

FUSION GENE LANDSCAPE IN ACUTE LYMPHOBLASTIC LEUKAEMIA: AN EIGHT-YEAR OVERVIEW (2017–2025) FROM THE INSTITUTE FOR MEDICAL RESEARCH

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ABSTRACT

Acute lymphoblastic leukaemia (ALL) is the most common malignancy in children, whereas adult cases are less frequent but often associated with poorer clinical outcomes. Fusion genes represent important molecular biomarkers that contribute to disease classification, risk stratification, and treatment selection. However, comprehensive data describing the molecular landscape of ALL in Malaysia remain limited. This retrospective study analysed 1253 referral samples received at the Leukaemia Translocation Laboratory, Institute for Medical Research, between 2017 and 2025. Demographic characteristics and molecular findings were evaluated. Among the patients analysed, 60.5% (n = 758) were paediatric, and 39.5% (n = 495) were adults. Male patients accounted for 58.2% of cases. The ethnic distribution comprised Malays (57.5%), Chinese (15.2%), Indians (4.6%), and other ethnicities (22.7%). Fusion genes were detected in 32.5% (n = 407) of cases, while 67.5% (n = 846) showed no detectable rearrangements. Among the fusion-positive cases, *BCR::ABL1* was the most frequent abnormality (41.0%), followed by *ETV6::RUNX1* (32.0%), *TCF3::PBX1* (9.0%), and *KMT2A::AFF1* (7.0%). *BCR::ABL1* was predominantly detected in adult B-ALL, whereas *ETV6::RUNX1* occurred almost exclusively in paediatric cases. Several rare rearrangements and TAL1-associated deletions were also identified, highlighting the molecular heterogeneity of ALL. Overall, these findings provide an updated overview of the fusion gene landscape in Malaysian ALL patients and emphasise the importance of molecular diagnostics in supporting accurate classification, prognostic stratification, and targeted treatment strategies.

KEYWORDS: acute lymphoblastic leukaemia, B-ALL, T-ALL, *ETV6::RUNX1*, *BCR::ABL1*

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a malignant disorder of the haematopoietic system characterised by uncontrolled proliferation of lymphoid progenitor cells. It is a prevalent type of blood cancer linked to the lymphoid lineage. Although ALL can occur at any age, it is predominantly recognised as the most frequent malignancy in children, accounting for 25 to 30% of all paediatric cancers worldwide (1,2). According to the Malaysian National Cancer Registry, lymphoid leukaemia predominantly affects children, with the highest age-specific incidence observed among those aged 0 to 4 years, reaching approximately 4 to 5 cases per 100,000 population (3). In comparison, ALL is rarer in adults, yet tends to be more aggressive and is linked to worse prognoses (4,5).

ALL is broadly classified into two major immunophenotypic subtypes: B-cell acute lymphoblastic leukaemia (B-ALL) and T-cell acute lymphoblastic leukaemia (T-ALL), based on the lineage of the malignant lymphoid precursor cells. B-ALL represents the majority of cases, particularly in paediatric patients, whereas T-ALL accounts for a smaller proportion and is more frequently observed in adolescents and young adults. These immunophenotypic subtypes exhibit distinct biological characteristics, genetic alterations, and clinical outcomes, highlighting the importance of molecular characterisation in disease classification and management (6).

Advances in risk stratification and therapy have improved survival rates over recent decades, particularly in children, where cure rates are now approaching 90% in developed countries (2). Among the most important prognostic factors are chromosomal abnormalities and fusion genes, which not only inform disease biology but also guide diagnosis, risk assessment, and therapeutic strategy (5,6). For instance, *ETV6::RUNX1* is associated with favourable outcomes, whereas *BCR::ABL1* and *KMT2A::AFF1* are associated with poorer prognosis and require tailored treatment approaches (5,7).

In Malaysia, a multi-ethnic nation with substantial Malay, Chinese, Indian, and other populations, molecular epidemiological data on ALL remain limited and may be influenced by population-specific genetic admixture, environmental factors, and consanguinity rates that differ from those in Western cohorts (8). As a major referral centre for molecular haematology diagnostics, the Institute for Medical Research has received and analysed many ALL specimens from hospitals across Malaysia. Characterising the fusion gene profiles observed among these referred cases may contribute to a better understanding of the molecular landscapes of ALL encountered in routine diagnostic practise in Malaysia and support future research and precision medicine initiatives.

The objective of this study was to determine the frequency and distribution of fusion genes among ALL cases referred to the Institute for Medical Research (IMR) for molecular testing between 2017 and 2025. This study provides an overview of fusion gene occurrences in referred ALL cases, highlighting common and uncommon rearrangements, their distribution across age groups, and their clinical relevance. The reported frequencies reflect the study cohort of cases submitted for molecular diagnostic evaluation rather than estimates of the true population prevalence of fusion genes among Malaysian patients with ALL.

MATERIALS AND METHODS

Sample selection

This retrospective study analysed 1253 samples from patients with ALL received at the Leukaemia Translocation Laboratory, Haematology Unit, between January 2017 and December 2025. These comprised peripheral blood and bone marrow specimens from paediatric (aged 1 to 14 years) and

adult patients (aged ≥ 15 years) referred from hospitals throughout Malaysia. All submitted cases meeting the predefined inclusion criteria during the study period were enrolled. Demographic and clinical data were recorded at the time of diagnosis. Individuals aged ≥ 15 years were classified as adults in this study, as this age threshold corresponds to a transition in disease characteristics, reduced tolerance to therapy, and poorer survival outcomes compared with younger paediatric patients (9).

Molecular testing

Total ribonucleic acid (RNA) was extracted from mononuclear cells according to the manufacturer's instructions using standard laboratory protocols, followed by complementary deoxyribonucleic acid (cDNA) synthesis. For samples analysed between 2017 and 2022, fusion transcript detection was performed using the HemaVision® kit (DNA Technology, Denmark). This assay employs multiplex nested polymerase chain reaction (PCR) for the detection of multiple leukaemia-associated fusion genes and is capable of analysing up to 28 clinically relevant translocations and more than 145 breakpoint variants. The nested PCR design provides high analytical sensitivity and broad breakpoint coverage; however, this assay requires post-amplification processing and gel-based interpretation, resulting in a more labour-intensive workflow and a potentially higher risk of amplicon contamination.

From 2023 onwards, fusion gene detection was performed using the QuanDx® Q30 Fusion Gene Detection Kit (QuanDx Inc., USA), a multiplex real-time PCR (RT-qPCR) assay capable of simultaneously screening for 30 leukaemia-associated fusion genes, including most clinically relevant breakpoint variants covered by the HemaVision® kit. Besides, the multiplex RT-qPCR used technology with fluorescent probe-based detection in a closed system, providing faster turnaround time, reduced contamination risk, and automated result interpretation. As two different molecular platforms were used during the study period, their detectable fusion targets and coverage were listed and compared (Supplementary Table 1).

Despite employing different detection technologies, both assays are validated qualitative diagnostic methods for the detection of clinically relevant leukaemia-associated fusion transcripts and were performed according to the manufacturer's instructions. Internal, positive, and negative controls were included in each assay to ensure analytical reliability and quality assurance. Previous studies have demonstrated that nested RT-PCR and RT-qPCR provide comparable diagnostic performance for the qualitative detection of recurrent fusion genes in acute leukaemia (10). Consequently, any differences between the assays are expected to primarily influence the analytical sensitivity and detection limit rather than identification of clinically significant fusion transcripts. As this study focused on the qualitative presence or absence of fusion genes, results generated by both platforms were considered comparable and were analysed collectively.

Data analysis

For the HemaVision assay, fusion transcripts were identified based on the presence of expected band sizes following agarose gel electrophoresis. For the QuanDx assay, amplification curves and cycle threshold (Cq) values were interpreted using QuanDx® analysis software according to the manufacturer's instructions. Positive results were determined by the presence of valid fusion-specific signals together with internal control amplification. Negative controls were included in each run to ensure assay reliability.

Statistical analysis

All data were analysed using SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA). Numerical variables, including age, white blood cell (WBC) count, haemoglobin (Hb), and platelet count, were expressed as mean and standard deviation (SD). Categorical variables, such as gender, race, and the

presence of a fusion gene, were presented as frequencies and percentages. The Chi-square and Fisher's exact test were used to compare the association of fusion genes between age groups of immunophenotypic subtype ALL. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics and clinical features

A total of 1253 patients with ALL were included, comprising 758 (60.5%) paediatric and 495 (39.5%) adult patients. The demographic and clinical characteristics are summarised in Table 1. The overall mean (SD) age was 17.16 (17.83) years, with a mean age of 5.85 (3.68) years in paediatric patients and 34.46 (17.0) years in adults. Male patients constituted the majority (729, 58.2%), while 524 (41.8%) were female. Within the paediatric group, 447 (59.0%) were males, and 311 (41.0%) were females, while among adults, 282 (57.0%) were males and 213 (43.0%) were females.

Malay patients represented the largest ethnic group (720, 57.5%), followed by Chinese (190, 15.2%), others (285, 22.7%), and Indian (58, 4.6%). Among paediatric patients, 433 (57.1%) were Malay, 104 (13.7%) Chinese, 34 (4.5%) Indian, and 187 (24.7%) from other ethnic groups. In adults, 287 (58.0%) were Malay, 86 (17.4%) Chinese, 24 (4.8%) Indian, and 98 (19.8%) belonged to other ethnicities.

The mean (SD) WBC count was 84.20 (197.54) $\times 10^9/L$, with paediatric patients showing 75.70 (183.10) $\times 10^9/L$ and adults 97.06 (217.15) $\times 10^9/L$. The mean (SD) Hb level was 8.50 (2.40) g/dL, with comparable values observed in paediatric patients 8.48 (2.32) g/dL and adult patients 8.54 (2.49) g/dL. Besides, the mean (SD) platelet count was 119.74 (121.46) $\times 10^9/L$, with paediatric and adult patients showing comparable values of 116.95 (97.08) $\times 10^9/L$ and 123.94 (150.96) $\times 10^9/L$, respectively.

Breakpoint distribution in ALL patients

Of the 1253 cases included in this study, 1100 (87.8%) were classified as B-ALL and 153 (12.2%) as T-ALL. Among B-ALL cases, 682 (62.0%) were paediatric, while 418 (38.0%) were adults. In contrast, T-ALL cases were evenly distributed between paediatric (77/153, 50.3%) and adult patients (76/153, 49.7%) (Table 2).

Fusion genes were detected in 32.5% (407/1253) of patients, while 67.5% (846/1253) showed no detectable rearrangements. The distribution of fusion genes detected in the study cohort is illustrated in Supplementary Figure 1. The most frequent abnormality was *BCR::ABL1* (41.0%, *n* = 166), followed by *ETV6::RUNX1* (32.0%, *n* = 132), *TCF3::PBX1* (9.0%, *n* = 37), and *KMT2A::AFF1* (7.0%, *n* = 30). Less frequent rearrangements included *TAL1d40KBP* deletion (4.0%, *n* = 15), *KMT2A::MLLT3* (2.0%, *n* = 7), *KMT2A::AFDN* (1.0%), *KMT2A::MLLT10* (1.0%), *ETV6::ABL1* (1.0%), *STIL::TAL1* deletion (1.0%), and *KMT2A::ELL* (1.0%).

Further analysis of fusion gene distribution by age group is presented in Table 3. In B-ALL, *BCR::ABL1* was significantly more frequent in adults (75.3%) compared with paediatric patients (24.7%) (*P* < 0.001). Conversely, *ETV6::RUNX1* occurred predominantly in paediatric B-ALL (98.5%) and was rare in adults (1.5%) (*P* < 0.001). No significant differences between paediatric and adult B-ALL were observed for *TCF3::PBX1* (*P* = 0.292) or *KMT2A::AFF1* (*P* = 0.079).

In T-ALL, *STIL::TAL1* deletion was mainly detected in paediatric cases, whereas *TAL1d40KBP* deletion occurred in both paediatric and adult patients. However, these differences were not statistically significant (*P* = 0.120 and *P* = 0.327, respectively). Similarly, the proportion of cases with no detectable

fusion gene did not differ significantly between paediatric and adult patients in either B-ALL ($P = 0.069$) or T-ALL ($P = 0.400$). Overall, a clear age-associated pattern was observed, with *BCR::ABL1* predominantly detected in adult B-ALL, whereas *ETV6::RUNX1* was almost exclusively observed in paediatric B-ALL.

Table 1. Demographic and clinical data of patients with ALL.

Parameters	Total patients, n (%)	Paediatric (n, %)	Adult (n, %)
No of patients	1253 (100.0)	758 (60.5)	495 (39.5)
Age (years)			
Mean (SD)	17.16 (17.83)	5.85 (3.68)	34.46 (17.0)
Gender			
Male	729 (58.2)	447 (59.0)	282 (57.0)
Female	524 (41.8)	311 (41.0)	213 (43.0)
Ethnicity, n (%)			
Malay	720 (57.5)	433 (57.1)	287 (58.0)
Chinese	190 (15.2)	104 (13.7)	86 (17.4)
Indian	58 (4.6)	34 (4.5)	24 (4.8)
Others	285 (22.7)	187 (24.7)	98 (19.8)
^a WBC count ($\times 10^9/L$)	84.20 (197.54)	75.70 (183.10)	97.06 (217.15)
^b Hb levels (g/dL)	8.50 (2.40)	8.48 (2.32)	8.54 (2.49)
^c Platelet count ($\times 10^9/L$)	119.74 (121.46)	116.95 (97.08)	123.94 (150.96)

a The reference range for WBC is 4.5–11.0 $\times 10^9/L$ (11).

b The reference range for Hb in males: 13.5–17.5 g/dL; females: 12.0–16.0 g/dL (11).

c The reference range for platelets is 150–400 $\times 10^9/L$ (11).

Table 2. Prevalence of ALL by immunophenotypic subtype and age group (n=1253)

Immunophenotypic subtype	Paediatric (n, %)	Adult (n, %)	Total (n)
B-ALL	682 (62.0)	418 (38.0)	1100
T-ALL	77 (50.3)	76 (49.7)	153

Table 3. Association between fusion gene distribution and age group according to immunophenotypic subtype in ALL (n=1253)

Fusion Gene	Chromosomal aberrations	No. fusion gene detection (n, %)	Type of ALL					
			B-ALL			T-ALL		
			Paediatric (n, %)	Adult (n, %)	*P	Paediatric (n, %)	Adult (n, %)	*P
<i>BCR::AB L1</i>	t(9;22) (q34;q11)	166 (13.2)	41 (24.7)	125 (75.3)	<0.001 ^a	0 (0.0)	0 (0.0)	NA
<i>ETV6::R UNX1</i>	t(12;21) (p13;q22)	132 (10.5)	130 (98.5)	2 (1.5)	<0.001 ^a	0 (0.0)	0 (0.0)	NA
<i>TCF3::PB X1</i>	t(1;19) (q23;p13)	37 (3.0)	26 (70.3)	11 (29.7)	0.292 ^a	0 (0.0)	0 (0.0)	NA
<i>KMT2A::AFF1</i>	t(4;11) (q21;q23)	30 (2.4)	14 (46.7)	16 (53.3)	0.079 ^a	0 (0.0)	0 (0.0)	NA
<i>KMT2A::AFDN</i>	t(6;11) (q27;q23)	5 (0.4)	1 (20.0)	1 (20.0)	1.000 ^b	0 (0.0)	3 (60.0)	0.245 ^b
<i>KMT2A::MLLT3</i>	t(9;11) (p21.3;q23.3)	7 (0.6)	5 (71.4)	2 (28.6)	0.715 ^b	0 (0.0)	0 (0.0)	NA
<i>KMT2A::MLLT10</i>	t(10;11) (p12;q23)	5 (0.4)	5 (100.0)	0 (0.0)	0.163 ^b	0 (0.0)	0 (0.0)	NA
<i>ETV6::A BL1</i>	t(9;12) (q34;p13)	4 (0.3)	2 (50.0)	2 (50.0)	0.637 ^b	0 (0.0)	0 (0.0)	NA
<i>KMT2A::ELL</i>	t(11;19) (q23;p13.3)	2 (0.2)	1 (50.0)	1 (50.0)	1.000 ^b	0 (0.0)	0 (0.0)	NA
<i>STIL::TA L1</i>	del(1)(p32)	4 (0.3)	1 (25.0)	0 (0.0)	1.000 ^b	3 (75.0)	0 (0.0)	0.120 ^b
<i>TAL1d40 kbp deletion 1p32</i>	40kb deletion 1p32	15 (1.2)	3 (20.0)	3 (20.0)	0.679 ^b	6 (40.0)	3 (20.0)	0.327 ^b
	No detection	846 (67.5)	453 (53.5)	255 (30.1)	0.069 ^a	68 (8.0)	70 (8.3)	0.400 ^a

Abbreviation: NA, not applicable.

*The P-values represent the comparisons between paediatric and adult groups within each immunophenotypic subtype.

a Chi-Square Test

b Fisher's Exact Test

DISCUSSION

This study describes the demographic, haematological, immunophenotypic, and molecular characteristics of ALL patients in a large Malaysian cohort over eight years. A higher proportion of paediatric cases and a slight male predominance were observed, consistent with previous studies showing that ALL occurs more frequently in children and males (12). The increased incidence among males may be influenced by biological and epidemiological factors associated with disease susceptibility (13). Immunophenotypic analysis demonstrated that B-ALL was the predominant subtype, accounting for 87.8% of cases, while T-ALL comprised 12.2% of the cohort. This distribution is comparable to findings reported in Western populations, including a United States study that documented frequencies of 77.0% for B-ALL and 23.0% for T-ALL (14). T-ALL showed a relatively balanced distribution between paediatric and adult patients, whereas B-ALL was more commonly found in younger children. These findings are consistent with the established age-related distribution patterns of ALL subtypes.

Upon diagnosis, patients exhibited elevated WBC counts with reduced Hb and platelet levels, indicative of marrow infiltration and suppression of normal haematopoiesis, which are characteristic features of ALL. Comparable Hb and platelet levels were observed between paediatric and adult patients, while adult patients demonstrated relatively higher mean WBC counts. Although no statistical comparisons were performed for haematological parameters, these findings are generally consistent with the clinical presentation of ALL reported in previous studies (15).

In this study, gene fusions were detected in 32.5% (407/1253) of patients with ALL, highlighting the important role of recurrent chromosomal rearrangements in the molecular landscape of the disease. Among the fusion-positive cases, *BCR::ABL1* was the most frequent abnormality, followed by *ETV6::RUNX1*, *TCF3::PBX1*, and *KMT2A::AFF1*. These recurrent rearrangements represent well-established molecular subtypes of ALL and play important roles in disease classification, prognostic stratification, and therapeutic decision-making (1,2). The overall detection rate observed in this study is consistent with prior reports, indicating that approximately one-third of ALL cases harbour recurrent fusion genes detectable by multiplex molecular assays.

The *BCR::ABL1* fusion gene was the most prevalent abnormality in this cohort, accounting for 41.0% of fusion-positive cases. The adult B-ALL group showed a significantly higher *BCR::ABL1* detection rate than the paediatric B-ALL group, with positivity rates of 75.3% and 24.7%, respectively ($P < 0.001$). This finding aligns with numerous studies reporting that the Philadelphia chromosome occurs more frequently in adult ALL than in paediatric disease (5,6). The *BCR::ABL1* fusion results from the t(9;22)(q34;q11) translocation, which causes ABL1 tyrosine kinase to become permanently active, and this leads to uncontrolled leukaemia cell growth and survival. Historically associated with poor prognosis and increased relapse risk, outcomes have significantly improved following the introduction of tyrosine kinase inhibitors (TKIs), including imatinib, dasatinib, and ponatinib. More recently, olverembatinib (HQP1351), a third-generation TKI, has emerged as a promising therapeutic option, particularly in patients harbouring T315I mutations associated with resistance to earlier-generation TKIs (16). These findings highlight the importance of early and accurate molecular detection of this fusion gene, which enables timely initiation of targeted therapy and improved clinical management.

The *ETV6::RUNX1* fusion, associated with the t(12;21)(p13;q22) translocation, represented the second most common rearrangement in this study and demonstrated a striking age-related distribution, with 98.5% of cases occurring in paediatric B-ALL and only 1.5% detected in adults ($P < 0.001$). The observation supports worldwide epidemiological studies, which show *ETV6::RUNX1* as one of the most

frequent genetic abnormalities found in childhood ALL cases, while it remains uncommon in adult patients (17). The *ETV6::RUNX1* fusion is thought to arise during early haematopoietic development and has been associated with a favourable prognosis and excellent response to therapy in most cases. The predominance of this fusion in paediatric patients in the present study reflects the well-established biological differences between childhood and adult ALL and further supports the role of *ETV6::RUNX1* as an important prognostic marker in paediatric disease (18).

The *TCF3::PBX1* fusion, resulting from the t(1;19)(q23;p13) translocation, accounted for 9.0% of fusion-positive cases in this cohort and was detected predominantly in B-ALL affecting both paediatric and adult patients. Unlike *BCR::ABL1* and *ETV6::RUNX1*, no statistically significant difference was observed between paediatric and adult B-ALL for this fusion gene ($P = 0.292$). The *TCF3::PBX1* rearrangement produces an aberrant transcription factor that contributes to leukemogenesis through dysregulation of gene expression pathways. Although historically associated with poorer outcomes, advances in contemporary treatment protocols have improved survival rates in patients harbouring this fusion, and it is currently considered to confer intermediate risk in many treatment stratification systems (19).

Similarly, *KMT2A::AFF1* accounted for 7.0% of fusion-positive cases and was detected in both paediatric and adult B-ALL, with no statistically significant difference between age groups ($P = 0.079$). Rearrangements involving the *KMT2A* gene are well recognised for their association with aggressive disease biology and adverse clinical outcomes. These rearrangements are particularly common in infant ALL, although they may also occur in older children and adults. *KMT2A* fusion proteins alter epigenetic regulation and transcriptional control, promoting leukemic transformation and resistance to therapy (5,20). Recent studies have identified menin inhibitors, such as revumenib, as promising targeted agents for *KMT2A*-rearranged ALL through disruption of the menin-*KMT2A* interaction and suppression of leukemogenic transcriptional pathways (21). Early clinical studies have demonstrated encouraging responses in relapsed and refractory *KMT2A*-rearranged leukaemias (22). The detection of *KMT2A* rearrangements in this cohort emphasises the importance of identifying high-risk genetic lesions that may require intensified treatment strategies or consideration for emerging targeted therapies.

In addition to these common abnormalities, several less frequent rearrangements were identified, including *KMT2A::MLLT3*, *KMT2A::AFDN*, *KMT2A::MLLT10*, *ETV6::ABL1*, and *KMT2A::ELL*. Although individually rare, these findings illustrate the genetic diversity and complexity of ALL. The identification of these uncommon fusion transcripts highlights the value of multiplex RT-PCR panels capable of simultaneously screening for multiple rearrangements in a single assay. Such comprehensive diagnostic approaches are particularly useful in referral laboratories, where a wide spectrum of genetic abnormalities may be encountered (10).

Distinct molecular features were also observed in T-cell ALL (T-ALL). In this study, *STIL::TAL1* deletion was detected predominantly in paediatric T-ALL (75%), whereas *TAL1*d40kbp deletion was identified in both paediatric and adult patients across B-ALL and T-ALL subtypes. However, these differences were not statistically significant ($P = 0.120$ and $P = 0.327$, respectively). *TAL1* alterations play a central role in T-cell leukemogenesis by promoting aberrant transcriptional programs that drive T-cell transformation (23). The detection of *TAL1*-related abnormalities in this cohort reflects the distinct molecular mechanisms underlying T-ALL compared with B-lineage disease.

Beyond helping to classify ALL and predict prognosis, fusion gene identification has become increasingly important in guiding targeted treatment approaches. Detecting clinically relevant fusion genes allows patients to receive more personalised therapies that may improve treatment response and overall outcomes. For example, the introduction of TKIs has markedly improved the prognosis of patients with *BCR::ABL1*-positive ALL, which was previously considered a high-risk subtype. Similarly, newer targeted therapies such as menin inhibitors have shown promising results in patients with *KMT2A*-rearranged leukaemias, particularly in relapsed or refractory cases. Advances in molecular technologies, including RNA sequencing, have also improved the detection of rare and novel fusion genes, allowing more comprehensive molecular characterisation and potentially expanding future therapeutic options for patients with acute leukaemia (24).

Interestingly, 67.5% of patients showed no detectable fusion gene, indicating that a large proportion of ALL cases in this cohort may harbour other genetic alterations not covered by the current multiplex PCR panel. These may include cryptic chromosomal rearrangements, copy number alterations, or sequence-level mutations that require more comprehensive genomic approaches, such as next-generation sequencing (NGS) for detection. The absence of detectable fusion genes did not significantly differ between paediatric and adult patients in either B-ALL ($P = 0.069$) or T-ALL ($P = 0.400$), suggesting that unidentified molecular drivers may occur across both age groups. The increasing application of NGS-based molecular profiling may therefore provide further insights into the genomic landscape of fusion-negative ALL cases.

When compared with international studies, the fusion gene distribution observed in this Malaysian cohort is broadly consistent with previously reported patterns. For example, a large study involving 2,479 Chinese patients with ALL reported a fusion gene detection rate of 28.7%, which is comparable to the prevalence observed in the present study (25). Similarly, Western studies have demonstrated a higher frequency of *BCR::ABL1* in adult ALL and predominance of *ETV6::RUNX1* in paediatric ALL, consistent with the findings in this cohort (14). However, the relatively higher proportion of *BCR::ABL1*-positive cases in this cohort may partly reflect the inclusion of a substantial number of adult patients, as adult ALL is known to harbour a higher frequency of this translocation compared with paediatric disease. Such variations may also be influenced by demographic characteristics, referral patterns, and differences in study populations.

Over the study period, an increase in referral samples was observed, reflecting the growing adoption of molecular diagnostic testing in the clinical management of ALL in Malaysia. A temporary decline in referrals during 2020–2021 may be attributable to disruptions associated with the COVID-19 pandemic, which affected healthcare services globally. Nevertheless, the overall trend suggests increasing awareness among clinicians regarding the importance of molecular testing in haematological malignancies. As a national referral centre for molecular haematology diagnostics, the IMR plays an important role in supporting clinical decision-making through the provision of reliable and comprehensive molecular diagnostic services.

Several limitations should be considered when interpreting the findings of this study. Initially, the study cohort was derived from cases referred to a single molecular diagnostic laboratory for fusion gene testing rather than a population-based national ALL registry. Consequently, referral patterns, testing practices, and clinical indications for molecular analysis may introduce selection bias. Therefore, the reported fusion gene frequencies reflect referred cases submitted for molecular testing and may not represent the true population prevalence of fusion genes among all patients with ALL in Malaysia. Additionally, fusion gene testing was performed using two distinct molecular platforms during the study period, specifically the HemaVision multiplex RT-PCR assay (2017–2022) and the

QuanDx RT-qPCR assay (2023–2025). Although both assays have been validated for detecting recurrent leukaemia-associated fusion transcripts, differences in target coverage, analytical sensitivity, detection limits, and fusion variant detection may have influenced the identification of specific abnormalities, particularly rare fusion transcripts. Third, the retrospective approach limited access to comprehensive clinical information. Clinical outcomes such as treatment response, minimal residual disease status, recurrence rates, event-free survival, and overall survival were not consistently available and therefore could not be evaluated in relation to fusion gene status. Consequently, the prognostic significance of the detected fusion genes could not be assessed within this cohort. Despite these limitations, the present study represents one of the largest analyses of recurrent fusion genes in Malaysia for ALL cases and provides valuable baseline data on the molecular characteristics of patients referred for diagnostic fusion gene testing nationwide.

CONCLUSION

This study provides an updated overview of the fusion gene landscape in ALL in Malaysia based on a large cohort of patients referred for molecular testing. Recurrent fusion genes were identified in approximately one-third of patients, with *BCR::ABL1* emerging as the most common abnormality, followed by *ETV6::RUNX1*, *TCF3::PBX1*, and *KMT2A* rearrangements. Clear age-related patterns were observed, with *BCR::ABL1* occurring more frequently in adult B-ALL, while *ETV6::RUNX1* was predominantly detected in paediatric cases, reflecting known biological differences between childhood and adult ALL.

The presence of several rare fusion transcripts and *TAL1*-associated deletions in T-ALL further illustrates the molecular diversity of the disease. At the same time, the large proportion of cases without detectable fusion genes suggests that additional genomic alterations may contribute to leukemogenesis and may require more comprehensive molecular approaches for further characterisation.

Overall, these findings provide important baseline data on the molecular epidemiology of ALL in Malaysia and reinforce the role of molecular diagnostics in supporting accurate classification, risk stratification, and treatment selection. Continued expansion of molecular testing and integration of genomic data with clinical outcomes will be important to further improve the management of ALL patients in Malaysia.

Supplementary Materials: Supporting information related to this study can be accessed at: www.imrj.com/x. This includes Figure S1: [Distribution of fusion gene rearrangements detected in patients with ALL], Table S1: [Comparison of fusion gene targets detectable by HemaVision[®] and QuanDx[®] Q30 Fusion Gene Detection assay]

Data Availability: Data are available upon reasonable request.

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Informed Consent Statement: Not applicable

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Supplementary material

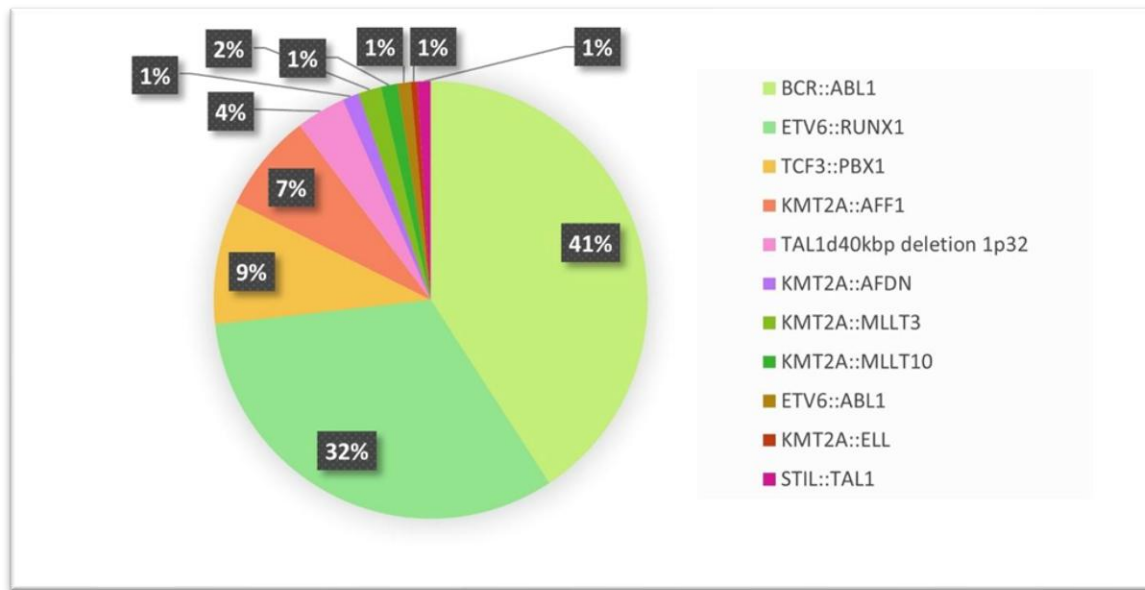


Figure S1. Distribution of fusion gene rearrangements detected in patients with ALL (n=407). The percentages indicate the proportion of each fusion gene among all fusion gene-positive cases identified in this study

Table S1. Comparison of fusion gene targets detectable by HemaVision[®] and QuanDx[®] Q30 Fusion Gene Detection assay

No.	Fusion Gene	Translocation	HemaVision [®]	QuanDx [®] Q30
1	<i>BCR::ABL1</i>	t(9;22)(q34;q11)	✓	✓
2	<i>ETV6::RUNX1</i>	t(12;21)(p13;q22)	✓	✓
3	<i>TCF3::PBX1</i>	t(1;19)(q23;p13)	✓	✓
4	<i>KMT2A::AFF1</i>	t(4;11)(q21;q23.3)	✓	✓
5	<i>STIL::TAL1</i>	40kb deletion 1p32	✓	✓
6	<i>ETV6::ABL1</i>	t(9;12)(q34;p13)	✓	✓
7	<i>KMT2A::AFDN</i>	t(6;11)(q27;q23.3)	✓	✓
8	<i>KMT2A::MLLT3</i>	t(9;11)(p21.3;q23.3)	✓	✓
9	<i>KMT2A::MLLT10</i>	t(10;11)(p12;q23.3)	✓	✓
10	<i>KMT2A::ELL</i>	t(11;19)(q23.3;p13.1)	✓	✓
11	<i>KMT2A::EPS15</i>	t(1;11)(p32;q23.3)	✓	✓
12	<i>KMT2A::MLLT11</i>	t(1;11)(q21;q23.3)	✓	✓
13	<i>NPM1::MLF1</i>	t(3;5)(q25.1;q35)	✓	✓
14	<i>RUNX1::MECOM</i>	t(3;21)(q26;q22)	✓	✓
15	<i>ETV6::PDGFRB</i>	t(5;12)(q33;p13)	✓	✓
16	<i>NPM1::RARA</i>	t(5;17)(q35;q21)	✓	✓
17	<i>DEK::NUP214</i>	t(6;9)(p23;q34)	✓	✓

18	<i>RUNX1::RUNX1T1</i>	t(8;21)(q22;q22)	✓	✓
19	<i>SET::NUP214</i>	t(9;9)(q34;q34)	✓	✓
20	<i>KMT2A::MLLT6</i>	t(11;17)(q23.3;q12-21)	✓	✓
21	<i>ZBTB16::RARA</i>	t(11;17)(q23;q21)	✓	✓
22	<i>KMT2A::MLLT1</i>	t(11;19)(q23.3;p13.3)	✓	✓
23	<i>DEK::NUP214</i>	t(6;9)(p23;q34)	✓	✓
24	<i>PML::RARA</i>	t(15;17)(q24;q21)	✓	✓
25	<i>CBFB::MYH11</i>	inv(16)(p13;q22)	✓	✓
26	<i>FUS::ERG</i>	t(16;21)(p11;q22)	✓	✓
27	<i>TCF3::HLF</i>	t(17;19)(q22;p13)	✓	✓
28	<i>KMT2A::FOXO4</i>	t(x;11)(q13;q23.3)	✓	✓
29	<i>FIP1L1::PDGFRA</i>	del(4)(q12)	X	✓
30	<i>AML1-MTG16</i>	t(16;21)(q24;22)	X	✓

Abbreviation: inv = inversion.