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IKZF1^{PLUS} alterations contribute to outcome disparities in Hispanic/Latino children with B-lymphoblastic leukemia

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Abstract

Background: Compared to other ethnicities, Hispanics/Latinos have a high incidence of acute lymphoblastic leukemia (ALL), enrichment of unfavorable ALL genetic subtypes and worse outcomes, even after correcting for socioeconomic factors. We previously demonstrated increased incidence of the high-risk genetic drivers *IKZF1* deletion and *IGH::CRLF2* rearrangement in Hispanic/Latino (HL) compared to non-H/L children with B-ALL. Here in an expanded pediatric cohort, we sought to identify novel genetic drivers and secondary genetic alterations in B-ALL associated with H/L ethnicity.

Procedure: Comprehensive clinicopathologic data from patients with B-ALL treated from 2016 to 2020 were analyzed. Subtype was determined from karyotype, fluorescence *in situ* hybridization (FISH), chromosome microarray (CMA) and our next-generation sequencing (NGS) panel (OncoKids®). Non-driver genetic variants were also examined. p-values <0.05 (Fisher's exact test) were considered significant.

Results: Among patients with B-ALL at diagnosis (n=273), H/L patients (189, 69.2%) were older (p=0.018), more likely to present with CNS2 or 3 disease (p=0.004) and NCI high-risk ALL (p=0.014) compared to non-H/L patients. Higher incidence of *IGH::CRLF2* rearrangement (B-ALL, BCR::ABL1-like, unfavorable; p=0.016) and lower incidence of *ETV6::RUNX1* rearrangement (favorable, p=0.02) were also associated with H/L ethnicity. Among secondary

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The authors have no relevant conflicts of interest.

(non-subtype-defining) genetic variants, B-ALL in H/L was associated with *IKFZ1* deletion alone (p=0.001) or with *IGH::CRLF2* rearrangement (p=0.003). The IKZF1^{PLUS} profile (*IKZF1* deletion plus *CDKN2A/2B*del, *PAX5*del or *P2RY8::CRLF2* rearrangement without *DUX4* rearrangement) was identified as a novel high-risk feature enriched in H/L patients (p=0.001).

Conclusions: Our study shows enrichment of high-risk genetic variants in H/L B-ALL and raises consideration for novel therapeutic targets.

Keywords

Pediatric; leukemia; acute lymphoblastic leukemia; B-ALL; Hispanic; ethnicity

Introduction

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy, with an annual incidence in the United States of 3.7–4.9 cases per 100,000 children aged 0–14.[1–3] It carries an overall excellent prognosis, with cure rates reaching approximately 90%.[3,4] Though the outcome is promising for many children diagnosed with ALL, the disease remains a significant burden on the pediatric population, and one that disproportionally impacts certain groups. There is a known ethnic disparity in both the incidence and outcomes in pediatric ALL.[5] Hispanic/Latino (H/L) individuals have a higher incidence of ALL,[6] and H/L children are 1.2–1.75 times more likely than non-Hispanic white (NHW) children to be diagnosed with ALL.[5,7] Additionally, H/L children are 1.4 times more likely to die from the disease than NHW children,[8] even after accounting for socioeconomic status[9,10] and medication adherence.[11]

B-ALL accounts for 85% of pediatric ALL cases and is subclassified by genetic driver lesions, rearrangements or mutations.[12–15] Many subtypes are associated with prognoses and have therapeutic implications.[15,16] For example, B-ALL characterized by an *ETV6*::*RUNX1* rearrangement or hyperdiploidy with double trisomy has an excellent survival rate of 93% and may be treated with less intensive therapy than other subtypes.[17,18] On the other hand, *KMT2A* rearrangement, *BCR::ABL1* (Philadelphia chromosome) rearrangement (Ph+) and Philadelphia-like (Ph-like, e.g. *CRLF2* rearrangement, often with *IKZF1* deletion) are among the subtypes associated with less favorable prognoses.[19–24]

We have previously shown that concomitant *CRLF2* rearrangement and *IKZF1* deletion are associated with H/L ethnicity.[25] In the current study, we sought to identify novel genetic drivers and secondary genetic alterations in B-ALL associated with H/L ethnicity.

Methods

Setting and Participants

Following IRB approval, we identified all patients with B-ALL diagnosed at 21 years of age or younger and treated at our tertiary pediatric referral center between January 2016 and December 2020. Inclusion criteria were available molecular genetic data from diagnostic leukemia samples processed and analyzed at our Center for Personalized Medicine (CPM).

Cases included all those from our previous study (n=239)[25] as well as additional cases collected after that study period.

Data Collection

Comprehensive clinicopathologic data were gathered from the electronic medical record, pathology and CPM databases, including demographic information [sex, ethnicity, constitutional trisomy 21 (Down syndrome) status], age, white blood cell (WBC) count, central nervous system (CNS) status by cerebrospinal fluid (CSF) cytomorphology, National Cancer Institute (NCI) risk group, treatment information, response to therapy, and outcome. Ethnicity was drawn from the self-reported race and ethnicity data in the electronic health record, which were collected at the time of registration to the hospital per NIH criteria. Patients were treated per ongoing or completed Children's Oncology Group (COG) frontline trials for ALL.[26,27]

The standard cytogenetic and molecular work-up for B-ALL subclassification at our institution has been previously described[28] and includes karyotype, B-ALL fluorescence *in situ* hybridization (FISH) panel, chromosome microarray (CMA), and an institutional next-generation sequencing (NGS) panel (OncoKids®),[29] for DNA and RNA variants across pediatric cancers, including hematologic malignancies. FISH include the standard Children's Oncology Group (COG) probe sets as well as additional probes for selected cases, including *ABL1*, *ABL2* and *PDGFRB* probes for NCI high-risk ALL and *IGH* and *CRLF2* probes for cases with CRLF2 expression identified by flow cytometry. CytoScan™ HD arrays (Thermo Fisher Scientific, Waltham, MA) were used for CMA testing. DNA preparation, hybridization, washing, and labeling followed the protocols recommended by the manufacturer, and the data were analyzed with the Chromosome Analysis Suite (ChAS) software (V3.1. Thermo Fisher Scientific, Waltham, MA). OncoKids® panel testing was performed as previously described.[28,29] Primary and secondary genetic lesions (fusions, mutations, deletions, and insertions) for all available samples were catalogued.

Outcomes and Measures

Primary outcome measures were the presence of *CRLF2* rearrangement and/or *IKZF1* deletion in B-ALL. Secondary outcome measures included the presence of other primary genetic drivers and secondary genetic alterations in B-ALL as determined by the OncoKids® assay (mutations) and CMA (copy number alterations). Exploratory clinical outcomes were event-free survival (EFS) and overall survival (OS). B-ALL subtypes based on primary genetic drivers were defined by the current WHO[13] and ICC[14] classifications and grouped into associated favorable, neutral, and unfavorable cytogenetic risk categories as follows: favorable = ETV6::RUNX1, hyperdiploidy with double trisomy, DUX4 and PAX5 P80R; neutral = ETV6::RUNX1-like, hyperdiploidy without double trisomy, TCF3::PBX1, dic(9;20), PAX5alt, ZNF384, IGH::BCL2, IGH::CEBPE, IGH::ID4, IGH::MYC, NUTM1, and not otherwise specified (NOS); and unfavorable = BCR::ABL1, BCR::ABL1-like (non-CRLF2), IGH::CRLF2, P2RY8::CRLF2, hypodiploidy, intrachromosomal amplification of chromosome 21 (iAMP21), KMT2A-R, and MEF2D. Event-free survival (EFS) was calculated as the interval from the date of initial diagnosis until the date of first relapse or

death from any cause. OS was calculated from date of initial diagnosis to date of death from any cause or date of last follow-up.

Statistical Analysis

Demographics and characteristics at diagnosis were summarized for the full cohort and across H/L ethnicity and non-H/L ethnicity groups using median and interquartile range (IQR) for continuous variables. Categorical variables were described as frequency and percentage. Differences between groups were assessed via Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. For primary outcomes, we utilized Fisher's exact tests as univariate analyses, as well as logistic regression models adjusting for sex and NCI Risk score. A penalized likelihood-based method, Firth's bias-reduced logistic regression (R package "logistf"), was used to accommodate the low prevalence rates.[30] We also performed the aforementioned univariate analyses for the secondary outcomes. As exploratory analyses, an ordinal logistic regression model was fit to determine whether prognosis is related to H/L ethnicity, with and without adjusting for sex and NCI Risk. Associations of ethnicity and cytogenetic risk groups with EFS and OS were evaluated via Kaplan Meier curves to visualize time to first relapse/death and death, accompanied by log-rank tests. A multivariate Cox proportional hazards regression model with ethnicity, cytogenetic risk groups, and sex was also fitted as we recognized the potential confounding effects of sex and cytogenetic risk groups on the observed relationship between ethnicity and survival outcomes based on literature and clinical perspective. To keep the probability of a type I error less than 0.05 with the multiple hypotheses tested in the secondary analyses, p-values were controlled with respect to false discovery rate (FDR) using Benjamini-Hochberg's procedure.[31] All tests were two-sided and a p-value < 0.05 was considered statistically significant. All statistical analyses were conducted by R-studio 4.2.2.

Results

The cohort consisted of 273 patients presenting with a new diagnosis of B-ALL. Of these, 239 patients had also been included in Raca *et al* Leukemia 2021; however, comprehensive molecular characterization was not included in the previous report.[25] Median (IQR) age was 6.5 (3.4, 12.5) years, 54.6% (149 patients) were male, and 69.2% (189 patients) identified as H/L. Detailed demographic and disease information with respect to ethnicity is presented in Table 1.

Clinicopathologic features

Compared to non-H/L patients, H/L patients were older (median [IQR] age: 7.4 [3.5, 13.2] vs. 5.2 [3.1, 9.6] years, p=0.018), more likely to present with CNS2 or CNS3 disease (29.9% vs. 13.1%, p=0.004) and NCI high-risk ALL (52.9% H/L vs. 35.7% non-H/L, p=0.009). The difference in NCI high-risk status was predominantly driven by age (Supplementary Table 1). There was no significant difference in sex, prevalence of Down syndrome, WBC at diagnosis, or MRD by flow cytometry at end of induction (EOI, day 29).

CRLF2 rearrangement and IKZF1 deletion

All univariate and multivariate analysis estimates are presented in Table 2. H/L patients had higher prevalence of *IGH::CRLF2* rearrangement (13.2% H/L vs. 3.6% non-H/L, p=0.016) than non-H/L patients. However, this relationship was confounded by sex and NCI Risk in the multivariate model (OR: 2.59, 95% CI: [0.89, 10.1], p = 0.08).

Confirming the reported finding in our previous study,[25] H/L ethnicity was associated with *IKZF1* deletion [54 of 189 (28.6%) H/L patients compared to 9 of 84 (10.7%) non-H/L patients, p=0.001]. H/L patients had higher prevalence of *IKZF1* deletion plus concomitant *IGH::CRLF2* rearrangement (22/189 [11.6%] H/L vs. 1/84 [1.2%], p=0.003) compared to non-H/L ethnicity. After adjusting for sex and NCI Risk, both *IKZF1* deletion and *IKZF1* deletion plus concomitant *IGH::CRLF2* rearrangement remained significantly associated with H/L ethnicity (OR: 2.56, 95% CI: [1.22, 5.86], p = 0.012 and OR: 5.15, 95% CI: [1.23, 47.7], p = 0.021, respectively).

IKZF1^{PLUS} B-ALL

IKZF1^{PLUS}, defined by *IKZF1* deletion plus *CDKN2A/2B*del, *PAX5*del or *P2RY8::CRLF2* rearrangement without *DUX4* rearrangement,[32–34] was also strongly associated with H/L ethnicity (19.6% in H/L vs 4.8% in non-H/L, p=0.001). IKZF1^{PLUS} remained significantly associated with H/L ethnicity in the multivariate model (OR: 3.53, 95% CI: [1.37, 11.4], p = 0.007). Among 41 patients with IKZF1^{PLUS} (36 H/L and 4 non-H/L, with one patient missing EOI MRD), 20 (50%) had positive MRD. 19/36 (52.8%) of H/L patients with IKZF1^{PLUS} (vs 1/4 (25%) of non-HL patients) had positive MRD. The genetic characteristics qualifying for IKZF1^{PLUS} designation in our cohort (n=41) are detailed in Supplementary Table 2.

VPREB1 deletion

Based on findings in previous studies demonstrating a link between *VPREB1* deletion and higher-risk B-ALL,[22–24] we tested whether *VPREB1* was associated with H/L ethnicity in our cohort. Among H/L patients, 56 of 189 (29.6%) harbored a leukemia-associated *VPREB1* deletion compared to 15 of 84 (17.9%) non-H/L patients. H/L patients also had a higher prevalence of *IKZF1* deletion plus concomitant *VPREB1* deletion than non-H/L patients (11.1% vs. 6%). However, these associations were not statistically significant in either univariate or multivariate analyses (p > 0.05).

Other genetic drivers

H/L patients with B-ALL had lower prevalence of *ETV6::RUNX1* fusion (13.2% H/L vs. 25.0% non-H/L, p=0.02) compared to non-H/L ethnicity. However, this association was no longer statistically significant after controlling for false discovery rate (p=0.3). H/L ethnicity was not associated with other B-ALL subtypes in our cohort as follows: BCR::ABL1, BCR::ABL1-like features, ETV6::RUNX1-like features, hyperdiploidy without double trisomy, hyperdiploidy with double trisomy, low hyperdiploidy, hypodiploidy, iAMP21, TCF3::PBX1, KMT2A-R, dic(9;20), DUX4, PAX5alt, PAX5 P80R, MEF2D, IGH::BCL2, IGH::CEBPE, IGH::ID4, IGH::MYC, NUTM1, ZNF384 and not otherwise specified (NOS) (Figure 1).

Secondary genetic alterations

Comprehensive cytogenetic and molecular data from CMA (CytoScan™ HD array) and NGS-based mutation panel (OncoKids®) testing was available for the leukemias of 189 of 273 patients (69.2%; 130/189, or 68.8%, of H/L patients; 59/84, or 70.2%, of non-H/L patients. H/L ethnicity group had a higher proportion of *CDKN2A*/*2B* deletion (40.2% H/L vs. 25.0% non-H/L, p=0.020) as well as *KRAS* mutation [24/130 (18.5%) H/L vs. 4/59 (6.8%) non-H/L, p=0.046]. However, these associations were no longer statistically significant after applying a false discovery rate correction to all secondary hypothesis tests (p=0.05 and p>0.9, respectively). There were no significant associations between H/L ethnicity and deletion of the following gene loci by CMA: *BTG1*, *BTLA*, *TBL1XR1*, *NSD2*, *NR3C2*, *LEF1*, *EBF1*, *NR3C1*, *HIST1H3B*, *TOX*, *PAX5*, *ADD3*, *ADARB2*, *ETV6*, *SH2B3*, *RB1*, *SERP2*, *PAN3*, *CREBBP*, *NF1*, *TP53*, *STAG2*, or *DDX3X*; gain of the *PAX5* locus by CMA; or mutations in the following genes by OncoKids®[29]: *ABL1*, *ASXL1*, *ATRX*, *BRAF*, *CCND3*, *CDKN2A*, *CREBBP*, *CRLF2*, *EZH2*, *FLT3*, *GATA3*, *IL7R*, *JAK1*, *JAK2*, *KMT2D*, *MTOR*, *NF1*, *NRAS*, *NSD2*, *NT5C2*, *PAX5*, *PTPN11*, *SH2B3*, *SETD2*, *TPMT* or *TP53*.

Clinical outcomes

Treatment information is summarized in Supplementary Results. After categorizing patients into favorable, neutral, and unfavorable cytogenetic risk groups based on subtype as described in the methods section, H/L patients were found to have higher proportions of less favorable subtypes compared to non-H/L patients (neutral: 30.7% H/L vs. 23.8% non-HL; unfavorable: 37.0% H/L vs. 28.6% non-HL, p = 0.056) (Table 1). The odds of having a less favorable subtypes are 1.71 times higher for H/L patients compared to non-H/L patients (95% CI: 1.1, 2.8, p=0.029). However, this relationship was confounded by sex and NCI risk in the multivariate model (OR=1.4, 95% CI: 0.8, 2.3, p=0.23).

In the overall cohort, there were 17 deaths (6.2%), 15 among H/L patients (15/189, or 7.9%) and 2 among non-H/L patients (2/84, or 2.4%). EFS and OS between ethnicity groups are depicted in Figure 2. In the overall cohort, there were 42 relapses (15.4%), 29 among H/L patients (29/189, or 15.3%) and 13 among non-H/L patients (13/84, or 15.5%). There was no difference in EFS or OS between the two groups in either long-rank tests (p=0.41 and p=0.08, respectively) or in the multivariable models with sex and cytogenetic risk groups (HR=1.17, 95% CI: 0.63, 2.16, p=0.60 and HR=3.19, 95% CI: 0.72, 14.0, p=0.13, respectively).

Differences in EFS and OS between cytogenetic risk groups were both significant via log-rank tests (p = 0.007 and p < 0.001, respectively) (Figure 3). Unfavorable subtypes were associated with poorer EFS compared to favorable and neutral subtypes (HR = 2.6, 95% CI: 1.3, 5.2, p = 0.005, HR = 1.9, 95% CI: 0.97, 3.7, p = 0.06, respectively). The hazard ratio for OS was 14.1 (95% CI: 1.9, 108, p=0.011) times higher in those with unfavorable subtypes as compared to those with favorable subtypes, and 6.1 times higher compared to those with neutral subtypes (95% CI: 1.4, 26.9, 0.02).

EFS and OS between EOI MRD levels among patients with IKZF1^{PLUS} (N = 41, with one patient missing MRD status) are depicted in Figure 4. Due to small sample size and exploratory nature of this aim, we only performed log-rank tests to compare survival outcomes between MRD levels. However, these were not statistically significant (p = 0.29 and p = 0.07). Similarly, statistically significant differences were not identified among relapses.

Discussion

The patient population at our tertiary pediatric referral center is significantly enriched for H/L ethnicity (approximately 70%), reflecting our catchment area and our safety-net hospital status. In this study, we have leveraged this patient population to identify novel genetic associations (including novel genetic drivers and secondary genetic alterations) that may further explain the disparity in outcomes in pediatric B-ALL observed among patients of H/L ethnicity.[5,7–9,11] Novel targeted therapeutic approaches are in development for this high-risk subtype,[27,35,36] and our findings may help provide pre-clinical evidence for their direction.

The association of IKZF1^{PLUS} B-ALL with H/L ethnicity identified in our cohort is a novel finding and could additionally account for the ethnic disparity in ALL outcomes. IKZF1^{PLUS} B-ALL is a relatively newly described category defined as *IKZF1* deletions co-occurring with deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* in the absence of *ERG* deletion (*ERG* deletion being a sensitive and specific surrogate for *DUX4* rearrangement). IKZF1^{PLUS} carries a very poor prognosis, particularly for patients who are MRD positive at EOI.[32]

Similarly, a higher prevalence of *IKZF1* deletion plus concomitant *VPREB1* deletion in H/L patients (11.1% vs. 6%), while not statistically significant in our cohort, it does raise consideration for this combination of genetic features contributing to the worse prognosis observed in H/L B-ALL patients overall. The association we found expands on the data reported by Mangum *et al*[22] of an association between unfavorable outcome and combined *VPREB1* (focal 22q11.22) deletion and *IKZF1* alterations in pediatric B-ALL. Our relatively small cohort size (N=273, all B-ALL subtypes) could explain the lack of statistical significance compared to that identified by Mangum *et al* (n=1310, predominantly high-risk disease).

A particular strength of the current study is comprehensive analysis of secondary (non-driver) genetic alterations identified through clinical testing by our institutional OncoKids® DNA and RNA NGS panel[29] paired with CMA (OncoScan) copy number assessment and conventional cytogenetics.[28] Our data corroborate existing reports that somatic *CDKN2A*/*2B* deletions in B-ALL are associated with relapse and overall inferior prognosis irrespective of patient age.[37–39] The kinase inhibitors encoded by the *CDKN2A*/*2B*, tumor suppressors that regulate cell cycle, are mutated across many cancer types[40] and may be amenable to pharmacologic modification in the future.[41] Additionally, our study identified *KRAS* mutation as enriched in B-ALL of patients of H/L ethnicity compared to those of non-H/L ethnicity. Like *CDKN2A*/*2B* deletions, *KRAS* mutations are the most common

oncogenic alterations across cancer types, and are recognized as frequent alterations in subsets of B-ALL. Ras pathway abnormalities are reported in 6% of B-ALL[42] and are emerging as targets of immunotherapeutic approaches.[43]

Ethnic differences are known to underlie pathophysiology, subclassification and prognosis in pediatric B-ALL across genetic ancestries.[10] Indeed, Lee *et al* aggregated the results of cooperative group trials from around the world to show significant associations between *DUX4* and *ZNF384* rearrangements and East Asian ancestry, *CRLF2* rearrangement and Native American ancestry, and T-cell phenotype (T-ALL) with African ancestry.[10] However, that large study was not proportionally enriched for H/L ethnicity (21.4% Hispanic patients, drawn from COG, St. Jude and Guatemalan cohorts), and despite a large absolute number of Hispanic patients (n=520), the authors note that their Hispanic study population is particularly diverse with genetic subpopulations, similar to the genetic subpopulations observed among Native Americans,[44] precluding specific genetic associations.[10] Nevertheless, Hispanic patients in that study showed the most inferior EFS, OS and cumulative incidence of relapse among all ethnic groups in the cohort.[10]

Limitations of our study include its retrospective nature and a relatively small cohort size. In addition, ethnicity data consisted of self-reported race; we did not have access to genetic sequencing data from which to infer ethnicity. As noted in Lee *et al*, H/L populations are highly diverse compared to some others.[10,44] Another limitation is the relatively short clinical follow-up interval, particularly for patients diagnosed in the latter part of the study period (2020) among whom any late relapses are not captured in the current study.

In summary, we report a novel association of the IKZF1^{PLUS} profile in pediatric B-ALL patients of Hispanic/Latino ethnicity, as well as confirmatory associations with enrichment of *IGH::CRLF2* rearrangement and *IKFZ1* with or without *IGH::CRLF2* rearrangement, raising consideration for novel therapeutic strategies in this high-risk group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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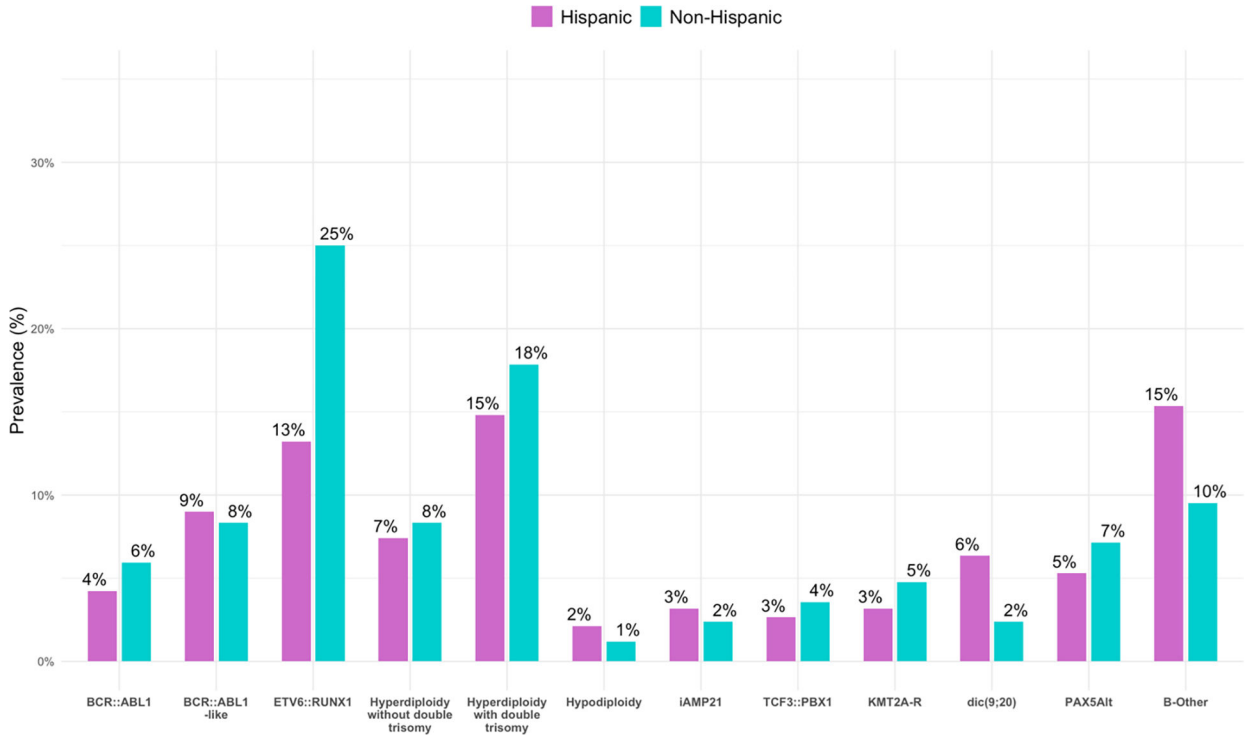

Figure 1. Prevalence of B-lymphoblastic leukemia (B-ALL) genetic drivers by patient ethnicity

Higher incidence of *IGH::CRLF2* rearrangement (B-ALL, BCR::ABL1-like, unfavorable; p=0.016) and lower incidence of *ETV6::RUNX1* rearrangement (favorable, p=0.02) were associated with H/L ethnicity.

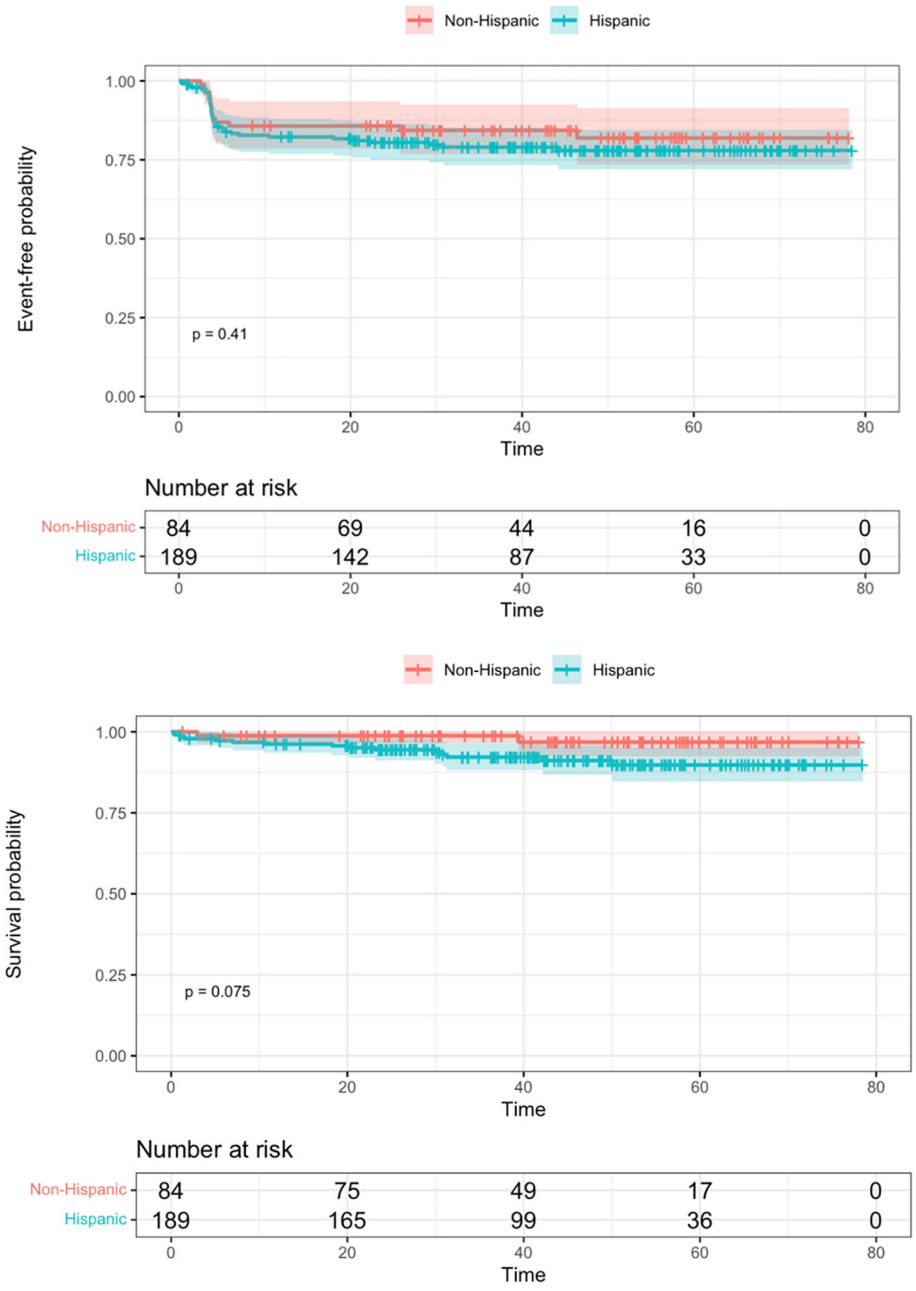

Figure 2. Kaplan-Meier survival curves, with log-rank test, by ethnicity groups

A. Event-free survival. B. Overall survival. Time is shown in months.

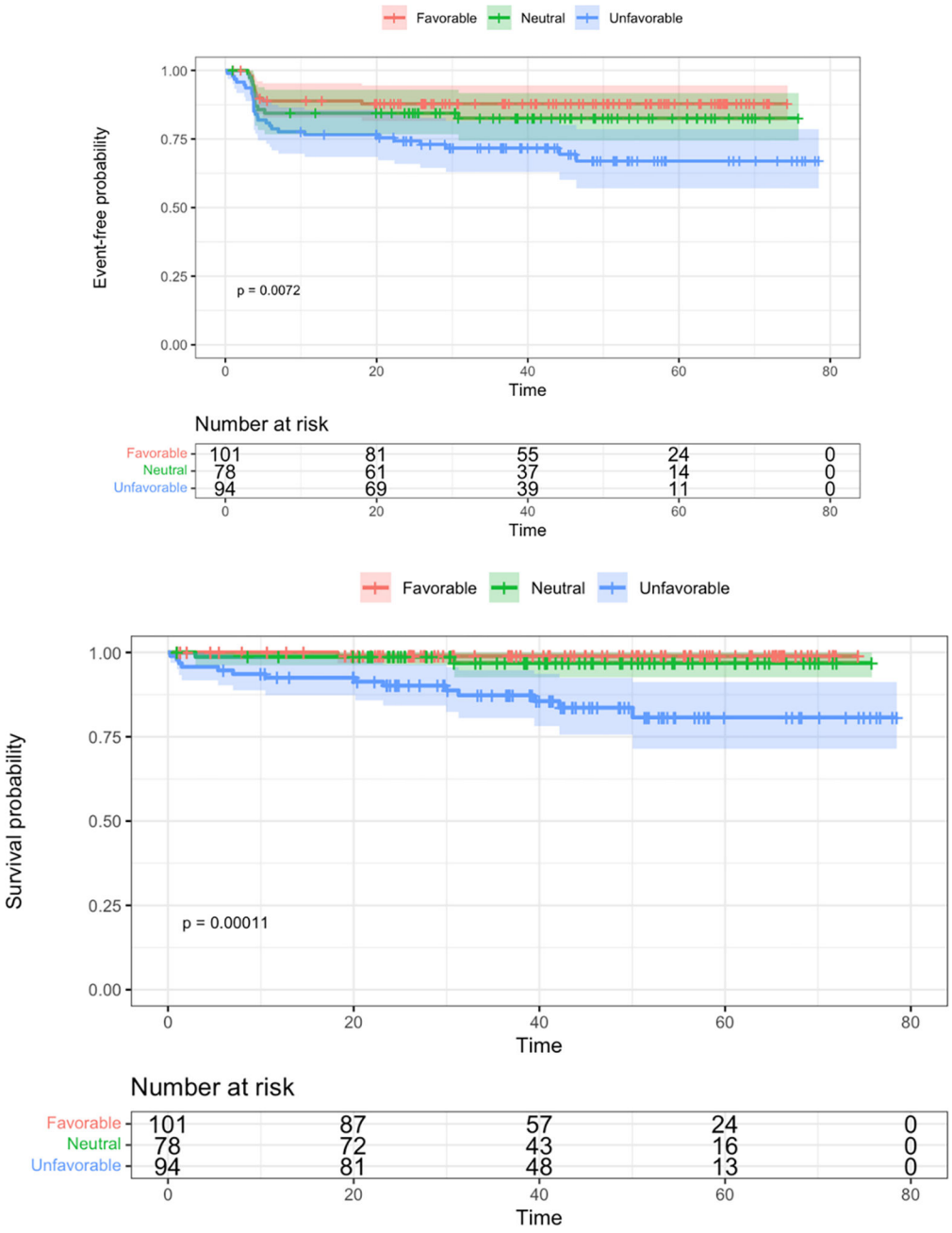

Figure 3. Kaplan-Meier survival curves by cytogenetic risk groups

A. Event-free survival. B. Overall survival. Time is shown in months.

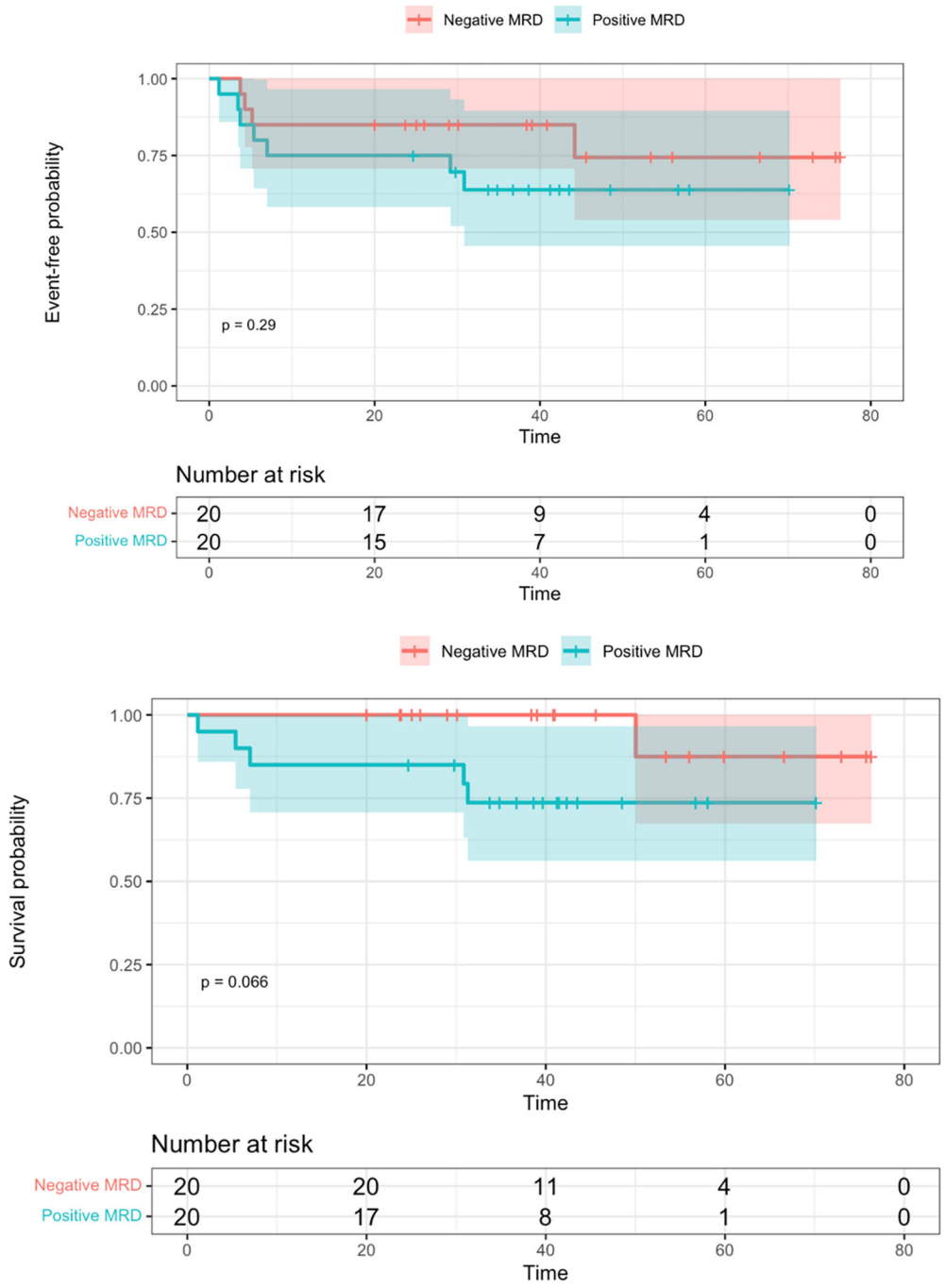

Figure 4. Kaplan-Meier survival curves, with log-rank test, by minimal/measurable residual disease (MRD) at end of Induction (EOI)

A. Event-free survival. B. Overall survival. Time is shown in months.

Table 1.

Demographic and disease information by ethnicity

	Overall N = 273	Hispanic N = 189	Non-Hispanic N = 84	p-value[1]
Age (median), years (IQR)	6.5 (3.4, 12.5)	7.4 (3.5, 13.2)	5.2 (3.1, 9.6)	**0.018**
Male, n (%)	149 (54.6)	108 (57.1)	41 (48.8)	0.2
Down syndrome, n (%)	14 (5.1)	10 (5.3)	4 (4.8)	0.9
WBC (median), K/μL (IQR)	7.7 (3.1, 32.1)	9.0 (3.1, 47.5)	6.9 (3.0, 15.7)	0.2
Subtype, n (%)				
Favorable	101 (37.0)	61 (32.3)	40 (47.6)	0.056
Neutral	78 (28.6)	58 (30.7)	20 (23.8)	
Unfavorable	94 (34.3)	70 (37.0)	24 (28.6)	
CNS2 or CNS3, n (%) [2]	67 (24.7)	56 (29.9)	11 (13.1)	**0.004**
NCI high risk, n (%)	130 (47.6)	100 (52.9)	30 (35.7)	**0.009**
EOI MRD+, n (%) [2]	66 (24.4)	50 (26.7)	16 (19.0)	0.2

[1] Wilcoxon rank-sum test, Fisher's exact test

[2] N=271 (Hispanic: 187, Non-Hispanic: 84); IQR, interquartile range; WBC, white blood cell count; BM, bone marrow; CNS2, central nervous system 2 status at diagnosis; NCI high risk, National Cancer Institute risk score of 2 or 3; EOI, end of Induction; MRD, minimal/measurable residual disease.

Table 2.

Associations of key genetic rearrangements and deletions with Hispanic/Latino ethnicity

	Prevalence by ethnicity				Multivariate logistic regression adjusted for sex and NCI risk		
	Overall N = 273[1]	**Hispanic N = 189**[1]	**Non-Hispanic N = 84**[1]	**p**[2]	**OR**[3]	**95% CI**[3]	**p**[3]
***IGH::CRLF2* rearrangement**	28 (10.3%)	25 (13.2%)	3 (3.6%)	**0.016**	2.59	0.9, 10.1	0.08
***IKZF1* deletion**	63 (23.1%)	54 (28.6%)	9 (10.7%)	**0.001**	2.56	1.22, 5.86	**0.012**
***IKZF1* deletion + concomitant *IGH::CRLF2* rearrangement**	23 (8.4%)	22 (11.6%)	1 (1.2%)	**0.003**	5.15	1.2, 47.7	**0.021**
IKZF1 PLUS	41 (15%)	37 (19.6%)	4 (4.8%)	**0.001**	3.53	1.37, 11.4	**0.007**
***VPREB1* deletion**	71 (26%)	56 (29.6%)	15 (17.9%)	0.052	1.81	0.97, 3.51	0.061
***IKZF1* deletion + concomitant *VPREB1* deletion**	26 (9.5%)	21 (11.1%)	5 (6%)	0.3	1.38	0.53, 4.14	0.5

[1] n (%)

[2] Fisher's exact test

[3] Adjusted logistic regression; OR, Odds Ratio; CI, Confidence Interval.