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ORIGINAL ARTICLE

Impact of timely *BCR-ABL1* monitoring before allogeneic stem cell transplantation among patients with *BCR-ABL1*-positive B-acute lymphoblastic leukemia

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Background
With the emergence of tyrosine kinase inhibitors and the incorporation of stringent measurable residual disease (MRD) monitoring, risk stratification for *BCR-ABL1*-positive acute lymphoblastic leukemia (ALL) patients has changed significantly. However, whether this monitoring can replace conventional risk factors in determining whether patients need allogeneic stem cell transplantation is still unclear. This study aimed to determine the impact of *BCR-ABL1* monitoring on the outcome of patients with *BCR-ABL1*-positive ALL after allogeneic stem cell transplantation.

Methods
We retrospectively analyzed the survival outcome of patients with *BCR-ABL1*-positive ALL based on the quantification of *BCR-ABL1* at 3 timepoints: the end of induction (timepoint 1), post-consolidation week 16 (timepoint 2), and the end of treatment for patients who were either transplant-eligible or non-transplant eligible (timepoint 3).

Results
From 2006 to 2018, a total of 96 patients newly diagnosed with *BCR-ABL1*-positive ALL were treated with chemotherapy and tyrosine kinase inhibitors. Thirty-eight (41.3%) patients achieved complete remission, and 33 patients underwent allogeneic stem cell transplantation. Our data showed that pre-transplant MRD monitoring by real-time quantitative polymerase chain reaction had the highest correlation with survival in patients with *BCR-ABL1*-positive ALL, especially for those who underwent allogeneic stem cell transplantation.

Conclusion
Patients without MRD pre-transplantation had superior survival compared with those who had MRD, and they had excellent long-term outcomes after allogeneic stem cell transplantation.

Key Words ALL, BCR-ABL1, Philadelphia, Survival, TKI

INTRODUCTION

B-cell acute lymphoblastic leukemia (B-ALL) is a hematological malignancy in which the bone marrow produces neoplastic lymphoblasts that are committed to the B-cell lineage. The complexity and spectrum of hematological malignancies highlight the importance of clinicopathologic correlation with the availability of ancillary studies [1]. Approximately 20–30% of adult ALLs harbor the Philadelphia chromosome, which produces the *BCR-ABL1* fusion gene that has a significant prognostic and survival impact in patients [2]. About half of these cases harbor a translocation that produces the p210 fusion protein, which is the characteristic transcript

of *BCR-ABL1* detected in cases of chronic myeloid leukemia, and the remainder harbor a translocation that produces the p190 protein. The incidence of *BCR-ABL1*-positive ALL increases with age, and it is identified in up to 50% of ALLs diagnosed in patients over 50 years old [3, 4]. This genetic alteration confers a poor prognosis that leads to shorter remission and decreased survival, in addition to increased resistance to standard chemotherapy [5-7]. The presence of this fusion gene also serves as a unique molecular signature, and it is an effective tool for monitoring measurable residual disease (MRD) to identify patients who would likely benefit from stem cell transplantation (SCT) [8-10]. Several studies have suggested that detection of *BCR-ABL1* transcripts by quantitative real-time polymerase chain reaction (qRT-PCR) is associated with an increased risk of relapse, whereas deeper molecular responses have been associated with improved outcomes [9-11]. However, the effectiveness of MRD monitoring in *BCR-ABL1*-positive ALL has not been well defined [12, 13]. Further, the impact of achieving a complete molecular response (CMR) in *BCR-ABL1*-positive ALL remains undefined. A timepoint (TP) analysis for the quantitation of the *BCR-ABL1* transcript could reveal its ability to predict CMR in these patients. Therefore, this study aimed to retrospectively investigate the prognostic impact of *BCR-ABL1* molecular monitoring at different TPs on the survival of patients with *BCR-ABL1*-positive ALL from 2006 to 2018 in a major transplant center in Malaysia.

MATERIALS AND METHODS

Patients

This was a retrospective, single-center, observational study in the Department of Hematology at the Hospital Ampang, Selangor Malaysia, which is a national hematology referral center in Malaysia. A total of 176 patients with B-ALL underwent allogeneic SCT at the Hospital Ampang, Malaysia between 2006 and 2018. All patients diagnosed with *BCR-ABL1*-positive ALL were retrospectively analyzed to determine the impact of the *BCR-ABL1* molecular response on overall survival (OS) and disease-free survival (DFS) after allogeneic transplantation. In brief, chemotherapy protocols were administered in 3 phases: induction, consolidation, and maintenance. The protocols used for the treatment of *BCR-ABL1*-positive ALL followed the modified GMALL 07/2003 [14], BFM [15], and Hyper-CVAD [16] regimens, which were administered depending on the patient's clinical presentation. After the induction phase, the patients received a total of 3–4 courses of consolidation therapy before SCT. Central nervous system prophylaxis was also instituted for all patients, consisting of at least 4 doses of intrathecal chemotherapy. Tyrosine kinase inhibitors (TKIs) were only made available after 2011, when our national health program offered imatinib to patients with *BCR-ABL1*-positive ALL. Bone marrow assessment was performed at least 4 weeks before SCT to assess remission status. This included aspiration and trephine for morphological review, cytogenetics, and molecular studies. Because risk stratification based on genetic identification and MRD monitoring was not fully accessible in the past, our center offered SCT to all eligible ALL patients, even those with standard risk, if a matched sibling donor was available. Allogeneic SCT recipients received grafts from either a human leukocyte antigen-identical sibling or an unrelated donor. For transplantation, HLA-matching was determined by allelic typing using a resolution of 4 digits per allele. Matched sibling donors were assigned to siblings that demonstrated a 10/10 loci match. If a family-related donor was unavailable, a matched unrelated donor would be accepted with a 10/10, 9/10, or 8/10 loci match. If a suitable donor could not be identified by the methods above, a haploidentical match demonstrating a 5–8/10 loci match from a family-related donor was an option. Stem cell sources were either peripheral blood, bone marrow, or unrelated donor cord blood, whichever was available.

Molecular monitoring strategy

MRD evaluations at 3 different TPs were analyzed: post-induction (TP1), post-consolidation or week 16 (TP2), and end of treatment (TP3). *BCR-ABL1* copies were quantified using qRT-PCR as previously described [17-20]. Any MRD-positive sample beyond the quantitative range was defined as below the limit of detection. A sample was defined as "negative" when all replicates were negative, with at least 1,000 *ABL1* copies detected. The MRD value of each follow-up sample was calculated as the logarithmic reduction with respect to the diagnostic value.

Definitions

CMR was defined as the absence of detectable *BCR-ABL1* transcripts with a sensitivity of 0.01%. The major molecular response (MMR) was defined as a *BCR-ABL1*:*ABL1* ratio of ≤0.1% on IS for the major transcript of *BCR-ABL1*, p210, or a 3-log reduction in transcripts for the minor transcript of *BCR-ABL1*, p190, but not meeting the criteria for CMR. The first complete remission (CR1) referred to remission achieved during the first cycle of induction chemotherapy. OS was calculated from the time of treatment initiation until death, with patients alive at the time of the last follow-up being administratively censored. DFS was calculated from day 0 to any type of relapse or death during remission. Relapse was defined as the recurrence of ≥5% blasts in the bone marrow aspirate, presence of extramedullary disease, or a *BCR-ABL1*:ABL1 ratio >0.1% on the IS for 2 consecutive analyses.

Statistical analysis

Continuous variables are summarized using the median and range. Categorical variables are summarized using the count (N) and proportion (%). Differences between subgroups were assessed with t-test, ANOVA, or Kruskal-Wallis test, depending on the sample size and distribution. Associations between categorical variables were analyzed using the chi-square test or Fisher's exact test. Probabilities of OS and DFS were calculated using the Kaplan-Meier meth-

od, and differences between subgroups were tested using the log-rank test. The prognostic significance of baseline and transplantation covariates was determined using the Cox proportional hazard regression model. Covariates were selected based on statistical significance in the univariate analysis, which included MRD status and treatment responses. A prognostic factor was considered statistically significant if the *P*-value was <0.05 using the likelihood ratio test. Statistically significant patient characteristics were included in the multivariate model. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (SPSS Inc, Chicago, IL, USA). Survival analysis was performed with R version 3.6 and packages like "survival".

RESULTS

Patient demographics and characteristics

The study included a total of 96 patients (42 males and 54 females) with a median age of 37.5 years (range, 14–69 yr). Eight patients (8.3%) were in the adolescent age group of 12 to 19 years old, and 45 patients (46.9%) were young adults aged 20–39 years. The remaining 43 patients (44.8%) were aged 40 years and above. The most common ethnic group was Malay (50%, N=48), followed by Chinese (38.5%, N=37) and Indian (14%, N=19). Over half of the patients (53.1%) presented with a high white blood cell count ($>30\times10^9$/L), with a median of 36×10^9/L. A total of 49 patients received the GMALL/BFM protocol (51%), whereas 47 patients (49%) received the HyperCVAD protocol. Of the 96 patients, 62 received TKIs, mostly imatinib, during chemotherapy and were still receiving TKIs as maintenance therapy at the time of SCT. All patients who underwent SCT received TKIs and chemotherapy (19 received imatinib, 13 received nilotinib, and 1 received dasatinib). Of the 38 patients who underwent SCT, 33 received allogeneic stem cells and 5 received autologous stem cells (Table 1).

Table 1. Baseline clinical characteristics of all patients with *BCR-ABL1*-positive ALL.

Total (N=96)	Parameter					
Age, years	15–39 (AYA)		40–59 (adult)		≥60 (elderly)	
N (%) Median (range)	53 (55.2)		38 (39.6) 37.5 (14–59)		5 (5.2)	
Sex	Male				Female	
N (%)	42 (43.8)				54 (56.3)	
Ethnicity	Malay		Chinese		Indian	Others
N (%)	48 (50.0)		37 (38.5)		9 (9.4)	2 (2.1)
WCC, at diagnosis	$>30\times10^9$/L				$<30\times10^9$/L	
N (%) Median (range), $\times10^9$/L	51 (53.1)		36 (2–500)		45 (46.9)	
MRD status	TP1		TP2		TP3	
	≥0.1%	<0.1%	≥0.1%	<0.1%	≥0.1%	<0.1%
N Missing	31 40	25	25 31	40	13 47	36
Treatment modalities	GMALL/BFM		Hyper-CVAD		TKIs	
					Yes (2012–2018)	No (2006–2011)
N (%)	49 (51)		47 (49)		62 (64.6)	34 (35.4)
Treatment response	Remission post-induction	Overall remission	Relapse		Refractory	Induction death
N (%)	80 (83.3)	38 (41.3)	34 (37.0)		10 (10.9)	4 (4.3)
Transplant	Yes				No	
N (%)	38 (39.6) (33-Allogeneic; 5-Autologous)				58 (60.4)	

Values are presented as mean, median (range), or number (%).
Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; MRD, measurable residual disease; TKI, tyrosine kinase inhibitor; TP1, timepoint 1; TP2, timepoint 2; TP3, timepoint 3; WCC, white cell count.

Table 2. Allogeneic stem cell transplant recipient details.

Total (N=33)	Parameter			
Age, years	15–39 (AYA)	40–59 (adult)	≥60 (elderly)	
N (%)	20 (60.6)	13 (39.4)	0 (0)	
Median (range)	37 (15–59)			
Sex	Male	Female		
N (%)	16 (48.5)	17 (51.5)		
Ethnicity	Malay	Chinese	Indian	Others
N (%)	15 (45.5)	15 (45.5)	3 (9.0)	0 (0)
Disease status at transplant	CR1	CR>1		
N (%)	28 (84.8)	5 (15.2)		
Pre-transplant *BCR-ABL1* level	<0.1%	≥0.1%		
N (%)	25 (75.8)	8 (24.2)		
WCC at diagnosis	>30×10^9/L	<30×10^9/L		
N (%)	21 (63.6)	12 (36.4)		
Median (range), ×10^9/L	48 (2–500)			
Blood type mismatch	None	Minor	Major	Bidirectional
N (%)	25 (75.8)	4 (12.1)	3 (9.1)	1 (3.0)
Gender mismatch (donor-recipient)	Female to male	Male to female	Male to male	Female to female	Missing
N (%)	4 (12.1)	8 (24.2)	10 (30.3)	10 (30.3)	1 (3.0)
CMV status	Recipient negative	Recipient positive	Missing		
N (%)					
Donor negative	3 (9.1)	2 (6.1)	5 (15.1)		
Donor positive	1 (3.0)	22 (66.7)			
Type of allogeneic transplant	Matched- sibling	Matched- unrelated	Haplo-matched	Cord blood	
N (%)	27 (81.8)	3 (9.1)	2 (6.1)	1 (3.0)	
Stem cell source	Peripheral blood	Bone marrow	Umbilical cord		
N (%)	32 (97.0)	0	1 (3.0)		
Median stem cell dose (×10^6/kg)	5.0 (3.0-11)				
Conditioning regimen	Myeloablative	RIC	TBI-based	Non-TBI	
N (%)	29 (87.9)	4 (12.1)	22 (66.7)	11 (33.3)	
Post-transplant response	Remission	Relapse/death			
N (%)	23 (69.7)	10 (30.3)			
GVHD	Acute	Chronic			
N (%)	13 (44.8)	14 (50.0)			
	Grade I 4	Limited 7			
	Grade II 6	Extensive 7			
	Grade III 3				
	Grade IV 0				
Missing	4	5			
No GVHD					
N (%)	16 (55.2)	14 (50.0)			
Mortality rate	Alive	Dead			
N (%)	20 (60.6)	13 (39.4)			
		Relapse/disease progression 6			
		Infection/transplant-related mortality 7			

Values are presented as mean, median (range), or number (%).
Abbreviations: AYA, adolescent and young adult; CR, complete remission; GVHD, graft-versus-host disease; RIC, reduced intensity conditioning; TBI, total body irradiation; GVHD, graft-versus-host disease; WCC, white cell count.

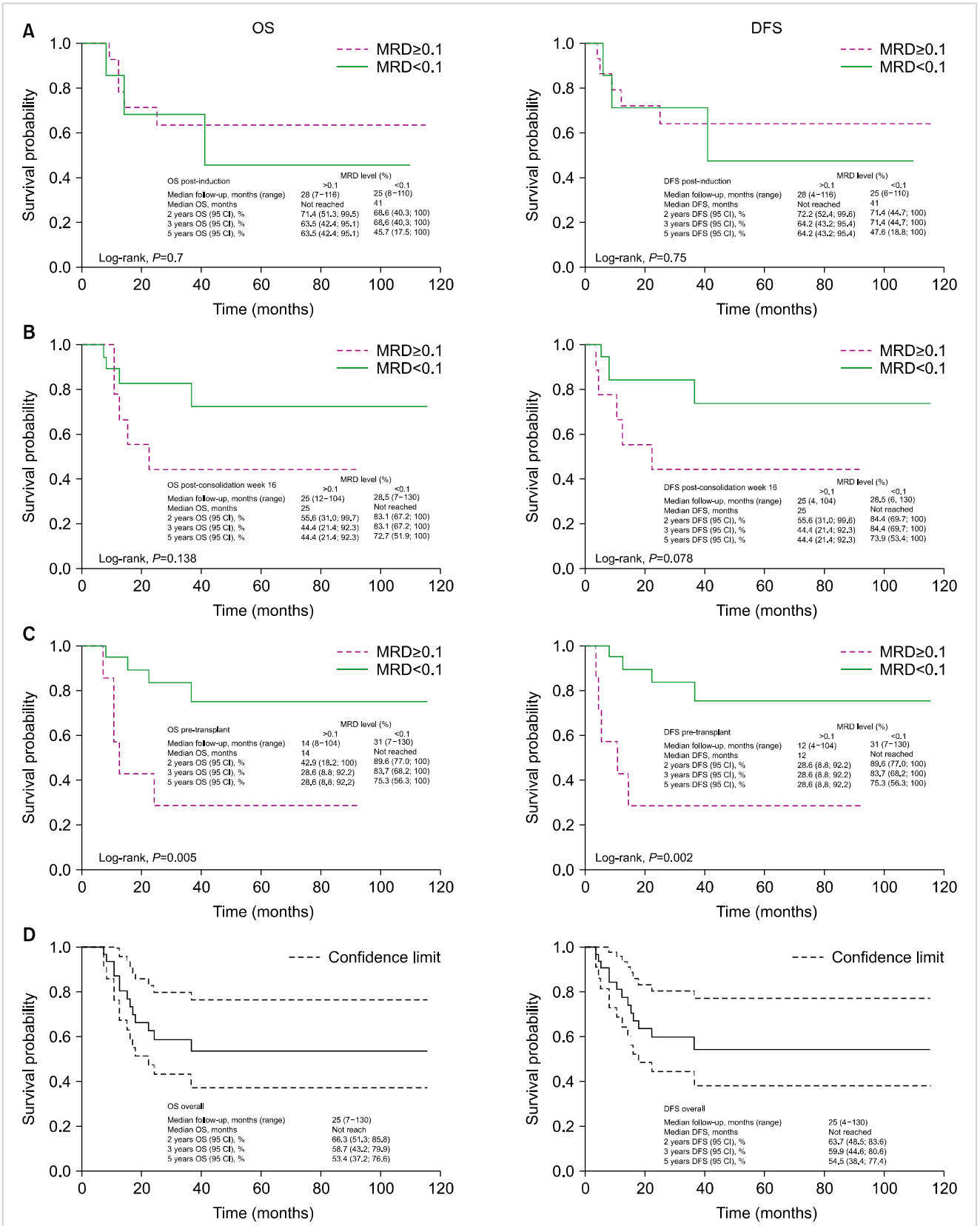

Fig. 1. OS and DFS after stem cell transplantation according to *BCR-ABL1* transcript level at certain timepoints. Post-induction MRD **(A)**. Post-consolidation week 16 **(B)**. End of treatment **(C)**. The overall cohort **(D)**.
Abbreviations: DFS, disease-free survival; MRD, measurable residual disease; OS, overall survival.

CMR prediction using *BCR-ABL1* transcript levels at different TPs

A total of 33 patients (34.4%) who completed chemotherapy were transplant-eligible and underwent allogeneic SCT. The median age of transplant recipients was 37 years (range, 15–59 yr). All patients received allografts, with the majority being from a matched-sibling donor (N=27) (Table 2). Most patients (87.9%, N=29) underwent myeloablative conditioning chemotherapy, with a total body irradiation-based protocol being the main conditioning regimen (66.7%). Thirteen patients (44.8%) developed acute graft-versus-host disease (GVHD) and 14 (50.0%) developed chronic GVHD. MRD status based on the pre-transplant *BCR-ABL1* transcript levels was better able to predict OS (P=0.005) and DFS (P=0.002) than the post-induction (P=0.70 and P=0.75, respectively) and post-consolidation (P=0.138 and P=0.078, respectively) *BCR-ABL1* transcript levels (Fig. 1). The univariate analysis of the factors predictive of OS is shown in Table 3. Multivariate analysis showed that being in the high-risk group and transplantation in CR>1 were independent prognostic factors for inferior OS [pre-transplant *BCR-ABL1* levels: hazard ratio (HR), 4.358; P=0.017; CR>1; HR, 4.582; P=0.016] and DFS (pre-transplant *BCR-ABL1* levels: HR, 4.106; P=0.002; CR>1; HR, 3.787; P=0.033) (Table 4, Fig. 1).

At the time of analysis, 20 patients were alive (60.6%), whereas 13 died (39.4%), as shown in Table 2. With a median follow-up of 25 months, the median OS was not reached. With a median follow-up of 9 months, the median DFS was not reached. Six (46.2%) of 13 patients with MMR experienced relapse, with a median time to relapse of 14 months (range, 8–104). The 2-year, 3-year, and 5-year OS rates were 66.3%, 58.7%, and 53.4%, respectively, and the 2-year, 3-year, and 5-year DFS rates were 63.7%, 59.9%, and 54.5%, respectively (Fig. 1D).

DISCUSSION

It is widely accepted that MRD monitoring is paramount when considering the best treatment options for patients with *BCR-ABL1*-positive ALL [21, 22]. However, MRD monitoring requires high laboratory expertise and is costly in developing nations. Further, unlike chronic myeloid leukemia, the effect of MRD response to chemotherapy on long-term outcomes in *BCR-ABL1*-positive ALL has not been clearly defined.

With our low non-relapse mortality rate in matched-sib-

Table 3. Univariable analysis of factors predictive for OS.

Characteristic	All *BCR-ABL1*-positive ALL patients			Transplanted *BCR-ABL1*-positive ALL patients		
	3-year OS (%)		*P*	3-year OS (%)		*P*
Age group						
AYA	39.0		0.064	52.9		0.690
Adult and elderly	19.6			55.0		
Sex						
Male	33.6		0.876	54.2		0.906
Female	26.8			52.9		
WCC at diagnosis						
$>30\times10^9$/L	25.5		0.585	52.3		0.684
$<30\times10^9$/L	35.9			63.6		
MRD status (%)	≥0.1	<0.1		≥0.1	<0.1	
TP1	36.7	36.1	0.974			
TP2	23.5	53.1	0.077			
TP3	11.5	65.4	0.005	25.0	73.9	0.003
Chemotherapy						
GMALL/BFM	25.7		0.081			
Hyper-CVAD	33.7					
TKI						
Yes (2012–2018)	33.7		0.390			
No (2006–2011)	23.5					
Transplant						
Yes	58.9		<0.001			
No	10.6					
Disease status at transplant						
CR1				65.9		0.003
CR>1				16.7		

Significant P-value <0.05.
Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescent and young adult; CR, complete remission; MRD, measurable residual disease; OS, overall survival; TKI, tyrosine kinase inhibitor; TP1, timepoint 1; TP2, timepoint 2; TP3, timepoint 3; WCC, white cell count.

Table 4. Multivariable analysis of factors predictive of OS and DFS in transplant recipients.

Characteristic	Risk of relapse or death			Risk of death		
	HR	95% CI	*P*	HR	95% CI	*P*
Pre-transplant *BCR-ABL1* level ≥0.1%	4.106	1.226–13.752	0.022	4.358	1.301–14.597	0.017
Transplant in CR>1	3.787	1.113–11.520	0.033	4.582	1.352–15.528	0.016

P-value <0.05.
Abbreviations: CI, confidence interval; CR, complete remission; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

ling donor transplants, it was justifiable to perform SCT in ALL patients with standard risk in CR1, given the significantly higher rate of relapse and lower DFS among patients who did not undergo SCT. This echoed earlier observations of the UKALL/RCOG 2993 studies, which showed significant differences in survival between the transplanted and non-transplanted cohorts, even in ALL patients with standard risk [23], and they did not perform MRD monitoring or identification of high-risk genetic markers. Reports showing successful transplants in CR2 with a curative potential of 25–30% have been reported [24, 25]. However, these reports were highly selective and did not influence decisions against earlier transplants. In our retrospective observation, other factors, such as age, sex, and *BCR-ABL1* status, did not affect OS or DFS. However, patients who underwent SCT between 2012 and 2018 had superior 3-year OS compared to those who underwent SCT between 2006 and 2011 (Table 3). This was most likely due to the better selection of patients, improved supportive care, and availability of TKIs for patients with *BCR-ABL1*-positive ALL in the later cohort.

We showed that pre-transplant *BCR-ABL1* quantitation had a significant prognostic ability. This finding suggests that patients treated with chemotherapy and TKIs who achieve end-of-treatment MMR in CR1 have excellent long-term survival. The optimal timing of MRD assessment may vary based on the TKI; however, end-of-treatment and pre-transplant quantitation have proven to be extremely informative, and the results should be factored into the decision-making and counseling processes. Conversely, quantitation at earlier TPs did not retain statistical power in the multivariate analyses.

Patients who achieved CMR at 3 months had better OS and DFS than those who did not, regardless of whether they received chemotherapy or allogeneic SCT. Although there was a trend for better survival among patients treated with chemotherapy, the difference was not statistically significant. However, the relapse rate was higher in the chemotherapy group. The higher non-relapse mortality in patients who underwent allogeneic SCT may have contributed to this discrepancy. Therefore, chemotherapy plus TKIs may be an option for patients who achieve early CMR but are unwilling to undergo SCT.

Relapse or disease progression post-SCT remains a problem [26], as these patients have an extremely poor prognosis. Novel immunotherapies such as inotuzumab and blinatumomab, as well as chimeric antigen receptor T-cell therapy, have provided an opportunity for patients with relapsed or refractory ALL [25, 27]. Blinatumomab has been shown to eliminate MRD in ALL patients and has led to better survival outcomes post-SCT [28]. In this study, 6 patients with *BCR-ABL1* transcripts <0.1% at TP3 either declined SCT or were not eligible. Only 1 patient remained alive at the time of the census; 3 patients died, and 2 refused follow-up.

Our study focused on allogeneic SCT in the largest cohort of adult *BCR-ABL1*-positive B-ALL patients in Malaysia. Its retrospective nature makes it a true reflection of real-world practices in this part of the world. This is also one of the few studies to include a multi-ethnic group of patients. However, this study design also has inherent limitations, in which variables related to disease characteristics and cytogenetic profiles were missing or unavailable. The MRD data were also incomplete in earlier patient datasets. Patients were also unable to be further classified based on additional genetic mutations. A multicenter approach and collaboration are required to determine a more precise survival outcome.

In conclusion, end-of-treatment MMR was associated with a lower relapse rate and higher DFS among patients with *BCR-ABL1*-positive ALL who underwent allogeneic SCT. This suggests that, although frequent molecular monitoring and intervention are required for patients who do not show a reduction in *BCR-ABL1* transcript levels, only end-of-treatment levels are highly predictive of the post-transplant outcome. However, future prospective trials are needed to evaluate the effectiveness of MRD monitoring for risk stratification of patients with *BCR-ABL1*-positive ALL. The impact of different generations of TKIs on patient outcomes also warrants further evaluation. The current work may be used to guide surveillance plans for patients in Asian countries and could potentially be used as a platform or reference point to design future prospective trials.

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Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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