospital stay, and duration of induction can be seen in Table 2. There was no significant difference in CBC parameters between the two groups. Median leukocyte counts in the well-nourished and malnourished groups were 12.5 (range 1.0-551.17) x10³/µL vs. 6.94 (range 0.85 to 287.94) x10³/µL, respectively, but this difference was not statistically significant (P=0.66).

The median frequency of febrile neutropenia
in the malnourished group [2 (range 0 to 4)] was twice that in the well-nourished group [1 (range 0-3)] (P=0.04). We also found significant differences between the well-nourished and malnourished groups in median length of hospital stay [30 (range 19-56) days vs. 36 (range 22-49), P=0.001] and mean duration of induction phase [64.2 (SD 11.5) days vs. 71.2 (SD 10.6) days, P=0.046] (Table 2). There was no significant difference in remission status in the malnourished and well-nourished groups (85.7% vs. 71.4%, respectively; RR 0.833; 95%CI 0.604 to 1.15; P=0.454) (Table 3).

**Discussion**

Malnutrition has been proposed as a prognostic factor in childhood ALL. One study reported that malnutrition was found in 66% children who were newly diagnosed with ALL. Induction phase is a chemotherapy stage aiming to achieve remission (normal peripheral blood, normocellular bone marrow, and <5% lymphoblasts). In this phase, patients are at risk of experiencing severe infections or other complications.

Most patients in our study were male. Several other ALL studies also reported higher prevalences in males than females. The mean age was 7.5 years in the well-nourished group and 6.9 years in the malnourished group. A study in Semarang reported a
median age of 6.58 years in childhood ALL.\textsuperscript{15} ALL can be stratified into high- or standard-risk categories.\textsuperscript{12} In our study, more children in the malnourished group belonged to the high-risk category than to the well-nourished group. Overall, high-risk patients had twice the mortality rate of standard-risk ones.\textsuperscript{16} Malnutrition was associated with a lower survival rate due to bone marrow relapses. Relapses can occur if patients receive a sub-optimal chemotherapy dose during the maintenance phase, such as due to poor tolerance of treatment.\textsuperscript{17} In our study, one subject in each group had to receive a reduced chemotherapy dose due to granulocytopenia and/or thrombocytopenia.

In our study, there were no significant differences in CBC parameters between groups. A previous study found that only hemoglobin concentration was significantly lower in malnourished compared to well-nourished children.\textsuperscript{8} However, the incidence of febrile neutropenia was significantly higher in the malnourished group than in the well-nourished group. Febrile neutropenia in cancer is an emergency complication, requiring rapid identification and intervention.\textsuperscript{18} Malnutrition in children with cancer was associated with an increased risk of infections.\textsuperscript{19} Infections are still the major causes of morbidity and mortality in acute leukemia,\textsuperscript{20} with a higher incidence of sepsis in malnourished children with ALL.\textsuperscript{21}

Our malnourished patients had significantly longer length of hospital stay than well-nourished patients. This result was in agreement with previous findings.\textsuperscript{8,21} Prolonged hospital stay could be due to organ dysfunction, infectious or metabolic complications.\textsuperscript{22}

The duration of induction was significantly longer in the malnourished compared to the well-nourished group. Another study also found that the majority of ALL children who did not complete chemotherapy on time were severely malnourished.\textsuperscript{23} Disturbances in drug metabolism in malnourished children may lead to delayed chemotherapy and increased toxicity.\textsuperscript{24} A study reported a higher rate of rapid early response to chemotherapy in well-nourished than malnourished patients.\textsuperscript{21}

In our study there was no significant difference in remission status between the two groups. This finding is in contrast to those a previous study in which cases with undernutrition showed a downward tendency in remission following induction. Moreover, relapse cases often came from the moderate and severe malnutrition categories.\textsuperscript{23}

Previously, Tandon et al. demonstrated the importance of identifying nutritional status in pediatric ALL patients. They found that hypoalbuminemia, folate deficiency, and B12 deficiency were associated with increased toxicity, which resulted in increased mortality during the induction phase.\textsuperscript{11} During the induction phase, ALL patients were also at risk of weight loss. Twenty-six percent of ALL children lost weight during the induction phase and most had complications, such as infections and bleeding, during this period.\textsuperscript{25} Nutritional interventions in children with ALL may improve nutritional status and chemotherapy tolerance.\textsuperscript{24,26}

We found that ALL children with malnutrition experienced more episodes of febrile neutropenia, longer hospitalizations, and longer induction phase than well-nourished ones. Nutritional assessment and therapy are required for children with ALL to improve their quality of life, reduce infection and drug toxicity, as well as improve survival.\textsuperscript{27,28} However, we noted no difference in remission status between the two groups. These results could have been due to other factors that influence prognosis, such as initial leukocyte count, age, immunological phenotype, sex, and the presence of chromosome abnormalities.

In conclusion, malnourished children with ALL have a higher incidence of febrile neutropenia, a longer duration of the induction phase, and a longer length of hospital stay than well-nourished ones. Hematologic parameters in CBC and remission status were not significantly different between the two groups.

**Conflict of interest**

None declared.

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