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Research paper

Better survivals in adolescent and Young adults, compared to adults with acute lymphoblastic leukemia – A multicenter prospective registry in Thai population

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ABSTRACT

Adult acute lymphoblastic leukemia (ALL) is an uncommon hematologic malignancy with high relapse and mortality rate. This study aimed to describe characteristics and outcomes of Thai ALL patients, and to determine the differences between adolescent and young adult (AYA) and adult ALL. ALL patients aged > 15 years were prospectively enrolled from 2015 to 2017. AYA patients were defined as age ≤ 39 years.

Out of the 188 enrolled ALL patients, 9 were excluded due to changes in diagnosis or incomplete data. From the remaining 179 patients, 103 (57.5%) were AYA and 76 (42.5%) were adult. AYA ALL patients were predominantly male, had higher T-cell phenotype, higher white blood cells and hemoglobin, with lower frequency of Philadelphia chromosome or *BCR-ABL1* mutation. All patients received treatment by adult hematologist, however 40.8% of AYA ALL patients were treated with pediatric adapted protocol. The effects of stem cell transplantation (SCT) and age were determined by stratified patients as: AYA - no SCT 91 (51.1%), AYA - SCT 12 (6.7%), adult - no SCT 64 (36.0%) and adult - SCT 11 (6.2%). The 2-year overall survival were: 53.9%, 60.6%, 39.2% and 70.1%, respectively. The 2-year event-free survival were: 45.0%, 54.0%, 21.0% and 49.9%, respectively. This is a large multicenter ALL cohort study conducted in Thailand. Patients who underwent SCT showed significantly improved OS and EFS, confirming the benefit of graft-versus-leukemia effect in ALL. However, further studies with longer follow-up, expanded use of SCT, use of molecular data, and minimal residual disease status are warranted.

1. Introduction

Acute lymphoblastic leukemia (ALL) is an uncommon and unique entity in adulthood, which differs from pediatric group in terms of molecular pathogenesis and outcomes. The overlapping spectrum of lymphoblastic lymphoma form (with no or minimal marrow involvement) and leukemic form is well-recognized since the establishment of World Health Organization classification (WHO) of tumors of hematopoietic and lymphoid tissue in 2008 [1]. ALL is further subcategorized into precursor B and T lymphoid neoplasms. The advancements in cytogenetic and molecular techniques have helped in further defining the disease subgroups [2]. The reported incidence of

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ALL in total US population was 1.7 cases per 100,000-persons/year and more than half occurred at age < 20 years old. ALL represents approximately 20% of all adult acute leukemia [3]. Data regarding ALL in western countries has been published from multiple clinical trials and registries [4–11], whereas data from Asian countries is scarce and mostly reported in a small sample size or derived from single centers [12–15]. In the past 3 decades, the established standard induction treatments in ALL are multi-agent chemotherapy protocols consisting of corticosteroid, vincristine, anthracycline and L-asparaginase or hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with cytarabine and methotrexate (hyper-CVAD) [16]. Interestingly, the outcomes in pediatrics ALL have been excellent with long-term overall survival reaching 85% [17], but outcomes in adult ALL are still an area of unmet need with 3-year survival of 40–50% [18,19]. The use of pediatric adapted treatment protocol in adolescent and young adult (AYA) ALL patients have shown significant improvement in long-term event-free survival compared to adult ALL treatment [20]. A previous report on the outcome of ALL in Thailand showed dismal results with median survival of 8 months for Philadelphia (Ph1)-chromosome positive ALL and 22 months for Ph1-chromosome negative ALL [21]. In Thailand, there have been no reported outcomes in AYA ALL patients compared to adult ALL patients. Moreover, in the recent years, pediatric adapted protocol has been implemented in AYA ALL patients, which could have potentially improved their survival rates.

Therefore, the primary objective of this study was to prospectively describe clinical characteristics and outcomes of ALL patients in Thailand. The secondary objective was to determine the differences between AYA ALL and adult ALL patients, including the effects of allogeneic stem cell transplantation.

2. Material and methods

2.1. The Thai acute leukemia working group and the ALL registry

The Thai Acute Leukemia Working group was founded in 2012 under the supervision of the Thai Society of Hematology. The group's objective is to study all aspects of disease and create national guideline for the treatment of acute leukemias. Members consist of physicians from 9 major academic centers, covering approximately 70% of nationwide population. Allogeneic stem cell transplantation is offered in 4 member centers. The Thai ALL observational registry was initiated in 2015 to study the characteristics and outcomes of adult ALL. Patients' information was collected via encrypted web-based case record form hosted by the Thai Society of Hematology server. The study was registered at www.clinicaltrials.in.th as TCTR20150518001.

2.2. Study population

Patients, (aged ≥ 15 years) diagnosed with ALL between 1 January 2015 and 31 December 2017 according to WHO classification 2008 [1] were prospectively enrolled in this study. Lymphoblastic lymphomas were also included, whereas mixed phenotype acute leukemia and blastic phase of chronic myeloid leukemia were excluded. Written informed consents from the patients were obtained prior to enrollment. Data collected included demographics, manifestations, organs involvement, performance status, disease complications, laboratory investigations, treatment, physician determined protocol adherence, whole brain radiation, stem cell transplantation (SCT) and outcomes. Patients were followed from diagnosis until death or last follow-up (31 July 2018), with censoring for patients lost to follow-up at last visit. The study was approved by institutional review board of each participating center and conducted in accordance with the Declaration of Helsinki.

2.3. Treatments and outcomes

Treatment was based on institutional policy and physician's discretion. Common treatment included multi-agent chemotherapy containing corticosteroid, vincristine, anthracycline and L-asparaginase (adult/pediatric adapted ALL protocol) or hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with cytarabine and methotrexate (hyper-CVAD) as shown in supplementary appendix. Complete remission (CR) was defined as marrow lymphoblast < 5% and no circulating lymphoblast or extramedullary disease. Consolidation usually contains multi-agent chemotherapy, prophylactic whole brain radiation and maintenance chemotherapy. Relapsed disease was defined as disease recurrence in previously documented CR whereas patients who never attained CR were classified as primary refractory disease. The primary endpoint of this study was overall survival (OS), which was defined as the time from diagnosis until death or last follow-up. Secondary endpoints included event free survival (EFS), defined as the time from diagnosis until relapse, death or last follow-up; cumulative incidence of relapse (CIR) and non-relapse mortality (CI-NRM). Patients were censored at the time of last follow-up. Patients who underwent allogeneic SCT were not censored.

2.4. Statistical analyses

Patients were categorized into AYA ALL (age 15–39 years) and adult ALL (age ≥ 40). Categorical variables were described using number and percentage and compared with chi-square or Fisher's exact test. Continuous variables were presented as median and interquartile range (IQR) and compared with Mann-Whitney U test. Probabilities of OS and EFS were calculated using the Kaplan Meier's method and compared using Log-rank. The probabilities of CIR and CI-NRM were analyzed using cumulative incidence with competing risk analysis. Comparisons between cumulative incidences were carried out with Pepe-Mori method. All statistical analyses were performed using the Stata software version 13.0 (StataCorp, Texas, USA). All tests were two-sided and P-values < 0.05 were considered as statistically significant.

3. Results

3.1. Patients' characteristics

One hundred eighty-eight patients diagnosed with ALL, between January 2015 and December 2017, were prospectively enrolled in this study, among which 9 were excluded due to changes in diagnosis following institutional pathological revision (2 to prolymphocytic leukemia and 1 to mixed phenotype acute leukemia) or incomplete follow-up data (6 patients). A total of 179 patients were included in the final analysis database (Fig. 1). For the whole cohort, the median age of diagnosis was 34 years (IQR 22–49 years) and 83 patients (46.4%) were female. The ratio of B-cell and T-cell ALL were 129 (72.1%): 50 (27.9%). Ph1-chromosome and/or *BCR-ABL1* fusion were found in 30 patients (16.8%). Patients were categorized into adolescent and young adult (AYA) ALL group 103 (57.5%) and adult ALL group consisting 76 patients (42.5%).

Baseline characteristics were as shown in Table 1. Significant differences for AYA ALL when compared to adult ALL were as the following: predominantly affected male (67.0% vs. 35.5%, P-value < 0.001); having higher T-cell (37.9% vs. 14.5%, P-value < 0.001); higher white blood cell count (median 26.9 vs. 11.9 × 10^9 cells/L, P-value 0.003); higher hemoglobin levels (median 92 vs. 89 g/L, P-value 0.028); and less frequently harboring Ph1-chromosome or *BCR-ABL1* mutation (10.7% vs. 25.0%, P-value 0.011), respectively. Other characteristics at presentation were not statistically difference, including treatment centers, home region (northern, northeastern, central, eastern, western and southern), year of diagnosis, platelet level at diagnosis, circulating or bone marrow blast percentages,

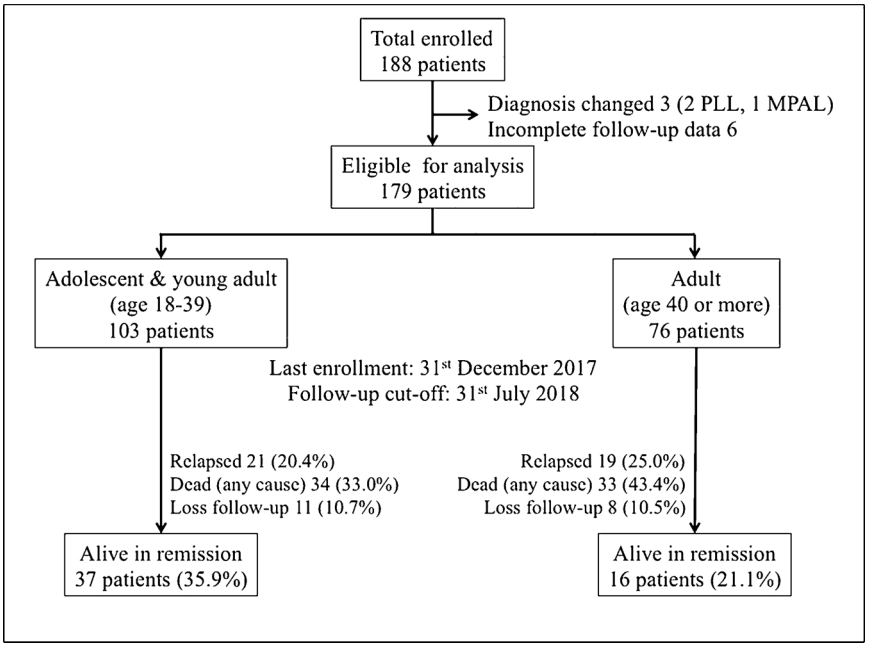

Fig. 1. Patient flow diagram.

lymphadenopathies, hepatosplenomegaly, organ involvements, Eastern cooperative oncology group (ECOG) performance status and disease complications prior to diagnosis (including tumor lysis syndrome, hyperleukocytosis, disseminated intravascular coagulation and superior vena cava syndrome).

3.2. Treatments and responses

Table 2 shows the treatment given and responses to treatments. The majority of patients in AYA ALL group received pediatric adapted ALL protocol while the majority of adult ALL received adult ALL protocol or Hyper CVAD regimen. Pediatric adapted ALL protocol were not given to any patients in the adult ALL group. A small number of patients in both groups (5.8% and 14.5%) did not receive any induction treatment and were offered palliative care. For 6 patients in AYA group, 1 patient did not receive any treatment and died within 1 week after diagnosis, while other 5 patients decided to have only palliative low dose chemotherapy for logistic reasons (living too far away from the medical centers). For adult ALL, 9 patients elected to receive palliative care due to the following reasons: 1. logistic reasons (2 patients); and 2. advanced age (7 patients). Another 2 patients in the adult group died from severe disease complication before any treatment was given. Only in approximately half of the patients who had Ph1-chromosome or *BCR-ABL1* mutation, tyrosine kinase inhibitors were incorporated into induction treatment (AYA 45.4% vs. adult 47.4%). The majority of patients attained complete remission (CR) after 1 cycle of induction treatment (AYA 65.1% vs. adult 57.9%, P-value = 0191). The rate of 30-day mortality in patients who received induction chemotherapy were 3.9% in both AYA and adult ALL group. The rates of protocol adherence and prophylactic whole brain radiation were similar in both groups. High risk patients, as defined by white blood cell > 30,000 cells/uL in B-ALL or > 100,000 cells/uL in T-ALL, Philadelphia chromosome or *BCR-ABL1* mutation positive, t(4;11), t(1;19) or failure of first induction chemotherapy, were similar in both groups (AYA 41.7% vs. adult 42.1%, P-value = 0.902). A small number of patients underwent allogeneic stem cell transplantation (AYA 11.7% vs. adult 14.7%, P-value = 0.554) with similar time to transplant (median time: AYA 10 months vs. adult 8 months, P-value = 0.667). The decisions on SCT were mostly based on risk status (as above) with a few cases based on patient's preference and donor status. In 12 SCT patients in AYA group, 6 were due to high risk disease, 4 due to patient's preference, 1 due to MRD positivity at the end of induction and 1 performed at relapsed. In 11 SCT patients in adult group, 7 were due to high risk disease, 2 due to patient's preference, 1 due to MRD positivity at the end of induction and 1 due to suspicious (but not definite) central nervous system involvement at presentation. The transplantations were performed according to standard adult protocols, without adaptation in AYA group. Information regarding conditioning regimen and donor type were not recorded in the present registry. The 100-day transplantation related mortality occurred in only 1 patient in adult ALL group (9.1%), but no early mortality occurred in AYA patients who underwent SCT.

3.3. Survival outcomes

The median follow-up time for surviving patients was 14 months (IQR 6–21 months). At the data cut-off date, death occurred in 67 patients, 48 from disease, 16 from non-relapse mortality (NRM) and 3 from unknown cause. All of the NRM (16 patients) were from infection and sepsis with disease in complete remission. One of these patients were considered transplantation-related mortality. There was no mortality from treatment related adverse event. For the whole cohort, the median OS and EFS were 22 months (IQR 9 months – not reached) and 15 months (IQR 7 months – not reached), respectively. The OS and EFS for AYA and adult ALL were as shown in Fig. 2. Overall survivals for AYA and adult ALL were as followed: 1-year OS 72.1% vs. 58.3% and 2-year OS 54.0% vs. 44.1%, respectively. Event-free survivals were: 1-year EFS 61.5% vs. 48.1% and 2-year EFS 45.5% vs. 26.2%, respectively. Patients in AYA ALL had significantly better EFS when compared to adult ALL (P-value = 0.019) while there was also a trend toward better OS in AYA group (P-value = 0.092). In the AYA group, induction with pediatric-adapted protocol (42 patients) resulted in similar OS when compared to other non-pediatric adapted regimen (HyperCVAD - 30 patients and adult ALL protocol – 23 patients) with log-rank P-value = 0.969 (data not shown).

To determine the effect of SCT (in conjunction with age group), patients were further categorized into 4 subgroups as followed: AYA ALL - no SCT 91 (51.1%), AYA - underwent SCT 12 (6.7%), adult - no SCT 64 (36.0%) and adult - underwent SCT 11 (6.2%). The effect of SCT and age on OS and EFS were as shown in Fig. 3. Overall survivals at 1 year were AYA - no SCT 69.2%, AYA - SCT 90.9%, adult - no SCT

Table 1
Baseline characteristics.

	AYA ALL (n = 103)		Adult ALL (n = 76)		P-value
	N or median	% or IQR	N or median	% or IQR	
Median age - year	23	19-29	54	46-61	N/A
Female sex	34	33	49	64.5	< 0.001
Diagnosis					< 0.001
- B-cell ALL	64	62.1	65	85.5	
- T cell ALL	39	37.9	11	14.5	
Median WBC (x10^9 cells/L)	26.9	7.9-104.7	11.9	4.1-33.3	0.003
Median circulating blast (%)	37	2-77	27	2-72	0.286
Median hemoglobin (g/L)	92	78-120	89	74-101	0.028
Median platelet (x10^9/L)	71	35-183	62	17-165	0.137
Hepatomegaly	22	21.4	12	15.8	0.348
Splenomegaly	17	16.5	9	11.8	0.382
Lymphadenopathy	29	28.2	12	15.8	0.052
Leukemia cutis	2	1.9	3	3.9	0.652
CNS involvement	10	9.7	3	3.9	0.243
Mediastinal mass	10	9.7	4	5.3	0.400
Other extranodal involvement	4	3.9	2	2.6	0.646
ECOG performance status					0.762
- 0-1	72	69.9	56	73.7	
- 2-4	31	30.1	20	26.3	
Complications at diagnosis					
- Tumor lysis syndrome	18	17.5	6	7.9	
- DIC	4	3.9	0	0	
- Hyperleukocytosis	11	10.7	1	1.3	
- SVC syndrome	4	3.9	1	1.3	
Chromosome result available	92		66		0.022
- Normal	58	63.0	27	40.9	
- Hyperdiploid	2	2.2	1	1.5	
- 11q23 abnormalities (*KMT2A)*	1	1.1	2	3.0	
- Numerical alterations	10	10.9	4	6.1	
- Complex karyotype (> 2)	7	7.6	7	10.6	
- Philadelphia (Ph+)	5	5.4	3	4.5	
- Ph + with complex karyotype	5	5.4	14	21.2	
BCR-ABL1 positive	8/26	30.8	12/24	50.0	
Ph or *BCR-ABL1* positive	11	10.7	19	25.0	0.011

Data presented as number and % unless indicated otherwise.
Abbreviations: ALL – acute lymphoblastic leukemia, AYA – adolescent and young adult, CNS – central nervous system, DIC – disseminated intravascular coagulation, ECOG – Eastern cooperative oncology group, IQR – interquartile range, N/A – not applicable, Ph – Philadelphia, SVC – superior vena cava and WBC – white blood cell.

Table 2
Treatments and outcomes.

	AYA ALL (n = 103)		Adult ALL (n = 76)		P-value
	N or median	% or IQR	N or median	% or IQR	
Induction treatment					< 0.001
- Adult ALL protocol	23	22.3	32	42.1	
- Hyper CVAD regimen	30	29.1	32	42.1	
- Pediatric adapted ALL protocol	42	40.8	0	0	
- Other regimen	2	1.9	1	1.3	
- No treatment/ palliative	6	5.8	11	14.5	
TKI added	5/11	45.5	9/19	47.4	
- Imatinib	3		6		
- Dasatinib	2		3		
Result of 1st induction cycle					0.006
- Complete remission	67	65.0	44	57.9	
- Not in complete remission	22	21.4	8	10.5	
- Not evaluated	14	13.6	24	31.6	
Received second line induction	17	16.5	7	9.2	0.291
Second induction - total	17		7		0.257
- Hyper CVAD regimen	10	58.8	7	100.0	
- MEC regimen	1	5.9	0		
- FLAG +/- Idarubicin	5	29.4	0		
- Other	1	5.9	0		
CR after 2nd cycle	8	47.1	4	57.1	0.767
Protocol adherence	87	84.5	56	73.7	0.076
WBRT	43	41.7	32	42.1	0.902
High risk disease*	43	41.7	32	42.1	0.902
SCT	12	11.7	11	14.7	0.554
Median time to SCT (month)	10	6-13	8	6-11	0.667

Data presented as number and % unless indicated otherwise.
Abbreviations: ALL – acute lymphoblastic leukemia, AYA – adolescent and young adult, CR – complete remission, FLAG – fludarabine + cytarabine + granulocyte colony stimulating factor, Hyper CVAD - hyperfractionated cyclophosphamide, vincristine, adriamycin and dexamethasone alternating with cytarabine and methotrexate, IQR – interquartile range, MEC – mitoxantrone + etoposide + cytarabine, SCT – stem cell transplantation, TKI – tyrosine kinase inhibitor and WBRT – whole brain radiation.
* High risk was determined by white blood cell > 30,000 cells/uL in B-ALL or > 100,000 cells/uL in T-ALL, Philadelphia chromosome or *BCR-ABL1* mutation positive, t(4;11), t(1;19) or failure of first induction chemotherapy.

54.6% and adult - SCT 81.8%; at 2 years were AYA - no SCT 53.9%, AYA - SCT 60.6%, adult - no SCT 39.2% and adult - SCT 70.1%. Event-free survivals at 1 year were AYA - no SCT 58.3%, AYA - SCT 82.5%, adult - no SCT 43.7% and adult - SCT 72.7%; at 2 years were AYA - no SCT 45.0%, AYA - SCT 54.0%, adult - no SCT 21.0% and adult - SCT 49.9%. Patients who underwent SCT had significantly better OS (P-value = 0.032) and EFS (P-value = 0.009) as compared to patients who did not received SCT. The effect of SCT was more pronounced in adult ALL group.

To determine the effects of Ph-1 chromosome and *BCR-ABL1* mutation, patients were categorized into AYA – Ph1 negative 92 (51.4%), AYA – Ph1 positive 11 (6.2%), adult – Ph1 negative 57 (31.8%) and adult – Ph1 positive 19 (10.6%). The OS between subgroups were not statistically different (data not shown). Event-free survivals at 1 year were AYA – Ph1 negative 64.0%, AYA – Ph1 positive 41.6%, adult – Ph1 negative 49.9% and adult – Ph1 positive 40.6%; at 2 years were AYA – Ph1 negative 47.6%, AYA – Ph1 positive 31.2%, adult – Ph1 negative 25.2% and adult – Ph1 positive 30.5% (P-value = 0.038).

3.4. Cumulative incidences of relapse and non-relapse mortality

The cumulative incidences of relapse and non-relapse mortality (NRM) were as shown in Fig. 4. The 2-year cumulative incidences of relapse were AYA 27.7% and adult 40.0% (P-value = 0.704). There was a trend of increased non-relapse mortality in adult ALL patients with 2-year cumulative incidences of NRM in AYA 31.4% and adult 43.2% (P-value = 0.060).

4. Discussion

In this large, multicenter prospective observational study on adult ALL (including adolescent and young adult) in Thailand, the following features were observed that were in concordance with previous studies: predominantly B-cell subtype [1,22], presentation of hepatosplenomegaly and lymphadenopathies presented in about 20% of patients [23], central nervous system involvement in < 10% of patients [24,25], rare cases with hyperdiploid and *KMT2A* rearrangement (11q23 abnormalities by standard cytogenetics) [1] and approximately one fifth with Ph1-chromosome or *BCR-ABL1* mutation [21,26].

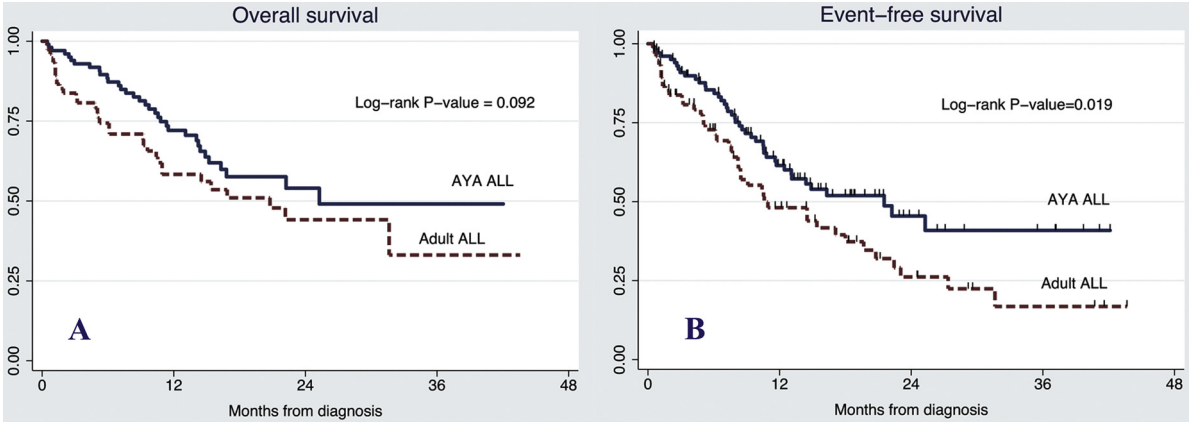

Fig. 2. Overall survival (A) and event-free survival (B) stratified by age group.

AYA ALL patients in this study showed significant differences from adult ALL as follows: a slightly male preponderance, higher rate of T-cell phenotype when compared to adult, significantly lower rate of Ph1-chromosome or *BCR-ABL1* positivity, significantly higher levels of white blood cells and hemoglobin at diagnosis. These finding were similar to a previous reported large multicenter study [27].

Surprisingly, the adoption of age-adapted therapy was well-received among the treating physicians in Thailand. Almost a half of patients in AYA ALL received pediatric adapted multi-agent chemotherapy regimen. This would have been likely due to the influence of previous published trials and systematic reviews [17,28]. However, in patients with Ph1-chromosome or *BCR-ABL1* mutation, tyrosine kinase inhibitors (TKI) were given in approximately 50% of the patients. This low TKI usage was probably due to prior restriction in the access to TKI, especially for patients under the universal health coverage program, which did not cover the cost of TKIs until early 2018. The response to induction in this study was approximately 60%, largely due to the high number of patients in whom CR cannot be evaluated due to early death or loss to follow-up. The non-CR rates were nearly 20%, which were slightly higher than previous reported studies [29]. This may have been due to the fact that 30% of patients in this cohort were deemed high risk by white blood cell criteria. The 2-year OS and EFS in this study were lower than previously published studies [6,13–15,18,27,29]. This effect could mostly be explained by high-risk features and limited access to allogeneic SCT in this study. Only 12.8% of patients underwent allogeneic SCT, regardless of their age or Ph1 status. Analysis of patient subgroups based on age group and SCT status revealed significant improvement in OS and EFS in patients who received SCT, with OS as high as 90% in AYA ALL and 80% in adult ALL. These impressive results of SCT were comparable to that of a previous study [30].

The strength of this study was the nature of multi-center study, which could gain a large sample size to represent patients with this uncommon disease from the entire country. This observational study also gave us an insight into real world practice in the treatment of ALL in Thailand. The relatively low rate of patients, who were loss to follow-up, was also one of the study's strengths, which provided reliable data regarding treatments and their outcomes. However, the findings were limited by a relatively short follow-up and heterogeneity in treatment regimen. Minimal residual disease (MRD) data is lacking in the current study due to technical difficulty but improvement of flow cytometry to detect MRD is an ongoing effort countrywide. The expansion of access to TKIs and advances in supportive care would improve outcomes of patients with ALL, especially those with Ph1-chromosome or *BCR-ABL1* mutation. The improvement in access to allogeneic stem cell transplantation is one of our group's endeavors for improving care of ALL patients. Further multicenter study with longer follow-up, better risk stratification, increasing rate of allogeneic SCT, incorporating molecular data and minimal residual status analysis would help to confirm our preliminary result of better outcomes with SCT.

5. Conclusions

We reported herein the findings of first large multicenter ALL cohort in Thailand with comparable disease characteristics to other studies. The lower survival rates observed in our study could have been likely due to lower utilization rate of allogeneic stem cell transplantation. Subgroup analysis in patients who underwent SCT showed significantly improved OS and EFS, confirming the benefit of graft-versus-leukemia effect in ALL. Further studies with longer follow-up, expanded use of SCT, use of molecular data and minimal residual disease status are

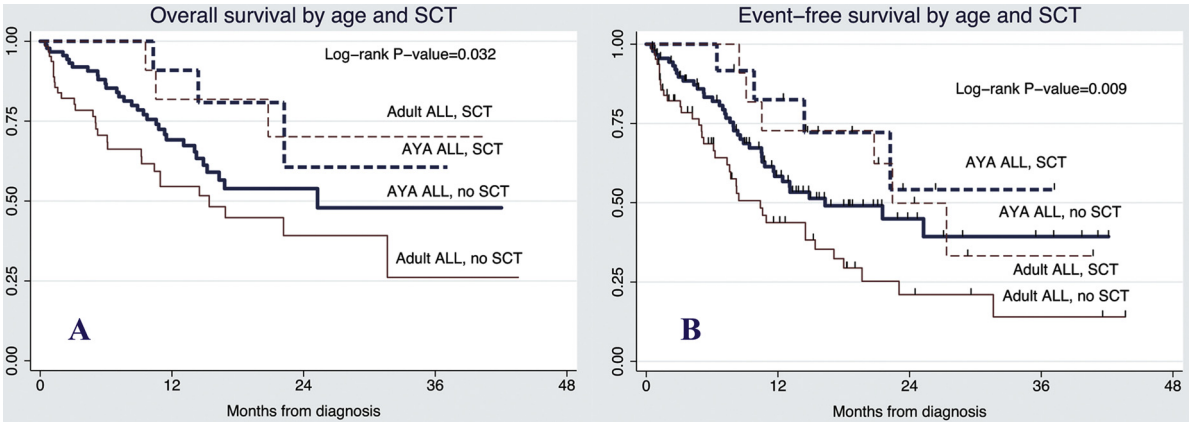

Fig. 3. Overall survival (A) and event-free survival (B) stratified by age group and stem cell transplantation.

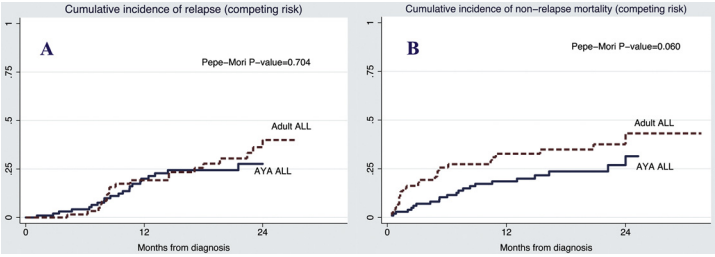

Fig. 4. Cumulative incidences of relapse (A) and non-relapse mortality (B) stratified by age group.

warranted.

Contributions

WL designed the study, maintained the study database, collected data, performed all statistical analyses and drafted the manuscript. KP supervised the study and revised the manuscript. All co-authors (WO, EU, PN, TP, AT, TR, SS, CS, JJ, PS, CP, KW and CW) contributed data to the study, read the manuscript and approved the final version.

Declaration of Competing Interest

The authors have no conflict of interests to declare.

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