Treatment outcomes in childhood acute lymphoblastic leukemia: 40-year experience from a single tertiary center in Thailand

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February 22, 2024

Abstract

Background. Studies on the long-term treatment outcomes of childhood acute lymphoblastic leukemia (ALL) in resource-limited countries are scarce. The purpose of this study was to assess the evolution of survival outcomes of pediatric ALL in a tertiary care center in Thailand over a 40-year period. **Patients and methods.** We retrospectively reviewed the medical records of pediatric patients who were diagnosed with ALL and treated at our center between June 1979 and December 2019. We classified the patients into 4 study periods depending on the therapy protocol used to treat the patients (period 1: 1979-1986, period 2: 1987-2005, period 3: 2006-2013, and period 4: 2014-2019). The Kaplan Meier method was used to determine overall and event-free survival for each group. The log-rank test was used to identify statistical differences. **Results.** Over the study period, 726 patients with ALL were identified, 428 boys (59%) and 298 girls (41%), with a median age at diagnosis of 4.7 years (range: 0.2–15 years). The study periods 1, 2, 3, and 4 had 5-year event-free survival (EFS) rates of 27.6%, 41.6%, 55.9% and 66.4%, and 5-year overall survival (OS) rates of 32.8%, 47.8%, 61.5%, and 69.3%, respectively. From period 1 to period 4, both the EFS and OS rates increased significantly ($p<0.0001$). Age, study period, and white blood cell (WBC) count were all significant prognostic indicators for survival outcomes. **Conclusions.** The overall survival of patients with ALL treated in our center improved significantly over time from 32.8% in period 1 to 69.3% in period 4.

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Word count : **Word count** : Abstract 251 words, Main text 2,620 words**,** Total 19 pages

Number of Tables : 4

Number of Figures: 2

Short running title : Pediatric acute lymphoblastic leukemia in Thailand

This manuscript has not been previously published and is not currently being submitted to any other journals. All authors contributed significantly to the study and read and approved the final draft. There are no financial or commercial interests in this work.

Abbreviations

ALL	Acute lymphoblastic leukemia
EFS	Event-free survival
OS	Overall survival
APC	Annual percent change
FAB	French-American-British
CNS	Central nervous system
CCSG	Children's Cancer Study Group
WBC	White blood cell
IT	Intrathecal

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AbstractBackground. Studies on the long-term treatment outcomes of childhood acute lymphoblastic leukemia (ALL) in resource-limited countries are scarce. The purpose of this study was to assess the evolution of survival outcomes of pediatric ALL in a tertiary care center in Thailand over a 40-year period. **Patients and methods.**We retrospectively reviewed the medical records of pediatric patients who were diagnosed with ALL and treated at our center between June 1979 and December 2019. We classified the patients into 4 study periods depending on the therapy protocol used to treat the patients (period 1: 1979-1986, period 2: 1987-2005, period 3: 2006-2013, and period 4: 2014-2019). The Kaplan Meier method was used to determine overall and event-free survival for each group. The log-rank test was used to identify statistical differences. **Results.** Over the study period, 726 patients with ALL were identified, 428 boys (59%) and 298 girls (41%), with a median age at diagnosis of 4.7 years (range: 0.2–15 years). The study periods 1, 2, 3, and 4 had 5-year event-free survival (EFS) rates of 27.6%, 41.6%, 55.9% and 66.4%, and 5-year overall survival (OS) rates of 32.8%, 47.8%, 61.5%, and 69.3%, respectively. From period 1 to period 4, both the EFS and OS rates increased significantly ($p<0.0001$). Age, study period, and white blood cell (WBC) count were all significant prognostic indicators for survival outcomes. **Conclusions.** The overall survival of patients with ALL treated in our center improved significantly over time from 32.8% in period 1 to 69.3% in period 4.

Key words : acute lymphoblastic leukemia, childhood leukemia, long-term treatment outcome

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer, accounting for 26% of all cancers diagnosed in children, including around 80% of acute leukemia cases.[1–3]Between 1990 and 2011, both the incidence and survival rates of leukemia in Thailand increased, but remained lower than in the

United States.[4] Previous studies in Thailand found that the annual percent change in incidence of childhood ALL ranged from 1.4–1.8%, and that this had increased dramatically.[4,5]

Patients with ALL treated in developed countries have had significantly improved outcomes, with 5-year EFS rates improving from 10% 50 years ago to >90% presently.[6–10] A variety of factors have contributed to the constant improvement in outcomes, including risk-adjusted chemotherapy, targeted therapy, hematopoietic stem cell transplantation, and effective supportive care.[11–13] However, treatment outcomes for childhood patients with ALL in resource-limited countries remain poor when compared to developed countries, where 30-60% EFS rates are reported.[14–17] Disease relapses, treatment abandonment, and chemotherapy toxicity have all been recognized as substantial barriers to achieving improved treatment outcomes in developing countries, such as Thailand.[15,18]

To date, there have been few studies of childhood ALL survival outcomes in resource-limited countries. The purpose of this study was to assess the change of outcomes over the last 40 years, with the goal of using this information to produce therapeutic guidelines that would improve treatment outcomes. A secondary objective was to assess survival predictors in children with ALL in a tertiary treatment center in southern Thailand.

Patients and methods.

We retrospectively reviewed the medical records of patients under the age of 18 years newly diagnosed with ALL between June 1979 and December 2019 and treated at the Hematology Clinic of Songklanagarind Hospital, the major tertiary medical institute and referral hospital in Southern Thailand. The diagnoses were based on morphologic assessment of bone marrow aspiration smears, immunophenotyping by flowcytometry, and immunohistochemistry of clotted bone marrow. The study was approved by the institute's Ethics Committee. All patients' parents or guardians gave written or verbal informed consent in accordance with the Ethics Committee's criteria. The patient variables recorded included gender, age, initial clinical presentation, subtype, treatment protocol, remission of induction, follow-up date, and cause of death. Patients with incomplete data, therapy discontinuation, or uncertain post-treatment response were excluded.

Risk grouping and treatment

Before 2000, ALL subclassifications were based on the French-American-British (FAB) criteria.[19] Since 2000, patients diagnosed with ALL have been divided into three types, B-cell, T-cell, and Burkitt-cell leukemia, based on the World Health Organization ALL classification system.[20] The patients enrolled in the study were separated into four groups based on the different protocols used to treat ALL during the study period, designated as study periods 1-4.

During study period 1 (1979 to 1986), all patients received Siriraj II regimen chemotherapy.[21] This regimen consisted of induction of remission (prednisolone, mercaptopurine, methotrexate), an intense course (prednisolone, mercaptopurine, methotrexate, cyclophosphamide), and central nervous system (CNS) prophylaxis (intrathecal (IT) methotrexate, cranial radiation).

In study period 2 (1987 to 2005), following the Children's Cancer Study Group (CCSG) criteria, the protocol divided patients into 3 prognosis groups: good (CCG-104), intermediate (CCG-105), and poor (CCG-106).[22,23] However, we did not identify any patients with a 'good' prognosis in this study. For the CCG-105 protocol, the chemotherapy treatment consisted of prednisolone, vincristine, and doxorubicin for the induction phase and mercaptopurine, IT methotrexate, cyclophosphamide, cytarabine, and cranial radiation for the consolidation phase. The CCG-106 protocol followed the same induction and consolidation phases as the CCG-105 protocol but with the addition of interim maintenance and delayed intensification chemotherapy. During the maintenance phase, both CCG-105 and CCG-106 patients received the same chemotherapeutic treatments: mercaptopurine, methotrexate, vincristine, and prednisolone.

Thai Pediatric Oncology Group's standard protocols for treating pediatric leukemia were implemented in 2006.[24,25] In study period 3 (2006 to 2013), the Thai national protocol ALL-01-05 (standard risk ALL) was introduced for patients aged 1 to 10 years with an initial white blood cell (WBC) count $< 50{,}000/\text{mm}^3$.

With this protocol, standard risk ALL patients received 4 weeks of induction chemotherapy, which consisted of prednisolone, vincristine, doxorubicin, L-asparaginase, and IT methotrexate. Following that, patients received consolidation chemotherapy and CNS prophylaxis for a total of 7 weeks, which consisted of mercaptopurine, methotrexate (1.5 gm/m^2), and IT methotrexate. The maintenance phase treatment consisted of vincristine, prednisolone, mercaptopurine, and oral and IT methotrexate for a total of 2.5 years in females and 3 years in males. The ALL-02-05 (high-risk ALL) criteria were age $>$ 10 years or $<$1 year, WBC $>$ 50,000/mm^3, CNS or testicular involvement, and T cell ALL. Patients with high-risk ALL received the same treatment as patients with standard risk ALL during the induction phase, but for 2 weeks longer, with a 12-week consolidation phase consisting of mercaptopurine, cyclophosphamide, cytarabine, and oral and IT methotrexate. The maintenance phase treatment included the same chemotherapy as in standard risk ALL but was given for a total of 3 years in both males and females. The ALL VHR-08 (very high-risk ALL) protocol was used with patients with WBC$>$ 100,000/mm^3, Philadelphia chromosome positive, infant ALL, and patients who had had induction failure with another protocol. Patients with very high-risk ALL received the same treatment as patients with high-risk ALL during the induction and consolidation phases but was given for 2 weeks longer. They also received interim maintenance, delayed intensification, 2nd interim maintenance and 2nd delayed intensification, which was followed by a 3-year maintenance phase.

In period 4 (2014 to 2019), the latest version of the Thai national protocol, which was modified from the Children's Oncology Group (COG)-AALL00P2 and COG-AALL0232 regimens, was administered to ALL patients.[26] The ALL 1301 (standard-risk ALL) was introduced for patients aged 1-9 years with an initial WBC count$<$ 50,000/mm^3 or with underlying Down syndrome. Patients with standard-risk ALL received a 6-week remission induction regimen with vincristine, prednisone, L-asparaginase and IT methotrexate, followed by 4 weeks of consolidation therapy with vincristine, mercaptopurine and IT methotrexate. The patients were then given vincristine, high-dose methotrexate (2.5 gm/m^2), and IT methotrexate every 2 weeks as interim maintenance for 8 weeks. During the maintenance phase, vincristine, prednisolone, mercaptopurine, and methotrexate were used for a total duration of 20 months in females and 32 months in males. The ALL 1302 (high-risk ALL) protocol was introduced for patients with T-cell ALL or B-cell ALL and who met the following criteria: age 10-13 years, initial WBC [?]50,000/mm^3, all male patients who had testicular disease and/or steroid pretreatment. High-risk ALL patients received 6 weeks of remission induction with vincristine, prednisone, doxorubicin, L-asparaginase and IT methotrexate, followed by 8 weeks of consolidation therapy with cyclophosphamide, cytarabine, mercaptopurine, L-asparaginase, vincristine and IT methotrexate, followed by vincristine, high-dose methotrexate (5 gm/m^2), and IT methotrexate every 2 weeks as augmented interim maintenance for 9 weeks. The same maintenance chemotherapy was then given to these patients as the standard-risk ALL group. The ALL 1303 (very high-risk ALL) protocol was used for patients with B-cell ALL, aged [?]14 years or CNS -3 ([?]5/μL of WBC in cerebrospinal fluid with cytospin positive for blasts) or induction failure. Very-high-risk ALL patients received the same induction, consolidation, and maintenance phase treatments as the high-risk ALL patients, with the addition of etoposide and cyclophosphamide in the consolidation phase. They also received an interim maintenance phase treatment with methotrexate (250 mg/m^2), vincristine and IT methotrexate for 8 weeks.

Statistical analysis

EFS was defined as the time from diagnosis to the first event, which was defined as induction failure, relapse, or the date of the last follow-up. OS was defined as the period from diagnosis to death or the date of last follow-up. The Kaplan Meier method was used to calculate the rates of EFS and OS. A univariate Cox proportional hazards regression model was used to identify clinical factors associated with poor EFS and OS. A multivariate Cox regression model was used to predict EFS and OS based on significant statistical factors from the univariate analysis. A p-value < 0.05 was considered statistically significant.

Results

Over the 40-year study period there were 770 patients under the age of 18 years diagnosed with ALL. After excluding 44 patients with incomplete data, 726 patients were included in the study. There were 428 boys (59%) and 298 girls (41%) and the median age at diagnosis was 4.7 years (range 0.2–15 years). The FAB

subtype was found in 254 patients (35%), the B-cell subtype in 401 patients (55.2%), and the T-cell subtype in 71 patients (9.8%).

The 5-year EFS rates in periods 1, 2, 3 and 4 were 27.6% (95% CI: 16.5-46.2), 41.6% (95% CI: 36.7-47.0), 55.9% (95% CI: 49.8-62.6) and 66.4% (95% CI: 56.7-77.8), respectively (Fig. 1). The EFS rates increased from period 1 to period 4 (p<0.0001). The 5-year OS rates for periods 1, 2, 3 and 4 were 32.8% (95% CI: 20.9-51.7), 47.8% (95% CI: 42.9-53.3), 61.5% (95% CI: 55.5-68.1) and 69.3% (95% CI: 59.0-81.4), respectively (Fig. 2). As with the EFS rates, the 5-year OS rates significantly improved over the study period.

As shown in Table 1, the remission rate of induction remained relatively constant at 96-98.8% in each study period. The rates of relapse gradually decreased over the 4 periods, from 59% in the first period to 40.1% in the second period, 29.6% in the third period, and 14.7% in the fourth period. Isolated bone marrow relapse (69.6%) was the most common site of relapse, followed by isolated CNS relapse (12.8%) and combined bone marrow and CNS relapse (8.8%).

From the first to the fourth study periods, both female and male patients experienced statistically significant improvements in both EFS and OS. Patients aged 1-9 years had gradually improved outcomes through the 4 periods, but there were no improvements in treatment outcomes for patients aged [?]10 years. Patients with an initial WBC count <100,000/uL had a larger improvement in outcomes over the 4 study periods. However, the outcomes were not significantly improved over time in the group with an initial WBC count [?]100,000/uL. When comparing the first and last periods, the 5-year EFS rate in the T-cell lymphoblastic leukemia group greatly improved, but the 5-year OS rates showed no difference. There were no changes in treatment outcomes between study periods in patients with B-cell lymphoblastic leukemia. In the NCI risk classification, neither the standard nor the high-risk groups differed in treatment outcomes for patients in both the B-cell and T-cell subtypes, except for those with FAB acute lymphoblastic leukemia, in which the NCI standard group had significantly better treatment outcomes when comparing the first and last periods (Table 2).

The univariate analysis (Table 3) showed that the factors related to EFS were patient age, WBC, and study period. In particular, patients 1-9 years of age had a hazard ratio of 0.41 (p-value=0.002) compared to patients less than 1 year of age. Patients with WBC counts of >10,000 to <50,000/μL, 50,000 to <100,000/μL, and [?]100,000/μL had hazard ratios of 1.34 (p-value = 0.041), 1.78 (p-value = 0.039), and 2.74 (p-value = 0), respectively, when compared with the reference group of WBC count [?]10,000/μL. In comparison to patients treated during study period 1, patients treated during study periods 3 and 4 had hazard ratios of 0.46 (p-value=0.003) and 0.35 (p-value=0.001), respectively.

The univariate analysis (Table 3) found that the factors significantly associated with OS were age, mediastinal mass, WBC count, and study period. When compared to patients aged <1 year, patients aged 1-9 years had a hazard ratio of 0.46 (p-value=0.009), while the hazard ratio for patients with a mediastinal mass was 2.38 (p-value=0.027). Patients with WBC counts of >10,000 to <50,000/μL and [?]100,000/μL had hazard ratios of 1.39 (p-value = 0.029) and 2.62 (p-value <0.001), respectively, when compared with the reference group of WBC count [?]10,000/μL. Patients treated during study periods 3 and 4 had hazard ratios of 0.44 (p-value=0.002) and 0.36 (p-value=0.002), respectively, compared to patients treated during study period 1.

From the multivariate Cox regression analysis (Table 4), factors significantly associated with OS were age, study period, and WBC count. When compared to patients aged <1 year, those aged 1-9 years had a hazard ratio of 0.46 (p-value=0.005). In comparison to study period 1, patients in study periods 2, 3, and 4 showed hazard ratios of 0.58 (p-value = 0.005), 0.34 (p-value 0.001), and 0.31 (p-value 0.001). When compared to the 10,000/μL group, patients with WBC counts of >10,000 to 50,000/μL, 50,000 to 100,000/μL, and 100,000/μL had hazard ratios of 1.38 (p-value = 0.016), 1.60 (p-value = 0.006), and 2.65 (p-value 0.001), respectively.

Discussion

This study compared treatment outcomes for ALL patients treated at a tertiary and referral center in

Southern Thailand over the last 40 years. The age and gender distributions and ALL immunophenotypes were similar to other studies published globally.[15,27,28]The 5-year EFS rates increased substantially over the study period, from 27.6% in study period 1 to 66.4% in study period 4. The 5-year OS also improved significantly, from 32.8% in study period 1 to 69.3% in study period 4.

The survival outcomes of our study were comparable to a study from Saudi Arabia, which found that the 5-year EFS improved from 30.6% in 1981-1992 to 64.2% in 1993-1998.[17] Another study from China found the 5-year EFS and OS were 51.3% and 57.7%, respectively.[29] However, other studies from Taiwan and Jordan reported higher survival rates than in our study. A study from Taiwan found that the EFS was 69%-77.4%, while a study from Jordan found 5-year EFS and OS rates of 80% and 89%, respectively.[28,30] Substantially better survival outcomes were seen from developed countries, with three studies reporting 5-year EFS rates ranging from 81%-87%.[13,31,32]

The overall rate of induction remission in this study was around 96-98%, which was comparable to patients in previous studies worldwide.[10] The improved treatment outcomes in recent years have been made possible by the use of long-term, risk-stratified, multi-agent systemic chemotherapy, effective CNS directed therapy utilizing IT methotrexate instead of cranial radiation, and enhanced supportive care.

Other major studies have reported relapse rates ranging from 12-20% between1984-2004.[33–35] In developing countries, the incidence of relapse disease has been reported to be relatively high, ranging between 24-60% within a similar study period.[14,17,29] In our study, the relapse rates were higher in study periods 1-2, with relapse incidences of 40 and 59%. However, by the 4th period of our study, the relapse rate had dropped to 14.7%. The rate of CNS relapse has decreased since study period 2 due to intrathecal and intravenous methotrexate, which has contributed to better survival outcomes.[36–38]Multivariate Cox regression analysis indicated that age, study period, and WBC count were prognostic factors related to survival outcomes, as previously reported in other studies.[10,39]

Our literature review revealed that there are still significant disparities in the outcomes of ALL treatments between developing and developed countries. Lack of sufficient supportive care, infection control, socioeconomic status, treatment compliance, and treatment abandonment were all reasons for the poorer outcomes.[40–42] Adopting a standardized treatment regimen, and providing intensive patient education, family financial assistance, and travel allowances are methods that can improve treatment outcomes. The major goal is to increase survival rates while enhancing the quality of life for patients.

Our study was conducted at a single tertiary and referral center in Southern Thailand, with a large sample size and long-term data of patients with ALL treated over a 40-year period. Our aim was to assess the change of treatment outcomes in a resource-constrained country and to identify ways to improve treatment outcomes in the future. However, this study spanned a 40-year period during which significant diagnostic and therapy advancements had occurred. As a result, our population may be heterogeneous, diluting our findings.

Conclusion

The treatment outcomes of patients with ALL in this study showed significant improvements over time. However, overall outcomes were poorer than in developed countries.

AcknowledgementsAssistance provided by Mr. Dave Patterson with English editing was greatly appreciated.

Conflict of Interest Statement There are no conflicts of interest reported by the authors.

Authorship contributions All authors made major contributions to this study and they all evaluated and approved the final version.

Data availability statement

Data supporting the conclusions of this investigation are available upon reasonable request from the corresponding author. The information is not publicly available due to privacy and ethical considerations.

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TABLE 1 Treatment outcomes according to study period

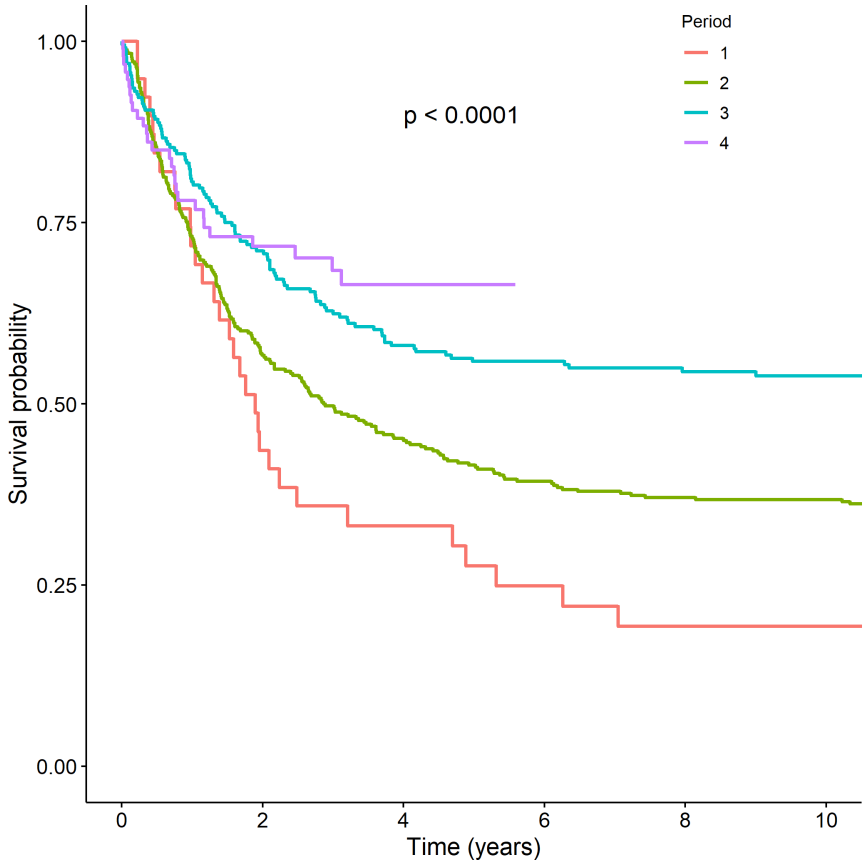
TABLE 2 Treatment outcomes based on the presenting characteristics of the patients

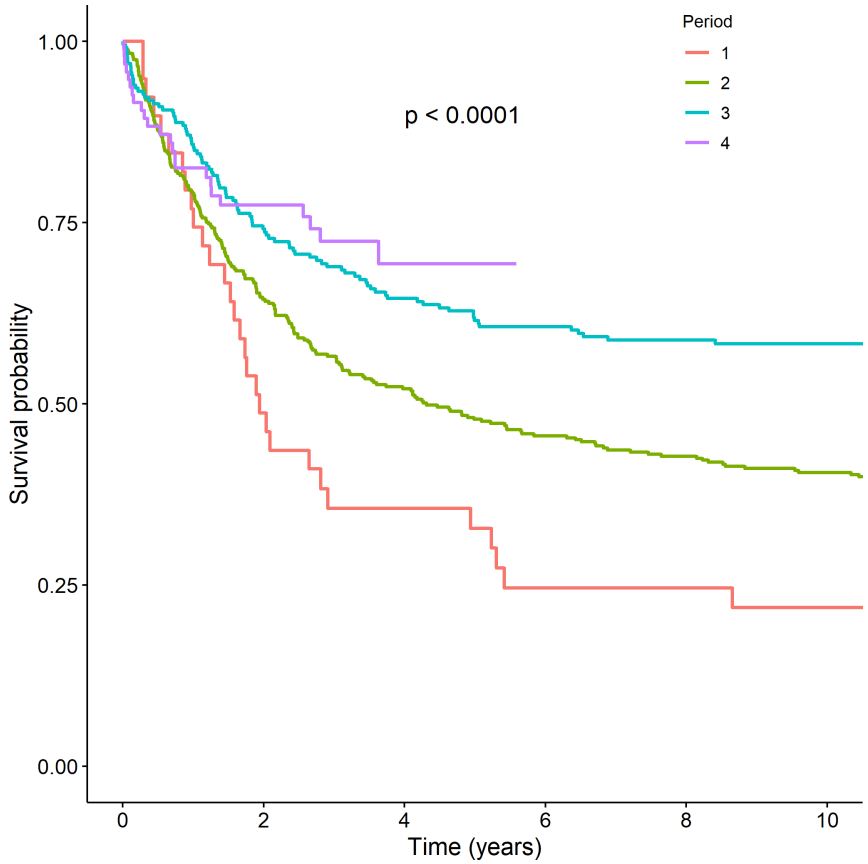
TABLE 3 Univariate analysis for event-free survival and overall survival by clinical parameters

TABLE 4 Multivariate Cox regression model to determine risk factors of overall survival

FIGURE 1 Event free survival by study period

FIGURE 2 Overall survival by study period





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0802-table1-Treatment outcomes according to study period.docx available at https://authorea.com/users/457957/articles/580824-treatment-outcomes-in-childhood-acute-lymphoblastic-leukemia-40-year-experience-from-a-single-tertiary-center-in-thailand

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0802-table2-Treatment outcomes based on the presenting characteristics.docx available at https://authorea.com/users/457957/articles/580824-treatment-outcomes-in-childhood-acute-lymphoblastic-leukemia-40-year-experience-from-a-single-tertiary-center-in-thailand

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0802-table4-Multivariate Cox regression model.docx available at https://authorea.com/users/457957/articles/580824-treatment-outcomes-in-childhood-acute-lymphoblastic-leukemia-40-year-experience-from-a-single-tertiary-center-in-thailand