

Poor Outcome of Pediatric Patients with Acute Lymphoblastic Leukemia Harboring Low $P16$ Deletion Ratio: A Post-Hoc Analysis from a Prospective Cohort

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Object: The prognostic significance of $P16$ (*CDKN2A*) deletion ($P16^{del}$) in pediatric acute lymphoblastic leukemia (ALL) remains controversial, potentially due to the historical reliance on binary classification.

Methods: In this prospective cohort study (SCCLG-ALL-2016 protocol), we analyzed 413 pediatric ALL patients. $P16^{del}$ status and ratio were quantified using standardized FISH. Statistical models adjusting for key prognostic factors were performed. Piecewise linear regression identified prognostic thresholds for $P16^{del}$ ratio. Survival outcomes (relapse-free survival, RFS; overall survival, OS) and interactions with minimal residual disease (MRD) were assessed.

Results: $P16^{del}$ prevalence was 18.2% (75/413). Multivariable analysis confirmed $P16^{del}$ as an independent adverse prognostic factor (RFS: $HR=2.2$, $p=0.020$; OS: $HR=2.7$, $p=0.024$). Crucially, a nonlinear dose-response relationship identified 0.8 as the critical $P16^{del}$ ratio threshold: Below 0.8, each unit ratio increase conferred a 93% higher relapse/death risk (adjusted $LogHR=1.93$, $p=0.031$); above 0.8, higher ratios reduced risk by 33% (adjusted $LogHR=0.67$, $p=0.048$). Patients with low ratios (<0.8 , $n=37$) had significantly inferior 5-year outcomes (RFS: 57.7%, OS: 72.2%) compared to high ratios (≥ 0.8 , $n=38$; RFS: 88.5%, OS: 94.7%) ($p<0.001$). The prognostic impact of MRD was critically dependent on $P16^{del}$ ratio: Low ratio with D33 MRD+ predicted catastrophic outcomes (5-year RFS=27.8%), while high ratio patients maintained excellent survival regardless of MRD status (D33 MRD+ RFS=100%). High-ratio patients exhibited enrichment for RAS mutations ($p=0.046$).

Conclusion: The identified $P16$ deletion ratio threshold of 0.8 may guide precision risk-adapted therapy in pediatric ALL, but its clinical utility must be validated in larger, diverse cohorts before implementation.

Keywords: children, acute lymphoblastic leukemia, $P16$ deletion, prognostic biomarker, minimal residual disease

Introduction

The $P16$ tumor suppressor gene (*CDKN2A*), a critical regulator of the G1/S cell cycle transition via the retinoblastoma pathway, is frequently inactivated in hematologic malignancies.¹ Homozygous deletion ($P16^{del}$) represents a predominant mechanism of inactivation in pediatric acute lymphoblastic leukemia (ALL), with reported incidence varying widely across studies, ranging from approximately 10% to 30%.²⁻⁵ The prognostic significance of $P16^{del}$ in childhood ALL, however, remains a subject of conflicting reports.^{6,7} While numerous studies have associated $P16^{del}$ with inferior outcomes, including higher relapse rates and reduced survival, other cohorts have failed to demonstrate a significant independent prognostic

impact.^{3–7} Current risk stratification schemas for pediatric ALL often treat P16 deletion as a binary variable, overlooking quantitative variation, which may limit prognostic accuracy.^{5,6} Critically, a key limitation shared by most prior investigations is the disregard for the potential influence of the quantitative burden of the deletion, specifically the ratio of cells harboring *P16^{del}*.⁸ Recent multicenter studies highlight the heterogeneity in P16 deletion impact, underscoring the need for quantitative approaches.⁷ This oversight – treating *P16^{del}* as a simple binary variable while neglecting the quantitative dimension – likely contributes significantly to the observed discrepancies in reported prognostic impact.⁹

However, a standardized quantitative threshold for P16 deletion ratio is lacking, hindering its integration into risk stratification. This study aims to address this gap by quantifying the P16 deletion ratio, with the objective of refining risk stratification and guiding therapy intensification or de-escalation. In this present study, we characterize the prevalence of *P16^{del}* and critically evaluate its prognostic significance, placing particular emphasis on the role of the *P16^{del}* ratio. Utilizing a large, well-annotated cohort of pediatric ALL patients, our primary aim is to determine an optimal prognostic cut-off value for the *P16^{del}* ratio. This evidence-based threshold is intended to refine risk stratification and prognostication, ultimately guiding therapeutic decisions within the *P16^{del}*-positive pediatric ALL population.

Patients and Methods

Study Participants

This is a post-hoc analysis of the prospective South China Children's Leukemia Group-2016 (SCCLG-ALL-2016) cohort. While patient enrollment and treatment followed a prospective protocol, the quantification of *P16^{del}* ratio and its association with outcomes were analyzed retrospectively using stored biospecimens. A total of 413 patients aged 1–18 years with newly diagnosed ALL at Sun Yat-sen Memorial Hospital from October 2016 to May 2023 were enrolled in this study. All patients were treated with the SCCLG-ALL-2016 protocol.

All inclusion and exclusion criteria are listed as follows: inclusion criteria (1) age ≤18 years; (2) clinical presentation consistent with ALL and diagnosis of ALL based on morphological review of bone marrow smears, immunophenotyping, cytogenetics, and molecular genetics according to the WHO 2008 criteria; (3) First-episode disease without prior therapy; (4) Centralized *P16^{del}* testing (including ratio quantification); (5) Complete minimal residual disease (MRD) data at D15/D33. Exclusion criteria (1) mature B-ALL, or mixed-phenotype leukemia; (2) Secondary ALL or immunodeficiency-associated malignancy; (3) as a second malignancy; (4) Down syndrome or other cancer predisposition syndromes; (5) Glucocorticoid therapy >1 week pre-diagnosis; (6) Missing *P16^{del}* ratio or MRD data. The study was conducted according to Declaration of Helsinki principles and approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital (Approval No. 2020-KY-004). Written informed consent was obtained from all patients' guardians. The trial is registered with the Chinese Clinical Trial Registry (Chi-CTR; <https://www.chictr.org.cn/>; number ChiCTR2000030357).

Chemotherapy Protocol

All enrolled patients received risk-adapted therapy per the institutional SCCLG-ALL-2016 guidelines, commencing with a 7-day prednisone prephase followed by induction using the VDLD regimen (vincristine, dexamethasone, L-asparaginase, and doxorubicin). Early intensification was subsequently administered with the CAM combination (cyclophosphamide, cytarabine, and 6-mercaptopurine). Consolidation therapy was then stratified by risk category: low-risk patients received either MM (high-dose methotrexate with 6-mercaptopurine) or eMV (escalating methotrexate plus vincristine and 6-mercaptopurine); intermediate-risk patients underwent high-dose methotrexate monotherapy; while high-risk patients sequentially received two cycles of the HR blocks—HR-1 (dexamethasone, vincristine, cyclophosphamide, high-dose methotrexate, high-dose cytarabine, L-asparaginase), HR-2 (dexamethasone, vindesine, ifosfamide, high-dose methotrexate, daunorubicin, L-asparaginase), and HR-3 (dexamethasone, high-dose cytarabine, etoposide, L-asparaginase). Therapy subsequently progressed to delayed intensification featuring VDLD reinduction and additional CAM, followed by eight weeks of maintenance chemotherapy with regular intrathecal injections, continuing under ongoing risk assessment with medication adjustments per institutional criteria throughout the maintenance phase. All patients were treated under the standardized SCCLG-ALL-2016 protocol, minimizing variability, but potential heterogeneity was accounted for in sensitivity analyses.

Treatment Response Assessment I I

Therapeutic efficacy was evaluated through multi-point monitoring of blast cell clearance. On Day 8 of induction therapy, peripheral blood blast quantification determined corticosteroid sensitivity. Patients demonstrating $<1,000$ blasts/ μL were classified as prednisone good responders (PGR), while those with $\geq 1,000$ blasts/ μL were designated prednisone refractory responders (PRR). Subsequent bone marrow aspirate examinations at Day 15 and Day 33 established cytomorphological remission depth via blast percentages: M1 ($<5\%$ blasts), M2 (5–24% blasts), and M3 ($\geq 25\%$ blasts). Complete remission (CR) required fulfillment of all criteria post-induction: $<5\%$ leukemic blasts in cellular marrow, absence of extramedullary disease, and peripheral blood count recovery. Relapse was confirmed upon either bone marrow infiltration $>25\%$ blasts or histologically proven extramedullary leukemia following prior CR attainment. MRD assessment via flow cytometry was performed in accordance with standardized methodologies established by collaborative French research consortia for ALL across pediatric and adult populations. Positivity thresholds for MRD were established at distinct timepoints: $\geq 0.1\%$ leukemic cells defined Day 15 MRD-positivity, whereas $\geq 0.01\%$ residual blasts constituted MRD-positivity at Day 33. Adverse clinical outcomes were defined as relapse or death.

$P16^{\text{del}}$ Detection Methods

Fluorescence in situ hybridization (FISH) analysis was performed according to standardized protocols (Abbott Molecular, IL, USA). Bone marrow specimens underwent synchronized 24-, 48-, and 72-hour culture cycles prior to metaphase preparation. Interphase nuclei assessment employed a dual-probe system comprising a chromosome 9 centromeric control and a 222-kb target probe spanning the 9p21.3 locus, which encompasses the complete $P16$ genes. Diagnostic thresholds were established using normal bone marrow reference controls, with deletion patterns considered clinically significant at $\geq 5\%$ frequency after evaluation of ≥ 100 interphase nuclei per sample. Signal pattern interpretation designated 2R2G (dual red/green signals) as normal; 1R2G (single red signal loss) as heterozygous deletion; and 0R2G (absence of both target signals) as homozygous deletion.

Statistical Analysis

Descriptive statistics characterized baseline variables using frequencies/percentages for categorical measures and medians for continuous variables. Group comparisons employed chi-square tests for categorical data, while ANOVA or Kruskal–Wallis tests analyzed continuous variables based on distributional assumptions. Time zero was defined as the date of diagnosis. The recruitment period was from October 2016 to May 2023, with a median follow-up of 5.2 years calculated using the reverse Kaplan–Meier method. Censoring was applied for patients lost to follow-up or at the study end. Relapse-free survival (RFS) was defined as time from diagnosis to relapse or death. Overall survival (OS) was defined as time from diagnosis to death from any cause. To identify critical thresholds for $P16^{\text{del}}$ ratio, piecewise linear regression modeling was performed using multi-variable Cox proportional hazards models. Piecewise linear regression was performed using multivariable Cox proportional hazards models, with results reported as hazard ratios (HR) and logHR for spline analyses. This approach assessed non-linear relationships between $P16^{\text{del}}$ ratio and survival outcomes while adjusting for established prognostic covariates. To avoid overfitting, predictors were selected a priori based on clinical relevance and univariate significance. The optimal ratio cut-off was determined through iterative model fitting across clinically plausible intervals. Interaction effects between $P16^{\text{del}}$ ratio and treatment response parameters (D15/D33 MRD status) were formally tested within the Cox framework. Survival curves were generated using the Kaplan–Meier method with log-rank comparisons. All analyses were conducted in SPSS 26.0 (IBM Corp) and R 4.2.2 (survival and rms packages) with statistical significance defined as two-tailed $p < 0.05$.

Results

Baseline Characteristics of the Study Population

In a cohort of 413 pediatric ALL patients, 75 cases (18.2%) harbored $P16^{\text{del}}$. Patients with $P16^{\text{del}}$ were significantly older (median age: 5.9 vs. 4.6 years, $p = 0.003$) and presented with higher baseline white blood cell counts (WBC) (median WBC: 22.1 vs. $9.0 \times 10^9/\text{L}$, $p = 0.004$) compared to non- $P16^{\text{del}}$ patients. No differences were observed in gender distribution (57.3% vs. 57.1% male, $p = 0.971$), hemoglobin (71.0 vs. 74.0 g/L, $p = 0.781$), or platelet levels (51.0 vs. $57.0 \times 10^9/\text{L}$, $p = 0.248$). $P16^{\text{del}}$

was absent in Pro-B ALL (0% vs. 3.6%) but enriched in Immature B-ALL (12.0% vs. 5.6%, $p=0.170$ for overall immunophenotype distribution). Genetically, *IKZF1* deletion was more frequent in $P16^{del}$ patients (18.7% vs. 8.9%, $p=0.013$), while *ETV6::RUNX1* fusion was reduced (8.0% vs. 17.3%, $p=0.045$). Clinically, $P16^{del}$ patients trended toward higher-risk stratification (40.0% vs. 27.8% high-risk, $p=0.112$), but early treatment responses (Day 15 M1 marrow: 73.3% vs. 74.3%, $p=0.868$; Day 33 M1: 100% vs. 97.6%, $p=0.178$), central nervous system leukemia (CNSL) (6.7% vs. 6.2%, $p=0.889$), and stem cell transplantation rates (12.0% vs. 10.7%, $p=0.734$) did not differ significantly. These results are summarized at Table 1.

Multivariable Analysis of RFS and OS Among Pediatric ALL Patients

There were 75 events for RFS and 40 events for OS. We used variable preselection ($p < 0.10$ in univariate analysis) to reduce the number of predictors in the multivariable Cox model, resulting in 12 key covariates (eg, demographics, $P16$ deletion, MRD status). Multivariable Cox regression analysis demonstrated that $P16^{del}$ was an independent adverse

Table 1 Baseline Characteristics of Study Participants with or Without $P16^{del}$

Variable	Total (n=413)	$P16^{del}$ Status		P value
		Non- $P16^{del}$ (n=338)	$P16^{del}$ (n=75)	
Gender, n (%)				0.971
Male	236 (57.1%)	193 (57.1%)	43 (57.3%)	
Female	177 (42.9%)	145 (42.9%)	32 (42.7%)	
Age (y), median (range)	4.8 (1.1–14.9)	4.6 (1.2–14.9)	5.9 (1.1–14.8)	0.003
WBC, $\times 10^9$ /L, median (range)	10.0 (0.5–1095.0)	9.0 (0.9–1095.0)	22.1 (0.5–383.0)	0.004
Hemoglobin, g/L, median (range)	73.0 (22.0–139.0)	74.0 (22.0–139.0)	71.0 (24.0–131.0)	0.781
Platelets, $\times 10^9$ /L, median (range)	56.5 (3.0–499.0)	57.0 (3.0–499.0)	51.0 (4.0–358.0)	0.248
Immunophenotype (%)				0.170
Pro-B	12 (2.9%)	12 (3.6%)	0 (0.0%)	
Common B	274 (66.3%)	226 (66.9%)	48 (64.0%)	
Pre-B	50 (12.1%)	41 (12.1%)	9 (12.0%)	
Immature B	28 (6.8%)	19 (5.6%)	9 (12.0%)	
T	49 (11.9%)	40 (11.8%)	9 (12.0%)	
Karyotype (%)				0.321
Hypodiploid	2 (0.5%)	1 (0.3%)	1 (1.4%)	
Normal	177 (44.1%)	143 (43.7%)	34 (45.9%)	
Hyperdiploid With trisomies of chromosomes 4 and 10	99 (24.7%)	85 (26.0%)	14 (18.9%)	
Hyperdiploid Without trisomies of chromosomes 4 and 10	43 (10.7%)	37 (11.3%)	6 (8.1%)	
Others	80 (20.0%)	61 (18.7%)	19 (25.7%)	
Risk group (%)				0.112
Standard risk	74 (17.9%)	63 (18.6%)	11 (14.7%)	
Intermediate risk	215 (52.1%)	181 (53.6%)	34 (45.3%)	
High risk	124 (30.0%)	94 (27.8%)	30 (40.0%)	
CNSL (%)	26 (6.3%)	21 (6.2%)	5 (6.7%)	0.889
Genetic fusion subtype (%)				
BCR::ABL	27 (6.6%)	19 (5.7%)	8 (10.7%)	0.115
KMT2A-r	12 (2.9%)	11 (3.3%)	1 (1.3%)	0.365
ETV6::RUNX1	64 (15.6%)	58 (17.3%)	6 (8.0%)	0.045
E2A::PBX1	18 (4.4%)	16 (4.7%)	2 (2.7%)	0.428
RAS mutation (%)	68 (16.5%)	58 (17.2%)	10 (13.3%)	0.419
IKZF1 ^{del} (%)	44 (10.7%)	30 (8.9%)	14 (18.7%)	0.013
Ph-like ALL (%)	59 (14.6%)	46 (13.9%)	13 (17.6%)	0.424
Prednisone response (%)				0.451
PGR	378 (91.5%)	311 (92.0%)	67 (89.3%)	
PPR	35 (8.5%)	27 (8.0%)	8 (10.7%)	

(Continued)

Table 1 (Continued).

Variable	Total (n=413)	PI6 ^{del} Status		P value
		Non-PI6 ^{del} (n=338)	PI6 ^{del} (n=75)	
D15 BM(%)				0.868
M1	306 (74.1%)	251 (74.3%)	55 (73.3%)	
M2/M3	107 (25.9%)	87 (25.7%)	20 (26.7%)	
D15 MRD positive (%)	262 (63.4%)	220 (65.1%)	42 (56.0%)	0.139
D33 BM (%)				0.178
M1	399 (98.0%)	325 (97.6%)	74 (100.0%)	
M2/M3	8 (2.0%)	8 (2.4%)	0 (0.0%)	
D33 MRD positive (%)	77 (18.9%)	65 (19.5%)	12 (16.2%)	0.512
SCT (%)	45 (10.9%)	36 (10.7%)	9 (12.0%)	0.734

Abbreviations: WBC, white blood cell counts; CNSL, central nervous system leukemia; PGR, prednisone good response; PPR, prednisone poor response; BM, bone marrow blast; MRD, minimal residual disease; SCT, stem cell transplantation.

prognostic factor for both RFS ($HR=2.2$, 95% CI: 1.1–4.1, $p=0.020$) and OS ($HR=2.7$, 95% CI: 1.1–6.6, $p=0.024$) after adjustment (Table 2). Significant associations were also observed for BCR::ABL1 fusion with worse RFS ($HR=3.0$, 95% CI: 1.0–8.6, $p=0.041$) and ETV6::RUNX1 fusion with improved RFS ($HR=0.1$, 95% CI: 0.0–1.0, $p=0.049$). High-risk group classification trended toward inferior OS ($HR=7.7$, 95% CI: 0.8–72.6, $p=0.073$), while Day 15 MRD positivity showed marginal significance for reduced RFS ($HR=2.3$, 95% CI: 1.0–5.5, $p=0.061$) and OS ($HR=2.8$, 95% CI: 0.7–10.2, $p=0.128$). In contrast, established prognostic markers including IKZF1 deletion (OS: $HR=0.2$, 95% CI: 0.0–1.0, $p=0.054$), Ph-like ALL (RFS: $HR=1.0$, $p=0.916$), KMT2A rearrangements (OS: $HR=0.6$, $p=0.683$), RAS mutations (RFS: $HR=2.1$, $p=0.085$), and Day 33 MRD positivity (RFS: $HR=1.7$, $p=0.191$) did not achieve statistical significance ($p \geq 0.05$).

The Threshold of PI6^{del} Ratio Among Pediatric ALL

Threshold effect analysis employing piece-wise linear regression identified a significant inflection point at a PI6^{del} ratio of 0.8 ($p < 0.05$ for both segments), revealing a biphasic dose–response relationship with clinical outcomes. In the low-ratio subgroup (<0.8), each unit increase in deletion burden conferred a 93% elevated risk of adverse events following comprehensive adjustment for 20 covariates (adjusted $\log HR = 1.93$, 95% CI: 1.06–3.49; $p = 0.031$). Conversely, in the

Table 2 Multivariable Analysis of Prognostic Factors for Overall and Relapse-Free Survival From Study Entry

Variables	Relapse-free Survival (RFS)		Overall Survival (OS)	
	HR (95% CI)	P value	HR (95% CI)	P value
PI6 ^{del}	2.2 (1.1, 4.1)	0.020	2.7 (1.1, 6.6)	0.024
High risk	1.2 (0.2, 5.6)	0.836	7.7 (0.8, 72.6)	0.073
BCR::ABL	3.0 (1.0, 8.6)	0.041	0.3 (0.7, 10)	0.140
KMT2A-r	3.0 (0.5, 18.7)	0.241	0.6 (0.1, 6.0)	0.683
ETV6::RUNX1	0.1 (0.0, 1.0)	0.049	0.0 (0.0, Inf)	0.997
RAS mutation	2.1 (0.9, 4.8)	0.085	2.2 (0.6, 7.9)	0.221
IKZF1del	0.7 (0.3, 1.9)	0.480	0.2 (0.0, 1.0)	0.054
Ph-like ALL	1.0 (0.4, 2.3)	0.916	0.7 (0.2, 2.9)	0.646
D15 M2/M3	0.6 (0.3, 1.5)	0.314	2.5 (0.7, 9.0)	0.176
D15 MRD	2.3 (1.0, 5.5)	0.061	2.8 (0.7, 10.2)	0.128
D33 M2/M3	0.0 (0.0, Inf)	0.996	0.0 (0.0, Inf)	0.999
D33 MRD	1.7 (0.8, 3.7)	0.191	0.9 (0.2, 3.2)	0.851

Abbreviations: WBC, white blood cell counts; CNSL, central nervous system leukemia; PGR, prednisone good response; PPR, prednisone poor response; BM, bone marrow blast; MRD, minimal residual disease; SCT, stem cell transplantation.

Table 3 Threshold Effect Analysis of the Association Between Different $PI6^{del}$ Ratios and Adverse Clinical Outcome Using Piece-Wise Linear Regression

$PI6^{del}$ ratios	Crude		Adjust*	
	logHR (95% CI)	P value	logHR (95% CI)	P value
<0.8	1.13 (1.04, 1.22)	0.001	1.93 (1.06, 3.49)	0.031
≥ 0.8	0.58 (0.37, 0.91)	0.019	0.67 (0.45, 1.00)	0.048

Notes: Crude: none adjustment. *Adjusted: Gender; Age; WBC; Hemoglobin; Platelets; Immunophenotype; Karyotype; Risk group; CNSL; Genetic fusion subtype; RAS mutation; IKZF1^{del}; Ph-like ALL; Prednisone response; D15 BM; D33 BM; D15 MRD; D33 MRD.

high-ratio subgroup (≥ 0.8), equivalent increments were associated with a 33% reduction in risk (adjusted logHR = 0.67, 95% CI: 0.45–1.00; $p = 0.048$). Crude models corroborated these directional associations (<0.8: logHR = 1.13, 95% CI: 1.04–1.22, $p = 0.001$; ≥ 0.8 : logHR = 0.58, 95% CI: 0.37–0.91, $p = 0.019$) (Table 3). This nonlinear association was graphically validated by restricted cubic spline analysis (Figure 1), demonstrating: (1) a steep positive logHR slope (indicating risk escalation) below the 0.8 threshold (95% CI excluding the null), and (2) a negative slope (indicating risk attenuation) above 0.8 (95% CI crossing the null but significant at the threshold). Collectively, these findings establish 0.8 as a critical biologic boundary demarcating opposing prognostic regimes.

Baseline Characteristics of ALL with High or Low $PI6^{del}$ Ratio

A comparative analysis of pediatric ALL patients stratified by $PI6^{del}$ ratio (low ratio <0.8, $n=37$ versus high ratio ≥ 0.8 , $n=38$) demonstrated two statistically significant differences: karyotype distribution ($p=0.038$) and RAS mutation frequency ($p=0.046$) (Table 4). Patients with a high ratio exhibited elevated proportions of hyperdiploid karyotypes without trisomies 4 and 10 (15.8% vs. 0%) and “other” cytogenetic abnormalities (31.6% vs. 19.4%), while RAS mutations were markedly enriched in this subgroup (21.1% vs. 5.4%). No significant differences were observed in demographics [gender (50.0% vs. 64.9% male, $p=0.193$), median age (6.2 vs. 5.3 years, $p=0.679$)], laboratory parameters WBC (26.2 vs. $13.8 \times 10^9/L$, $p=0.826$), hemoglobin (70.5 vs. 76.0 g/L, $p=0.177$), platelets (56.0 vs. $43.0 \times 10^9/L$, $p=0.366$), immunophenotypes (T-ALL: 10.5% vs. 13.5%, $p=0.751$), risk stratification (high-risk: 39.5% vs. 40.5%, $p=0.907$), CNS involvement (10.5% vs. 2.7%, $p=0.358$), major fusion genes [BCR::ABL1 (7.9% vs. 13.5%, $p=0.431$)], treatment responses [day 15

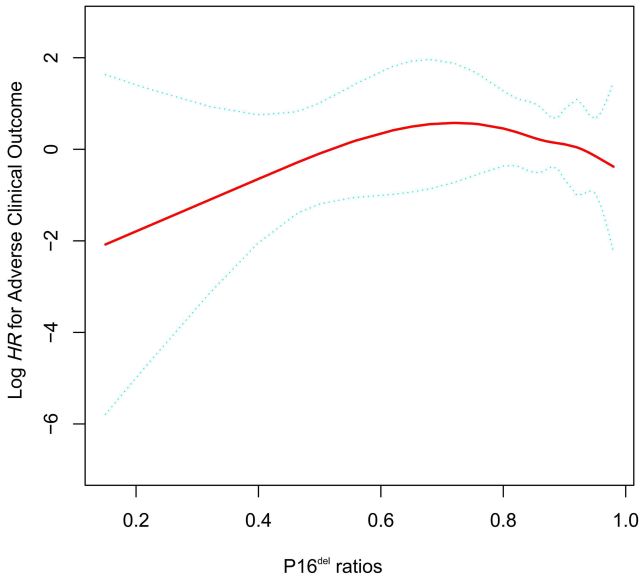


Figure 1 Restricted Cubic Spline of the Association of $PI6^{del}$ ratios With Risk of adverse clinical outcome. The resulting figures show the predicted log(relative risk) in the y-axis and the $PI6^{del}$ ratios in the x-axis.

Table 4 Characteristics of Patients with High or Low $PI6^{del}$ Ratio

Variable	Low Ratios (n=37)	High Ratios (n=38)	P value
Gender, n (%)			0.193
Male	24 (64.9%)	19 (50.0%)	
Female	13 (35.1%)	19 (50.0%)	
Age (y), median (range)	5.3 (1.1–13.8)	6.2 (1.1–14.8)	0.679
WBC, $\times 10^9$ /L, median (range)	13.8 (0.5–351.6)	26.2 (2.0–383.0)	0.826
Hemoglobin, g/L, median (range)	76.0 (24.0–125.0)	70.5 (36.0–131.0)	0.177
Platelets, $\times 10^9$ /L, median (range)	43.0 (4.0–358.0)	56.0 (7.0–266.0)	0.366
Immunophenotype (%)			0.751
Common B	24 (64.9%)	24 (63.2%)	
Pre-B	3 (8.1%)	6 (15.8%)	
Immature B	5 (13.5%)	4 (10.5%)	
T	5 (13.5%)	4 (10.5%)	
Karyotype (%)			0.038
Hypodiploid	1 (2.8%)	0 (0.0%)	
Normal	21 (58.3%)	13 (34.2%)	
Hyperdiploid With trisomies of chromosomes 4 and 10	7 (19.4%)	7 (18.4%)	
Hyperdiploid Without trisomies of chromosomes 4 and 10	0 (0.0%)	6 (15.8%)	
Others	7 (19.4%)	12 (31.6%)	
Risk group (%)			0.907
Standard risk	6 (16.2%)	5 (13.2%)	
Intermediate risk	16 (43.2%)	18 (47.4%)	
High risk	15 (40.5%)	15 (39.5%)	
CNSL (%)	1 (2.7%)	4 (10.5%)	0.358
Genetic fusion subtype (%)			
BCR::ABL	5 (13.5%)	3 (7.9%)	0.431
KMT2A-r	1 (2.7%)	0 (0.0%)	0.308
ETV6::RUNX1	3 (8.1%)	3 (7.9%)	0.973
E2A::PBX1	1 (2.7%)	1 (2.6%)	0.985
RAS mutation (%)	2 (5.4%)	8 (21.1%)	0.046
IKZF1 ^{del} (%)	5 (13.5%)	9 (23.7%)	0.258
Ph-like ALL (%)	5 (13.9%)	8 (21.1%)	0.418
Prednisone response (%)			0.431
PGR	32 (86.5%)	35 (92.1%)	
PPR	5 (13.5%)	3 (7.9%)	
D15 BM (%)			0.330
M1	29 (78.4%)	26 (68.4%)	
M2/M3	8 (21.6%)	12 (31.6%)	
D15 MRD positive (%)	19 (51.4%)	23 (60.5%)	0.424
D33 MRD positive (%)	6 (16.7%)	6 (15.8%)	0.919
SCT (%)	5 (13.5%)	4 (10.5%)	0.691
$PI6^{del}$ strata			0.206
Homozygous deletion	20 (54.1%)	15 (39.5%)	
Heterozygosity deletion	17 (45.9%)	23 (60.5%)	

Abbreviations: WBC, white blood cell counts; CNSL, central nervous system leukemia; PGR, prednisone good response; PPR, prednisone poor response; BM, bone marrow blast; MRD, minimal residual disease; SCT, stem cell transplantation.

marrow with M2/M3 status (31.6% vs. 21.6%, $p=0.330$), day 33 MRD⁺ (15.8% vs. 16.7%, $p=0.919$), or stem cell transplantation rates (10.5% vs. 13.5%, $p=0.691$). Notably, homozygous $PI6^{del}$ were less frequent in high-ratio patients (39.5% vs. 54.1%, $p=0.206$).

Survival Analysis

Kaplan–Meier survival analysis revealed that $P16^{del}$ was associated with significantly inferior outcomes in pediatric ALL. Patients harboring $P16^{del}$ exhibited markedly reduced 5-year RFS (RFS: 72.7% [95% CI: 62.1–85.1%] vs. 85.0% [95% CI: 80.6–89.7%], $p = 0.011$) and OS (OS: 85.1% [95% CI: 76.3–94.8%] vs. 94.1% [95% CI: 91.4–96.8%], $p = 0.034$) compared to those without $P16^{del}$ (Figure 2A and B). Molecular subtyping further indicated that patients with homozygous P16 deletion displayed survival rates comparable to those with heterozygous $P16^{del}$ (5-year RFS: 78.1% [95% CI: 64.5–94.1%] vs. 68.3% [95% CI: 53.4–87.5%], $p = 0.58$; OS: 83.4% [95% CI: 71.6–98.1%] vs. 86.8% [95% CI: 76.0–96.8%], $p = 0.71$) (Figure 2C and D).

Stratification of survival analysis based on the $P16^{del}$ ratio revealed significant prognostic disparities. Utilizing a threshold ratio of 0.8, as determined by piece-wise linear regression, patients were stratified into low $P16^{del}$ ratio (< 0.8 , $n = 37$) and high ($P16^{del}$ ratio ≥ 0.8 , $n = 38$) ratio groups. The 5-year recurrence-free survival (RFS) was significantly lower in the low-ratio group (57.7%; 95% CI, 42.1–79.1%) compared with the high-ratio group (88.5%; 95% CI, 78.5–99.8%) ($p = 0.025$; Figure 3A). Similarly, the 5-year OS was markedly worse in the low-ratio group (72.2%; 95% CI, 57.2–91.1%) than in the high-ratio group (94.7%; 95% CI, 87.7–100%) ($p = 0.047$; Figure 3B). These results indicate that a low $P16^{del}$ ratio (< 0.8) serves as a robust predictor of unfavorable clinical outcomes, associated with significantly reduced RFS and OS compared to a high $P16^{del}$ ratio (≥ 0.8).

Figure 4A–D illustrate the significant interaction between the $P16^{del}$ ratio level and early treatment response (D15 MRD) on survival outcomes. Stratified analysis revealed that within the low $P16^{del}$ ratio group, patients who were D15 MRD-positive experienced markedly inferior outcomes compared to those who were D15 MRD-negative. Specifically, the 5-year RFS declined from 72.7% (95% CI: 52.7–100.0%) in MRD-negative patients to 41.9% (95% CI: 22.5–77.9%) in MRD-positive patients ($p = 0.047$). Similarly, the 5-year OS decreased from 77.8% (95% CI: 58.4–100.0%) to 66.7% (95% CI: 46.1–96.6%) with positive (D15 MRD (Figure 4A and B). Conversely, within the high $P16^{del}$ ratio group, D15 MRD positivity had a much less pronounced impact on survival. High-ratio patients who were D15 MRD-positive maintained relatively favorable 5-year RFS [85.5% (95% CI: 71.5–100.0%)] and OS [91.1% (95% CI: 80.1–100.0%)], comparable to the excellent outcomes observed in D15 MRD-negative high-ratio patients [RFS: 93.3% (95% CI: 81.5–100.0%); OS: 100% (95% CI: 100–100.0%)] (Figure 4C and D). This demonstrates that the prognostic significance of early treatment response (D15 MRD status) critically depends on the $P16^{del}$ ratio level, with MRD positivity conferring a substantially worse prognosis only when combined with a low $P16^{del}$ ratio.

Figure 5A–D demonstrate that the prognostic impact of D33 MRD status is critically dependent on the $P16^{del}$ ratio level. Patients with a low $P16^{del}$ ratio who were D33 MRD-positive experienced extremely poor outcomes, with 5-year RFS plummeting to 27.8% and OS to 66.7%. In contrast, low-ratio patients achieving D33 MRD negativity had significantly better, albeit still modest, outcomes (5-year RFS: 64.5%; OS: 74.8%) (Figure 5A and B). Strikingly, patients with a high $P16^{del}$ ratio maintained excellent survival regardless of D33 MRD status: both D33 MRD-positive and -negative patients exhibited very high 5-year RFS (100% and 86.9%, respectively) and OS (100% and 93.8%, respectively) (Figure 5C and D). This highlights that while D33 MRD positivity signifies catastrophic risk in the context of a low $P16^{del}$ ratio, it confers no detrimental effect on survival for patients with a high $P16^{del}$ ratio, underscoring the $P16^{del}$ ratio as a crucial modifier for interpreting the risk associated with late treatment response.

Discussion

Over the past ten years, advancements in genome-wide analysis technologies, combined with the identification of leukemia-driving gene copy-number alterations (CNAs), have steadily illuminated the fundamental biology of pediatric ALL.^{10–12} Among the genes most frequently implicated by these alterations are $P16$ and these genes typically function as secondary collaborating lesions, exerting significant influence on cell cycle control mechanisms and modulating cellular sensitivity to chemotherapy.¹³

$P16^{del}$ represent the predominant copy-number lesion in pediatric acute ALL, and published reports indicate a prevalence of 20–25% in B-ALL.^{14,15} Consistent with this pattern, our cohort analysis revealed $P16^{del}$ frequencies of 18.2% (75/413) overall, with 18.1% observed in B-ALL, and with 35 cases (8.5%) exhibiting homozygous deletion and 40 cases (9.7%) exhibiting heterozygous deletion. Supporting findings from prior studies,^{6,7,13,14} $P16^{del}$ was linked to

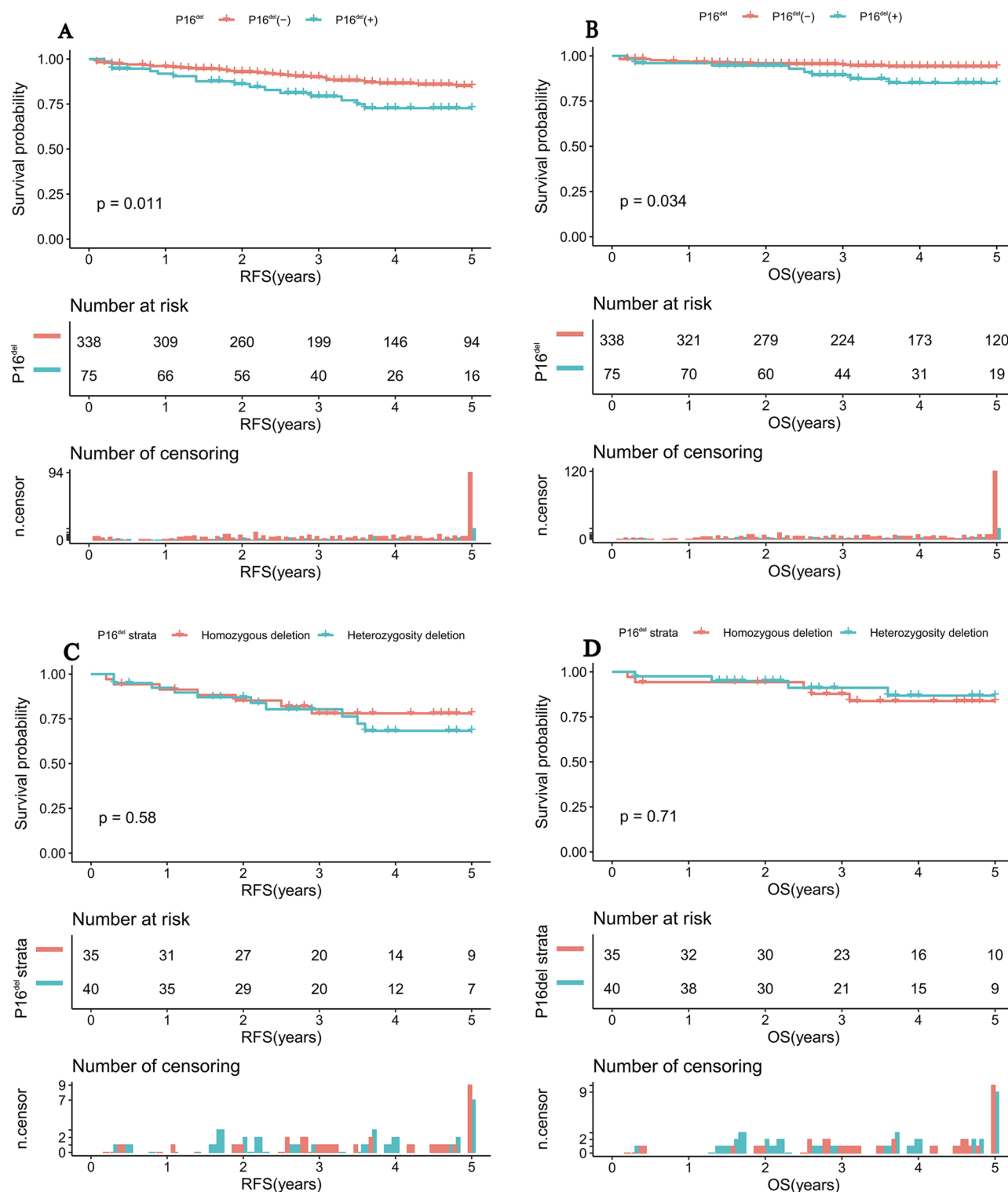


Figure 2 (A) The 5-year relapse-free survival of patients with or without $P16^{del}$. (B) The 5-year overall survival of patients with or without $P16^{del}$. (C) The 5-year relapse-free survival of patients with $P16$ homozygous deletion or heterozygous deletion. (D) The 5-year overall survival survival of patients with $P16$ homozygous deletion or heterozygous deletion.

adverse prognostic indicators, including elder age at diagnosis, higher initial WBC, and a marginal association with intermediate/high risk group assignment. Significantly, patients with this deletion also more frequently co-presented with the $IKZF1^{del}$ and less common with $ETV6::RUNX1$ fusion transcript.

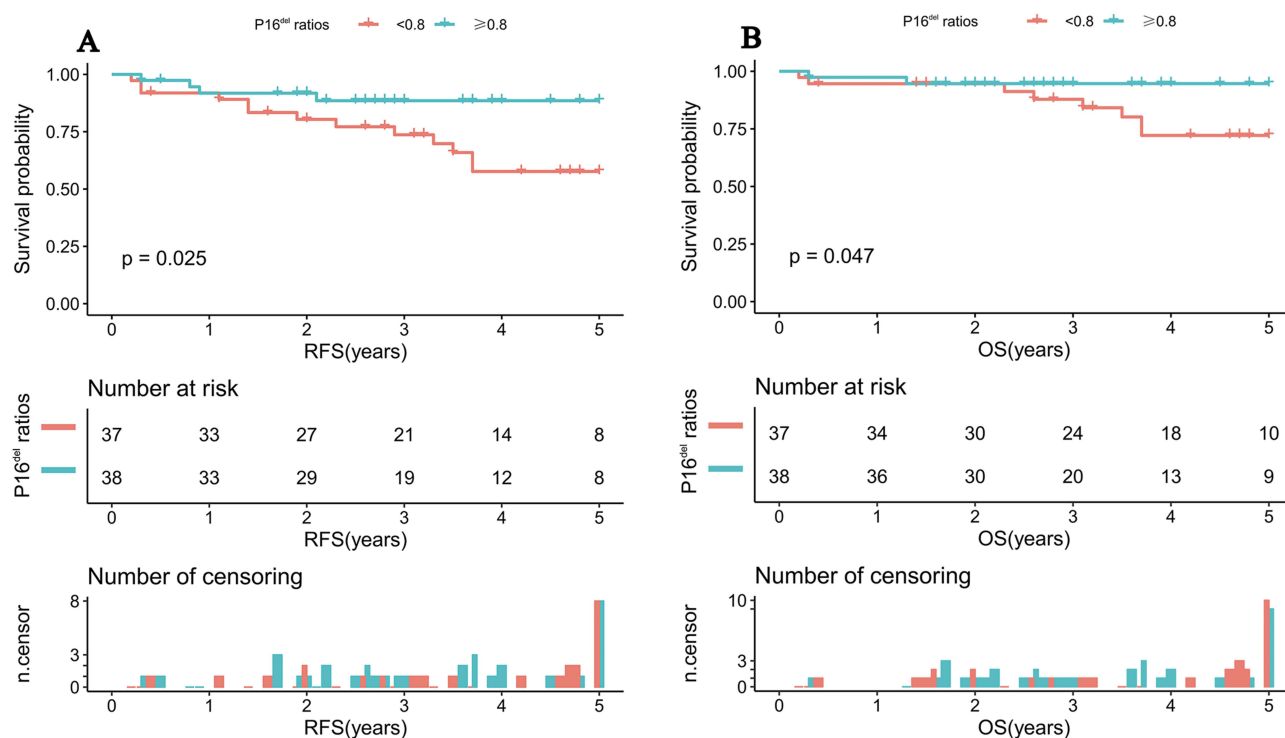


Figure 3 (A) The 5-year relapse-free survival for patients with different $P16^{del}$ ratio. **(B)** The 5-year overall survival for patients with different $P16^{del}$ ratio.

The prognostic impact of $P16^{del}$ in pediatric ALL remains debated.^{10–14,16–18} While numerous studies link these deletions to elevated relapse risk and poorer survival outcomes, conflicting evidence exists from Mirebeau et al,¹⁹ Kim et al,²⁰ and van Zutven et al,²¹ whose analyses in childhood ALL did not identify the deletion as an independent adverse prognostic marker. In contrast, our multivariate analysis revealed that $P16^{del}$ was an independent adverse prognostic factor for both RFS and OS. Furthermore, this present study showed that the 5-year RFS rate was 72.7% for patients harboring $P16^{del}$ versus 85% in the non- $P16^{del}$ group ($p=0.011$). Correspondingly, the 5-year OS was 85.1% among $P16^{del}$ cases compared to 94.1% in $P16^{del}$ -negative subset ($p=0.034$). The prognostic relevance of homozygous versus heterozygous deletion among $P16^{del}$ in pediatric ALL is a subject of ongoing investigation. While several studies indicate that any deletion (homozygous or heterozygous) predicts poorer outcomes, conflicting reports suggest heterozygous deletion may lack independent prognostic significance, especially in the context of co-occurring abnormalities.^{19–21} However, our study demonstrated that no association was found between homozygous or heterozygous $P16^{del}$ and survival outcome.

The major challenge in our study was to demonstrate $P16^{del}$ ratio prognostic significance among childhood ALL. Our finding that a low $P16^{del}$ ratio (<0.8) confers ultra-high risk aligns with observations in gliomas (Park et al²²), where subclonal deletions low thresholds predicted therapy resistance. However, the paradoxical protective effect of high $P16^{del}$ ratio (≥ 0.8) appears unique to ALL, potentially reflecting lineage-specific vulnerabilities to complete cell cycle checkpoint loss. To our knowledge, this is the first study to establish a quantitative threshold for P16 deletion ratio in pediatric ALL. Our data conclusively demonstrate that treating P16del as a binary variable—an approach that has fueled decades of contradictory literature—obscures fundamentally opposing biological behaviors contingent on quantitative deletion ratio.

By implementing piecewise linear regression and restricted cubic spline modeling, we uncovered a nonlinear dose-response relationship that traditional risk stratification had overlooked. Crucially, when $P16^{del}$ ratio falls below the 0.8 threshold, each incremental increase in the $P16^{del}$ ratio escalates relapse risk by 93% ($HR=1.93$; $p=0.031$), whereas beyond this inflection point, higher ratios associate with a 33% risk reduction ($HR=0.67$; $p=0.048$). This J-shaped curve fundamentally inverts conventional oncogene logic and suggests that low $P16^{del}$ ratio represents a genomically unstable, oligoclonal state where minor P16-intact subclones evade therapy through intrinsic chemoresistance or adaptive plasticity, while high ratio reflects a homogeneous, “all-in” genomic configuration where near-complete $P16^{del}$ creates lethal vulnerabilities to cytotoxic

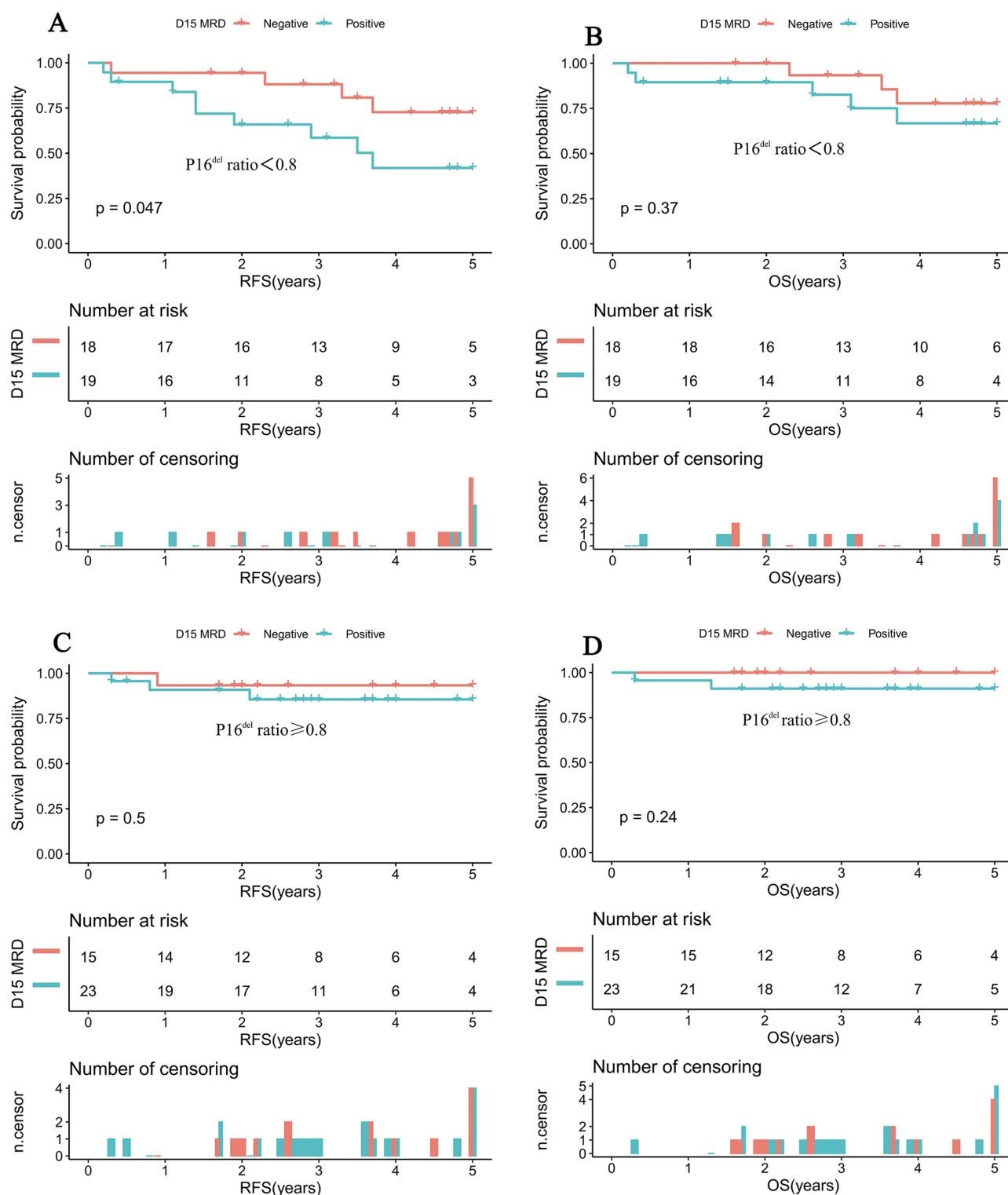


Figure 4 (A) The 5-year relapse-free survival for patients with different D15 MRD status among low $P16^{del}$ ratio. (B) The 5-year overall survival for patients with different D15 MRD status among low $P16^{del}$ ratio. (C) The 5-year relapse-free survival for patients with different D15 MRD status among high $P16^{del}$ ratio. (D) The 5-year overall survival for patients with different D15 MRD status among high $P16^{del}$ ratio.

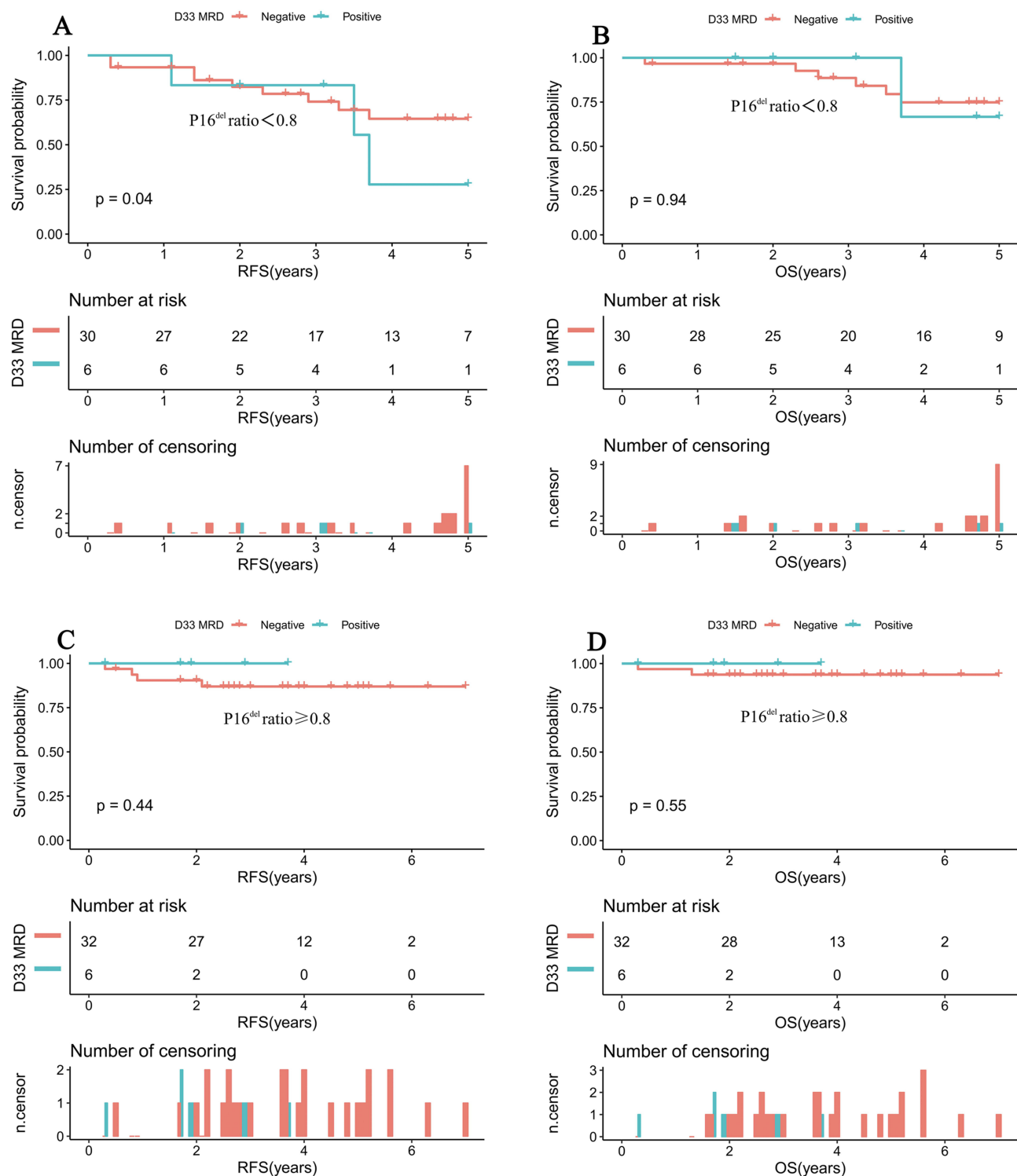


Figure 5 (A) The 5-year relapse-free survival for patients with different D33 MRD status among low $P16^{del}$ ratio. (B) The 5-year overall survival for patients with different D33 MRD status among low $P16^{del}$ ratio. (C) The 5-year relapse-free survival for patients with different D33 MRD status among high $P16^{del}$ ratio. (D) The 5-year overall survival for patients with different D33 MRD status among high $P16^{del}$ ratio.

therapy or oncogene-induced apoptosis.²³ The stark survival contrast between these subgroups is unprecedented: low-ratio patients suffered a 5-year RFS of only 57.7%—worse than many high-risk genetic subtypes (eg, BCR::ABL1 ALL)—while high-ratio patients achieved 88.5% RFS, rivaling non- $P16^{del}$ outcomes (85.0%). This bifurcation explains why prior studies

pooling all $P16^{del}$ patients yielded inconsistent results. While our cohort is prospective, multicenter validation is needed to confirm the generalizability of the 0.8 threshold.

The diametric outcomes of low- vs. High ratio subgroups demand mechanistic explanations, and our findings suggest that the economic milieu surrounding $P16^{del}$ dictates functional consequences. Low-Ratio “Escape Phenotype” (<0.8): The significantly higher frequency of IKZF1^{del} (18.7% vs. 8.9%, $p=0.013$) and trend toward hyperdiploidy without favorable trisomies indicate co-selection for cooperating lesions that enable clonal persistence. We posit that minor P16-intact subclones—undetectable by bulk FISH—harbor stem-like properties, metabolic adaptations, or drug-efflux mechanisms that drive relapse. Supporting this, low-ratio patients exhibited catastrophic outcomes when MRD persisted (D33 MRD⁺: 5-year RFS=27.8%), reflecting the lethal synergy between clonal heterogeneity and chemoresistance. High-Ratio “Vulnerable Phenotype”: Enrichment of RAS mutations (21.1% vs. 5.4%, $p=0.046$) and hyperdiploidy lacking trisomies 4/10 (15.8% vs. 0%, $p=0.038$) might suggest oncogene-induced apoptosis susceptibility. $P16^{del}$ combined with RAS activation may induce replicative stress, overwhelming DNA repair capacity in genomically unstable cells. This creates a “synthetic lethal” state where chemotherapy-triggered DNA damage becomes irreparable—explaining why high-ratio patients maintained near-normal survival even with MRD positivity.^{24–26} The biological mechanisms underlying the ratio’s effect require further investigation, and clinical application should await prospective multicenter validation.

The P16 deletion ratio may provide incremental prognostic value beyond conventional risk factors like MRD, potentially refining intermediate-risk stratification. However, validation is required before clinical implementation. In addition, MRD positivity carries opposing prognoses based on $P16^{del}$ ratio: Low ratio with D33 MRD⁺ signals a medical emergency requiring urgent CAR-T/linatumomab/transplant, while high ratio with D33 MRD⁺ might be a biologic false alarm where standard therapy suffices. This might help to resolve the “intermediate-risk” MRD+ management dilemma.

While transformative, our study has constraints requiring future attention. Firstly, this study has a single-center design, and FISH-based quantification may have inherent variability; thus, findings should be validated in multicenter cohorts. Secondly, biological understanding requires validating the mechanistic links between $P16^{del}$ ratio, RAS mutations, and apoptotic priming in PDX models. Thirdly, this study was a post-hoc design, potential model overfitting despite adjustments, single-center cohort, and lack of external validation. Future multicenter studies are needed to confirm the P16 ratio threshold.

Conclusion

Our data compel the P16 deletion ratio demonstrates a significant prognostic association in pediatric ALL, and shows promise as a prognostic tool, but its clinical utility must be validated in larger, diverse cohorts before implementation.

Data Sharing Statement

The data in the current study are available from the Professor Dun-Hua Zhou on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted according to Declaration of Helsinki principles and approved by the Institutional Review Board of Sun Yat-sen Memorial Hospital (Approval No. 2020-KY-004). Written informed consent was obtained from all patients’ guardians. The trial is registered with the Chinese Clinical Trial Registry (Chi-CTR; <https://www.chictr.org.cn/>; number ChiCTR2000030357).

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Author Contributions

Kun-Yin Qiu, Xiong-Yu Liao, Hai-Lei Chen, and Hong Zheng are co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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