Original Article

The Effect of Hyperleukocytosis on the Survival Rate for Childhood Acute Lymphoblastic Leukemia

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Background: Hyperleukocytosis or white blood cell count of more than 100,000/mm^3, in childhood acute lymphoblastic leukemia can cause serious complications and may affect outcome of the treatment.

Objective: To find the survival rate for childhood acute lymphoblastic leukemia in patients with or without hyperleukocytosis.

Materials and Methods: The present study was a retrospective study conducted by reviewing medical records and pediatric cancer records of newly diagnosed acute lymphoblastic leukemia in Khon Kaen Hospital between January 1, 2014 and December 31, 2018. The demographic data, treatment protocols, complications, and treatment outcomes were recorded. The survival analysis of treatment outcomes was analyzed by Kaplan-Meier analysis.

Results: One hundred sixteen children with acute lymphoblastic leukemia were included in the present study. Twenty-six (22.4%) of them had hyperleukocytosis. The male to female ratio was 1.6 to 1. The median age was five years old. The 5-year overall survival rate was 62.5% (95% CI 52.3 to 71.1). The 5-year survival rate of patients without hyperleukocytosis and patients with hyperleukocytosis were 70.2% (95% CI 58.7 to 79) and 36% (95% CI 17.5 to 54.9), respectively (p<0.01). Furthermore, the relapse rate tended to be the higher in the patients with hyperleukocytosis than the patients without hyperleukocytosis at 38.5% versus 23.3% (p=0.13).

Conclusion: Hyperleukocytosis still remains an important factor that worsens the survival rate for childhood acute lymphoblastic leukemia.

Keywords: Lymphoblastic leukemia; Hyperleukocytosis; Child; Survival rate

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Acute leukemia is the most common malignancy in children. The incidence of acute leukemia in Thailand is 50.9% of all childhood cancer cases. Acute lymphoblastic leukemia (ALL) is the most common leukemia, accounting for 72.4% of all acute leukemia in children[1]. After chemotherapy treatment, the survival rate improves. The range of the survival rate for childhood acute leukemia in developed countries varies between 83.8% and 95.4%[2-4]. In Thailand, the chemotherapy treatment used for childhood ALL is guided by the Thai National Protocol for the treatment of childhood ALL. The overall survival (OS) rate for childhood ALL in Thailand is 67.2%[5], which is lower than the figure reported from developed countries.

Hyperleukocytosis is defined as a white blood cell count (WBC) of more than 100,000/mm^3. This condition can be found in 7.8% to 19.2% of childhood ALL cases[6-10]. The complications of hyperleukocytosis, such as hyperviscosity, intracerebral hemorrhage, tumor lysis syndrome, and acute renal failure, often require emergency treatment and usually increase mortality. The risk factors associated with hyperleukocytois are younger than 1 or older than 9 years, T-cell phenotype, central nervous system (CNS) involvement, high lactate dehydrogenase (LDH), hyperuricemia, splenomegaly, and cytogenetic abnormalities such as hypodiploidy or MLL rearrangement[6,9].

The treatment of hyperleukocytosis aims to reduce and prevent hyperviscosity by hydration, avoiding giving red blood cell transfusion, allopurinol administration, preventing tumor lysis syndrome, early chemotherapy induction, and occasional leukoreduction by leukapheresis or exchange transfusion[11]. The advantages and disadvantages of leukapheresis are still being debated[12]. Leukapheresis

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can reduce white blood cell counts and may reduce tumor lysis syndrome or pulmonary leukostasis, but special equipment and trained personnel are required, and chemotherapy inductions may be delayed. In addition, infection and complications from the procedures may also occur and may not improve early morbidity or long-term survival rate[13]. The OS rate for patients with hyperleukocytosis varies from 52% to 53.7% compared with 79% to 79.6% in patients without hyperleukocytois[9,10]. However, reports have shown no difference in the survival rate of patients with or without hyperleukocytosis[8,14]. These studies found that there was no early toxicity-related death or recurrence in ALL patients with hyperleukocytosis of WBC 100,000 to 200,000/mm³ due to the improved management including intensive chemotherapy[8], while those without, with a poor prognosis in chromosomal abnormalities may respond more favorably to chemotherapy alone[14].

The present study aimed to evaluate the OS rate for childhood ALL in patients with and without hyperleukocytosis.

Materials and Methods

Between January 1, 2014 and December 31, 2018, 116 patients under the age of 15 who were newly diagnosed of ALL at Khon Kaen Hospital, a tertiary hospital, were retrospectively reviewed by using medical records and pediatric cancer records.

The diagnoses of ALL were based on clinical presentations, complete blood counts, blasts in bone marrow, flow cytometry for immunophenotyping, and cytogenetic studies. Chemotherapy treatment was administered according to the risk stratifications by the Thai National Protocol for ALL developed by the Thai Pediatric Oncology Group[15]. The standard risk protocol for ALL was used for patients between one and nine years old, with initial WBC of less than 50,000/mm³ or Down syndrome. The high-risk protocol for ALL was used for patients between 10 and 13 years old, with initial WBC of more than 50,000/mm³, T-cell phenotype, testicular involvement, or steroid pretreatment. The very high-risk protocol was used for patients older than 13-year-old, with CNS-3, induction failure, day 29 bone marrow minimal residual disease (MRD) of 0.01% or more, or unfavorable molecular features such as MLL rearrangement, and hypodiploidy. If the patient had the Philadelphia chromosome positive, the Philadelphia chromosome positive ALL protocol was used. Finally, the infant protocol was used for infants younger than one year old. Bone marrow aspiration, flow cytometry for immunophenotypic, cytogenetic, and MRD evaluation by flow cytometry method could be performed but with limitations due to the specimen obtained being inadequate, such as packed bone marrow, no metaphase in cytogenetic studies, and molecular studies currently unavailable in the present study institute. General supportive care including intravenous hydration, tumor lysis syndrome prevention, blood transfusion, infection prophylaxis, and antibiotic treatment if indicated were used for all newly diagnosed ALL cases.

The induction chemotherapies were started early, usually within 24 hours after adequate hydration, in hyperleukocytosis patients with close clinical and laboratory monitoring, hydration, alkalinization, allopurinol, platelet transfusion, avoid giving red cell transfusion, and tumor lysis syndrome prevention. Leukoreduction with leukapheresis or exchange transfusion was considered if hyperviscosity or extremely hyperleukocytosis with WBC of more than 300,000 to 400,000/mm³ and persistent high WBC after aggressive hydration were observed. In patients without hyperleukocytosis, chemotherapies were started after infection was controlled.

The characteristics recorded of the patients were age, gender, CNS involvement, mediastinal mass, testicular involvement, baseline hemoglobin, WBC, platelet, phenotype B cell, T cell or not otherwise specified (NOS), cytogenetic studies, risk stratifications chemotherapy protocols, hyper-leukocytosis treatment by leukoreduction such as leukaphereis or exchange transfusion, and early complications such as hyperviscosity, intracerebral hemorrhage, and tumor lysis syndrome. The outcomes of treatment were followed and recorded until June 30, 2021.

The present retrospective study was approved by the Ethical Committee of Khon Kaen Hospital (EC number: KEXP64036).

Statistical analysis

Descriptive statistics were reported as numbers and percentages for categorical variables and as medians and ranges for continuous variables. Differences in baseline characteristics, complications and outcomes were compared by using chi-squared test or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for continuous variables. The treatment outcomes were analyzed by the Kaplan-Meier method. OS was defined as the time from diagnosis to the date of the last follow-up or death. Event-free survival (EFS) was defined as

Table 1. Characteristics and laboratory findings of acute lymphoblastic leukemia with and without hyperleukocytosis

	WBC count (/mm^3)			p-value
	Total (n=116)	<100,000 (n=90; 77.6)	≥100,000 (n=26; 22.4)	
Sex; n (%)				0.44
Male	70 (60.3)	56 (62.2)	14 (53.8)	
Female	46 (39.7)	34 (37.8)	12 (46.2)	
Age (years); n (%)				0.10
Median (range)	5 (0.02 to 14.7)	4.9 (1 to 14.5)	8.9 (0.02 to 14.7)	
<1	5 (4.3)	1 (1.1)	4 (15.4)	
1 to 9	78 (67.2)	67 (74.5)	11 (42.3)	
>9	33 (28.5)	22 (24.4)	11 (42.3)	
Mediastinal mass; n (%)	6 (5.2)	3 (3.3)	3 (11.5)	0.18
CNS leukemia; n (%)	12 (10.3)	8 (8.9)	4 (15.4)	0.14
Hemoglobin (g/dL); median (range)	7.1 (2 to 16.6)	7 (2 to 13)	8.7 (3 to 16.6)	0.10
Hematocrit (%); median (range)	21.7 (9 to 40.5)	21.3 (9 to 36.7)	26.7 (10.9 to 40.5)	0.09
WBC; median (range)	15,050 (600 to 801,500)	8,200 (600 to 98,700)	229,800 (112,800 to 801,500)	<0.01
Platelet; median (range)	42,000 (2,000 to 531,000)	42,000 (2000 to 531,000)	43,000 (12,000 to 370,000)	0.70
Phenotype; n (%)				<0.01
B-cell	89 (76.7)	76 (84.4)	13 (50.0)	
T-cell	20 (17.2)	8 (8.9)	12 (46.2)	
NOS	7 (6.1)	6 (6.7)	1 (3.8)	
Cytogenetic; n (%)				0.29
Not done/not available	24 (20.7)	21 (23.3)	3 (11.5)	
Normal karyotype	64 (55.2)	50 (55.6)	14 (53.9)	
Abnormal	28 (24.1)	19 (21.1)	9 (34.6)	
Hyperdiploid	8 (6.9)	8 (8.9)	0 (0.0)	
Hypodiploid	0 (0.0)	0 (0.0)	0 (0.0)	
Translocation	11 (9.5)	5 (5.6)	6 (23.1)	
Deletion	3 (2.6)	2 (2.2)	1 (3.8)	
Complex	4 (3.4)	3 (3.3)	1 (3.8)	
Other	2 (1.7)	1 (1.1)	1 (3.8)	
Chemotherapy protocol; n (%)				<0.01
No chemotherapy	2 (1.7)	1 (1.1)	1 (3.9)	
Standard risk	50 (43.1)	50 (55.6)	0 (0.0)	
High risk	45 (38.8)	28 (31.1)	17 (65.4)	
Very high risk	14 (12.1)	11 (12.2)	3 (11.5)	
Philadelphia chromosome	2 (1.7)	0 (0.0)	2 (7.7)	
Infant	3 (2.6)	0 (0.0)	3 (11.5)	

WBC=white blood cell; CNS=central nervous system; NOS=not otherwise specified

the time from diagnosis to the date of relapse, death, or last follow-up. The survival rates of patients with or without hyperleukocytosis were compared by the log-rank test. A p-values less than 0.05 was considered as statistically different. The statistical analyses were performed by Stata, version 10 (StataCorp LP, College Station, TX, USA).

Results

One hundred sixteen childhood ALL patients were included in the present study. Twenty-six (22.4%) of these had hyperleukocytosis. The clinical and laboratory findings are shown in Table 1. The median age of the patients was five years old, and the male to female ratio was 1.6 to 1. The median of the white blood cell count was 15,050/mm^3 with a range from 600 to 801,500/mm^3. Most of the ALL-phenotypes were B-cells (76.7%), while 17.2% were T-cells. Seven of these patients (6.1%) were defined as ALL-NOS due to the dry tapping of bone marrow aspirations, inadequate bone marrow biopsy specimens, or no metaphase on cytogenetic studies.

Table 2. Cytogenetic abnormalities of ALL with and without hyperleukocytosis

WBC count (/mm³)	
<100,000 (n=19)	≥100,000 (n=9)
Hyperdiploidy	t(4;11)
48 chromosomes	t(4;11)
53 chromosomes	t(9;11)
54 chromosomes	t(9;11)
54 chromosomes	t(9;22)
55 chromosomes	t(9;22)
55 chromosomes	deletion 14
57 chromosomes	+21
65 chromosomes	47, X, –X, t(1;12), del(5), add(6), inv(11), add(14)
t(1:19)	
t(2:9)	
t(3;10)	
t(6:14)	
t(6;20)	
deletion 9	
deletion 9	
inversion 9	
54, XXX, t(9;22), +der(22)t(9;22)	
57, XXX, +1, del(1), –8, del(7)	
46, +9, der(9)t(9;22), i(9)/46XY	

WBC=white blood cell

Cytogenetic abnormalities were found in 28 patients (24.1%). Detail of chromosome abnormalities are shown in Table 2. No hypodiploidy was found in the present study. In the group with chromosome abnormalities, 10 patients died early in the induction to remission phase with a duration from diagnosis to death between 0.4 and 4 months, nine patients relapsed with a duration from diagnosis to relapse between 1.7 and 42.6 months, and eight of these relapsed cases died later. Only one case with deletion of chromosome 9 was still alive without relapse at the end of the study period. One case with hyperdiploidy, with 54 chromosomes, relapsed and died later.

Patients with hyperleukocytosis had a higher median age at 8.9 years versus 4.9 years (p=0.10), T-cell phenotype at 46.2% versus 8.9% (p<0.01), and abnormal cytogenetic at 34.6% versus 21.1% (p=0.29) compared with patients without hyperleukocytosis.

Most of the patients without hyperleukocytosis were treated with the standard risk protocol (55.6%), while the patients with hyperleukocytosis were treated with a high-risk protocol (65.4%), very high-risk protocol (11.5%), protocol for Philadelphia chromosome positive (7.7%), or infant protocol for three cases (11.5%).

According to the indications and availability for leukoreduction in the present study hospital as described in the method of the present study, emergency leukoreduction by leukapheresis was performed in two cases with WBC of 332,600 and 571,000/mm³ and exchange transfusions were performed in cases with WBC of 785,700 and 801,500/mm³. Patients with hyperleukocytosis who did not require leukoreduction had WBC of less than 300,000/mm³ except five cases who had WBC of 301,500, 378,500, 456,000, 483,000, and 580,200/mm³, with all five cases decreasing rapidly after aggressive hydration and corticosteroid administration during leukoreduction preparation was done.

Tumor lysis syndrome occurred in 20 cases (17.4%) and was successfully managed by hydration, allopurinol, and close monitoring. Hemodialysis was needed in one case only. One patient had complete induction to remission chemotherapy and had induction failure. This patient had initial WBC of 785,700/mm3. Two patients with hyperleukocytosis and one patient without hyperleukocytosis were MRD positive.

The outcomes of treatment are shown in Table 3. Forty-one patients (35.4%) died, with 25 of these not having hyperleukocytosis compared with 16 patients who had hyperleukocytosis thus, 27.8% versus 61.5% (p<0.01). Furthermore, 31 cases (26.7%) relapsed. The relapse rate of patients without hyperleukocytosis and with hyperleukocytosis were 23.3% and 38.5%, respectively (p=0.13). The major cause of death was infection in the neutropenic period and failure to respond to antibiotic treatment. Relapse with non-response to chemotherapy and subsequently neutropenic infection were the major causes of death in those with hyperleukocytosis.

The 5-year OS rate was 62.5% (95% CI 52.3 to 71.1). The 5-year survival rate for patients without hyperleukocytosis and patients with hyperleukocytosis were 70.2% (95% CI 58.7 to 79) and 36% (95% CI 17.5 to 54.9), respectively (p<0.01), as shown in Figure 1.

The 5-year EFS rate was 55.3% (95% CI 45.4 to 64.2). The 5-year EFS for patients without hyperleukocytosis and patients with hyperleukocytosis were 60.8% (95% CI 49.5 to 70.4) and 36.3% (95% CI 17.7 to 55.2), respectively (p=0.04), as shown in Figure 2. No patient was lost to follow-up in the present study. The median follow-up time was 44 months with a range of 0.5 to 87.8 months. The median time to relapse was 15.5 months with a range of 1.5 to 67.7 months. Furthermore, 21 patients

Table 3. Complications and outcomes of ALL with and without hyperleukocytosis

	WBC count (/mm³); n (%)			p-value
	Total (n=116)	<100,000 (n=90; 77.6)	≥100,000 (n=26; 22.4)	
Tumor lysis syndrome	20 (17.4)	7 (7.8)	13 (50.0)	<0.01
Intracerebral hemorrhage	1 (0.9)	0 (0.0)	1 (3.9)	0.22
Pulmonary leukostasis	0 (0.0)	0 (0.0)	0 (0.0)	
Death	41 (35.4)	25 (27.8)	16 (61.5)	<0.01
Death in induction phase	19 (16.4)	14 (15.6)	5 (19.2)	
Death in remission	1 (0.9)	1 (1.1)	0 (0.0)	
Death in relapse	20 (17.2)	10 (11.1)	10 (38.5)	
Death from other cause	1* (0.9)	0 (0.0)	1 (3.8)	
Relapse	31 (26.7)	21 (23.3)	10 (38.5)	0.13
Medullary	16 (13.8)	9 (10.0)	7 (26.9)	
Extramedullary	14 (12)	12 (13.3)	2 (7.7)	
Combined	1 (0.9)	0 (0.0)	1 (3.9)	

WBC=white blood cell

* Death at home after completion of treatment and off chemotherapy for 4 months due to autoimmune hemolytic anemia and dyspnea

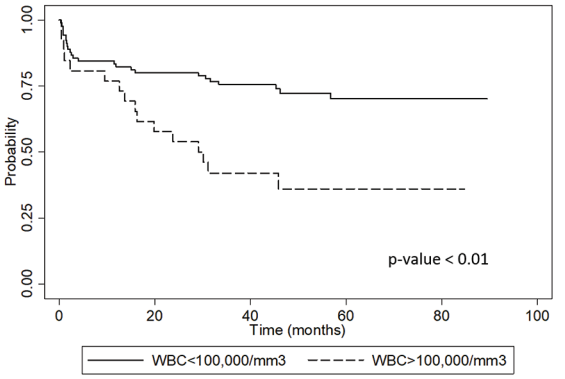

Figure 1. The 5-year overall survival rate (OS) analysis of patients with and without hyperleukocytois.

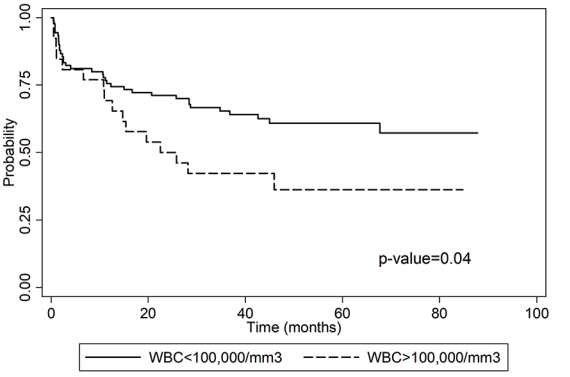

Figure 2. The 5-year event free survival rate (EFS) analysis of patients with and without hyperleukocytois.

(18.1%) died of disease severity or relapse, and 18 patients (15.5%) died of infections. The median survival time in relapsed patients was 31.2 months, with a range of 9.6 to 89.5 months.

Discussion

Hyperleukocytosis or WBC of more than 100,000/mm³, had been reported in 7.8% to 19.2% of childhood ALL cases[6-10]. The authors found that the incidence rate of hyperleukocytosis in newly diagnosed ALL cases in the present study tertiary hospital was 22.4%, which was higher than in the previous studies.

Patients with hyperleukocytosis had older median age at 8.9 years versus 4.9 years (p=0.12), more T-cell phenotype at 46.2% versus 8.9% (p<0.01), and more abnormal cytogenetic at 34.6% versus 21.1% (p=0.29) than patients without hyperleukocytosis. This is comparable to previous studies which mentioned the risk factors associated with hyperleukocytosis in childhood ALL were younger than 1 or older than 9 years, T-cell phenotype, and cytogenetic abnormalities[6,10].

The mortality of patient with hyperleukocytosis was associated with early complications such as CNS bleeding, hyperviscosity, and acute renal failure from tumor lysis syndrome[7,16]. Abla et al[17] reported in their study that neurological leukostasis occurred in six ALL cases (7.1%) and pulmonary leukostasis occurred in 16 ALL cases (19%). In the present study, the authors found only one case with WBC of 801,500/mm³, who had initial CNS bleeding before treatment with exchange transfusion and the patient died two weeks later. No pulmonary leukostasis was

found in the present study.

The early managements of hyperleukocytosis included hydration, alkalinization, allopurinol, platelet transfusion, avoid giving red blood cell transfusion, and leukoreduction. Leukoreduction by leukapheresis or exchange transfusion are still controversial in the management of hyperleukocytosis. Lowe et al[7] suggested that cytoreduction may be considered for patients with WBC of more than 400,000/mm^3 due to the serious leukostasis complications being uncommon in childhood ALL. Nguyen et al[6] demonstrated that leukapheresis may not reduce the occurrence of early adverse events. Due to the limited availability of blood bank to perform leukapheresis or blood products preparation for exchange transfusion in the present study hospital, patients with hyperleukocytosis were managed by hydration, preventing tumor lysis syndrome, platelet transfusion, avoid giving red cell transfusion, and close monitoring without leukoreduction procedures. In all cases with hyperleukocytosis, the authors also used corticosteroids and early induction of chemotherapy.

In the present study, death in the induction to remission phase was still high at up to 16.4%. Only one patient (0.9%) died in the remission phase. Unlike the study by the Children's Oncology Group (COG)[4], only 0.47% died during induction and 0.63% died in the remission phase. Death in the induction to remission phase was caused by severe prolonged neutropenia with severe infection occurring in both initial diagnoses before starting chemotherapy and toxicities after chemotherapy. Due to infection and severe prolonged neutropenia during the induction phase playing an important role in the cause of death, supportive care should be adapted, and the treatment protocol should be improved in the future. Furthermore, in the present study, the authors found a high incidence rate of relapse, especially in patients with hyperleukocytosis. The relapse rate in the hyperleukocytosis group was 38.5%, and all of them died. Therefore, relapse was an important cause of death. Hyperleukocytosis is associated with a high relapse rate and poor outcome as reported in the previous research[18].

Cytogenetic abnormalities were more common in patients with hyperleukocytosis than in patients without hyperleukocytosis at 34.6% versus 21.1% (p=0.29). Translocations such as t(1;19), t(4;11), t(9;11), t(9;22), and complex cytogenetic abnormalities were associated with unfavorable outcomes similar to the findings of the previous research[19].

The EFS and OS was found by Kaplan-Meier analysis to be significantly poorer in the hyperleukocytosis group than in patients without hyperleukocytosis, 36.3% (95% CI 17.7 to 55.2) versus 60.8% (95% CI 49.5 to 70.4), p=0.04, and 36% (95% CI 17.5 to 54.9) versus 70.2% (95% CI 58.7 to 79), respectively (p<0.01). Similar outcomes had been reported in previous studies. Eguiguren et al[9] reported that the 4-year survival rate for patients with hyperleukocytosis compared to patients without hyperleukocytosis was 52% versus 79%. This is consistent with the findings of the study of Koka et al[10], which found the 5-year survival rate of hyperleukocytois was 53.7%. Meanwhile, better outcomes were observed by Kong et al[8], who reported the EFS of ALL patients with hyperleukocytosis was 75%, while the OS was 81.2%, although they also reported that the outcomes of ALL patients with an initial leukocyte count of more than 200×10^9/L remained poor due to early toxicity-related death. Yang et al[14] reported no significant difference from their survival analysis of those with or without hyperleukocytosis at 82.8% versus 86.8%, due no poor chromosome abnormalities and good response to chemotherapy. Park et al[16] also reported the 10-year survival rate of hyperleukocytosis was 82.6% but the 10-year EFS rate for patients with initial extreme hyperleukocytosis or WBC of more than 200×10^9/L, was significantly lower than for patients with WBC counts of 100 to 200×10^9/L at EFS of 65.7% versus 91.2% (p=0.011). According to the small number of hyperleukocytosis patients in the present study, the authors did not perform subgroup analysis of extreme hyperleukocytosis.

The limitation of the present study is that it is a retrospective study and risk factors that influenced the outcome of treatment may be unavailable in the present study hospital, such as molecular genetic testing. Therefore, there is insufficient data for statistical analysis for this prognostic factor.

In summary, the incidence rate of hyperleukocytosis still remains high in childhood ALL. Hyperleukocytosis is a crucial factor that significantly reduces the outcome of treatment of childhood ALL in terms of both the OS and the EFS rate. The chemotherapy protocol for this group should be evaluated and adapted to further improve the survival outcome.

What is already known on this topic?

Hyperleukocytosis is frequently found in

childhood ALL. The effect of hyperleukocytosis on the survival outcome compared with patients without hyperleukocytosis remained inconclusive.

What this study adds?

The present study found a high incidence rate of hyperleukocytosis in childhood ALL. ALL with hyperleukocytosis is associated with a high relapse rate and poor survival rate. The specific protocol for ALL with hyperleukocytosis needs to be revised to improve the outcome.

Conflicts of interest

The author declares no conflicts of interest.

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