Age-specific mutation profiles and their prognostic implications in pediatric *KMT2A*-rearranged acute myeloid leukemia

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Received: June 15, 2025.
Accepted: October 16, 2025.
Early view: October 23, 2025.

https://doi.org/10.3324/haematol.2025.288481

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Supplementary Information

Supplementary Methods

Targeted sequencing

Samples from the AML-12 study were subjected to targeted sequencing of 507 genes. The target genes were selected based on the following criteria: (1) established driver genes in myeloid malignancies and other malignant neoplasms; (2) relevance to myeloid malignancies; (3) previously detected mutations in whole-exome sequencing studies; and (4) potential therapeutic targets.

Target enrichment was conducted using a SureSelect custom kit (Agilent, Santa Clara, CA, USA) designed to capture all coding exons of the 507 genes. Massively parallel sequencing of the captured targets was conducted on a HiSeq 2000/2500 system (Illumina, San Diego, CA, USA) with paired-end 126-133 bp reads, following the manufacturer's instructions.

Sequencing reads were aligned to the human genome (hg19) using Burrows-Wheeler Aligner (BWA)-mem version 0.5.8 with default parameters. BWA v0.7.12-r1039 (with default parameters and a -mem option; https://github.com/lh3/bwa) and VarScan2 [1] v2.3 (with default parameters and -min-var-freq 0.05 -min-coverage 5 -min-reads2 5 -min-avg-qual 15 -p-value 0.01) were used to detect single-nucleotide variants (SNVs) and small indels.

Variants were retained if they met all of the following criteria: (i) mapping quality score ≥ 40; (ii) base quality score ≥ 20; (iii) < 5 SNVs on the same read; (iv) < 2 indels on the same read; (v) total read count ≥ 10; (vi) variant read count ≥ 5; and (vii) variant allele frequency (VAF) ≥ 0.05. Variants were excluded if they were: (i) synonymous or annotated as "unknown" by ANNOVAR; (ii) listed in dbSNP138, ESP6500, or the 1000 Genomes Project (as of October 2014); (iii) present only in unidirectional reads; (iv) detected in 12 unrelated germline samples with mean VAF <0.01; or (v) missense SNVs with a VAF of 0.4-0.6 unless recorded as somatic mutations in hematopoietic or lymphoid tissue in the Catalogue of Somatic Mutations in Cancer (v90). Finally, an in-house pipeline retained only gene variants associated with hematologic malignancies, and potential sequencing or mapping artifacts were manually reviewed using Integrative Genome Viewer.

[1] Koboldt DC, Zhang Q, Larson DE, et al. VarScan 2: somatic mutation and copy number alteration discovery in cancer by exome sequencing. Genome Res. 2012;22(3):568–576.

Supplementary Table 1. Clinical characteristics of *KMT2A*-r AML in each cohort

	JCCG (Japan Children's Cancer Group)												TARGET AML cohort			
	AML99				AML-05				AML-12							
Description	**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**		**Infants (<1 year)**		**Children (≥1 year)**	
Number	1		10		14		44		15		43		29		83	
Percentage	9.1%		90.9%		24.1%		75.9%		25.9%		74.1%		25.9%		74.1%	
Sex																
Male	1	(100.0%)	9	(90.0%)	6	(42.9%)	19	(43.2%)	10	(66.7%)	16	(37.2%)	13	(44.8%)	40	(48.2%)
Female	0	(0.0%)	1	(10.0%)	8	(57.1%)	25	(56.8%)	5	(33.3%)	27	(62.8%)	16	(55.2%)	43	(51.8%)
Age (year)																
Median	0.47		2.7		0.58		6.4		0.58		4.4		0.63		8.5	
Range			1.0 – 13.5		0.00 – 0.92		1.0 – 15.1		0.17 – 0.92		1.0 – 15.8		0.15 – 0.97		1.1 – 18.2	
WBC (×10^9/L)																
Median	11.5		30.6		33.4		22.5		49.5		9.0		32.7		33.5	
Range			2.1 – 224		5.4 – 152		1.1 – 459		1.5 – 726		1.2 – 376		3.4 – 519		1.3 – 610	
FAB																
M0	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(3.4%)	2	(2.4%)
M1	0	(0.0%)	1	(10.0%)	0	(0.0%)	4	(9.1%)	0	(0.0%)	3	(7.0%)	0	(0.0%)	3	(3.6%)
M2	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	1	(6.7%)	3	(7.0%)	0	(0.0%)	2	(2.4%)
M3	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
M4	0	(0.0%)	2	(20.0%)	3	(21.4%)	11	(25.0%)	2	(13.3%)	2	(4.7%)	4	(13.8%)	12	(14.5%)
M5	1	(100.0%)	7	(70.0%)	9	(64.3%)	25	(56.8%)	12	(80.0%)	31	(72.1%)	22	(75.9%)	50	(60.2%)
M6	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
M7	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.7%)	0	(0.0%)	1	(1.2%)
NOS	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(2.4%)
RAEB-T	0	(0.0%)	0	(0.0%)	0	(0.0%)	2	(4.5%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Unknown	0	(0.0%)	0	(0.0%)	2	(14.3%)	1	(2.3%)	0	(0.0%)	2	(4.7%)	2	(6.9%)	11	(13.3%)
***KMT2A* rearrangement**																
KMT2A::*MLLT3*	1	(100.0%)	5	(50.0%)	4	(28.6%)	23	(52.3%)	4	(26.7%)	20	(46.5%)	7	(24.1%)	31	(37.3%)
KMT2A::*MLLT10*	0	(0.0%)	1	(10.0%)	3	(21.4%)	8	(18.2%)	2	(13.3%)	12	(27.9%)	8	(27.6%)	18	(21.7%)
KMT2A::*ELL*	0	(0.0%)	1	(10.0%)	5	(35.7%)	5	(11.4%)	2	(13.3%)	1	(2.3%)	3	(10.3%)	10	(12.0%)
KMT2A::*MLLT4*	0	(0.0%)	2	(20.0%)	0	(0.0%)	3	(6.8%)	0	(0.0%)	3	(7.0%)	0	(0.0%)	9	(10.8%)
KMT2A::*MLLT1*	0	(0.0%)	0	(0.0%)	1	(7.1%)	4	(9.1%)	1	(6.7%)	3	(7.0%)	1	(3.4%)	5	(6.0%)
Other *KMT2A* fusions	0	(0.0%)	1	(10.0%)	1	(7.1%)	1	(2.3%)	6	(40.0%)	4	(9.3%)	10	(34.5%)	10	(12.0%)
***FLT3*-ITD**	1	(100.0%)	0	(0.0%)	0	(0.0%)	3	(6.8%)	0	(0.0%)	1	(2.3%)	0	(0.0%)	3	(3.6%)
***KRAS* mutations**	0	(0.0%)	5	(50.0%)	2	(14.3%)	8	(18.2%)	1	(6.7%)	9	(20.9%)	9	(31.0%)	25	(30.1%)
KRAS G12 mutaions	0	(0.0%)	2	(20.0%)	1	(7.1%)	5	(11.4%)	0	(0.0%)	1	(2.3%)	1	(3.4%)	8	(9.6%)
KRAS G13 mutaions	0	(0.0%)	3	(30.0%)	1	(7.1%)	2	(4.5%)	0	(0.0%)	6	(14.0%)	5	(17.2%)	7	(8.4%)
KRAS G12&G13 mutations	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	0	(0.0%)	0	(0.0%)
Other *KRAS* mutations	0	(0.0%)	0	(0.0%)	0	(0.0%)	1	(2.3%)	1	(6.7%)	1	(2.3%)	3	(10.3%)	10	(12.0%)

Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.

Supplementary Table 2. Clinical characteristics of *KMT2A*-r AML

Description	Infants (<1 year)		Children (≥1 year)		*P* value
Number	59		180		
Percentage	24.7%		75.3%		
Sex					
Male	30	(50.8%)	84	(46.7%)	0.65
Female	29	(49.2%)	96	(53.3%)	
Age (year)					
Median	0.58		6.6		
Range	0.0 – 0.97		1.0 – 18.2		
WBC ($\times 10^9$/L)					
Median	38.1		24.9		0.058
Range	1.5 – 726		1.1 – 610		
FAB					
M0	1	(1.7%)	2	(1.1%)	0.57
M1	0	(0.0%)	11	(6.1%)	0.070
M2	1	(1.7%)	6	(3.3%)	1.00
M3	0	(0.0%)	0	(0.0%)	1.00
M4	9	(15.3%)	27	(15.0%)	1.00
M5	44	(74.6%)	113	(62.8%)	0.11
M6	0	(0.0%)	0	(0.0%)	1.00
M7	0	(0.0%)	3	(1.7%)	1.00
NOS	0	(0.0%)	2	(1.1%)	1.00
RAEB-T	0	(0.0%)	2	(1.1%)	1.00
Unknown	4	(6.8%)	14	(7.8%)	1.00
***KMT2A* rearrangement**					
KMT2A::*MLLT3*	16	(27.1%)	79	(43.9%)	0.031 *
KMT2A::*MLLT10*	13	(22.0%)	39	(21.7%)	1.00
KMT2A::*ELL*	10	(16.9%)	17	(9.4%)	0.15
KMT2A::*MLLT4*	0	(0.0%)	17	(9.4%)	0.0085 **
KMT2A::*MLLT1*	3	(5.1%)	12	(6.7%)	1.00
Other *KMT2A* fusions	17	(28.8%)	16	(8.9%)	< 0.001 ***
***FLT3*-ITD**	1	(1.7%)	7	(3.9%)	0.68
***KRAS* mutations**	12	(20.3%)	47	(26.1%)	0.49
KRAS G12 mutations	2	(3.4%)	16	(8.9%)	0.25
KRAS G13 mutations	6	(10.2%)	18	(10.0%)	1.00
KRAS G12&G13 mutations	0	(0.0%)	1	(0.6%)	1.00
Other *KRAS* mutations	4	(6.8%)	12	(6.7%)	1.00

Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Supplementary Table 3. Clinical characteristics of non-*KMT2A*-r AML

Description	Infants (<1 year)		Children (≥1 year)		*P* value
Number	13		525		
Percentage	2.4%		97.6%		
Sex					
Male	8	(61.5%)	272	(51.8%)	0.58
Female	5	(38.5%)	253	(48.2%)	
Age (year)					
Median	0.73		11.8		
Range	0.21 – 0.98		1.0 – 19.0		
WBC ($\times 10^9$/L)					
Median	115		34.2		0.019 *
Range	10.8 – 310		0.2 – 473		
FAB					
M0	3	(23.1%)	11	(2.1%)	0.0035 **
M1	0	(0.0%)	73	(13.9%)	0.23
M2	0	(0.0%)	148	(28.2%)	0.024 *
M3	0	(0.0%)	2	(0.4%)	1.00
M4	3	(23.1%)	131	(25.0%)	1.00
M5	2	(15.4%)	43	(8.2%)	0.30
M6	0	(0.0%)	8	(1.5%)	1.00
M7	1	(7.7%)	13	(2.5%)	0.29
NOS	0	(0.0%)	29	(5.5%)	1.00
RAEB-T	0	(0.0%)	0	(0.0%)	1.00
Unknown	4	(30.8%)	67	(12.8%)	0.079
Cytogenetic Abnormalities					
CBFB::*MYH11*	4	(30.8%)	88	(16.8%)	0.25
RUNX1::*RUNXT1*	0	(0.0%)	100	(19.0%)	0.14
Normal Karyotype	4	(30.8%)	155	(29.5%)	1.00
Other Cytogenetics	5	(38.5%)	182	(34.7%)	0.77
***FLT3*-ITD**	0	(0.0%)	119	(22.7%)	0.082

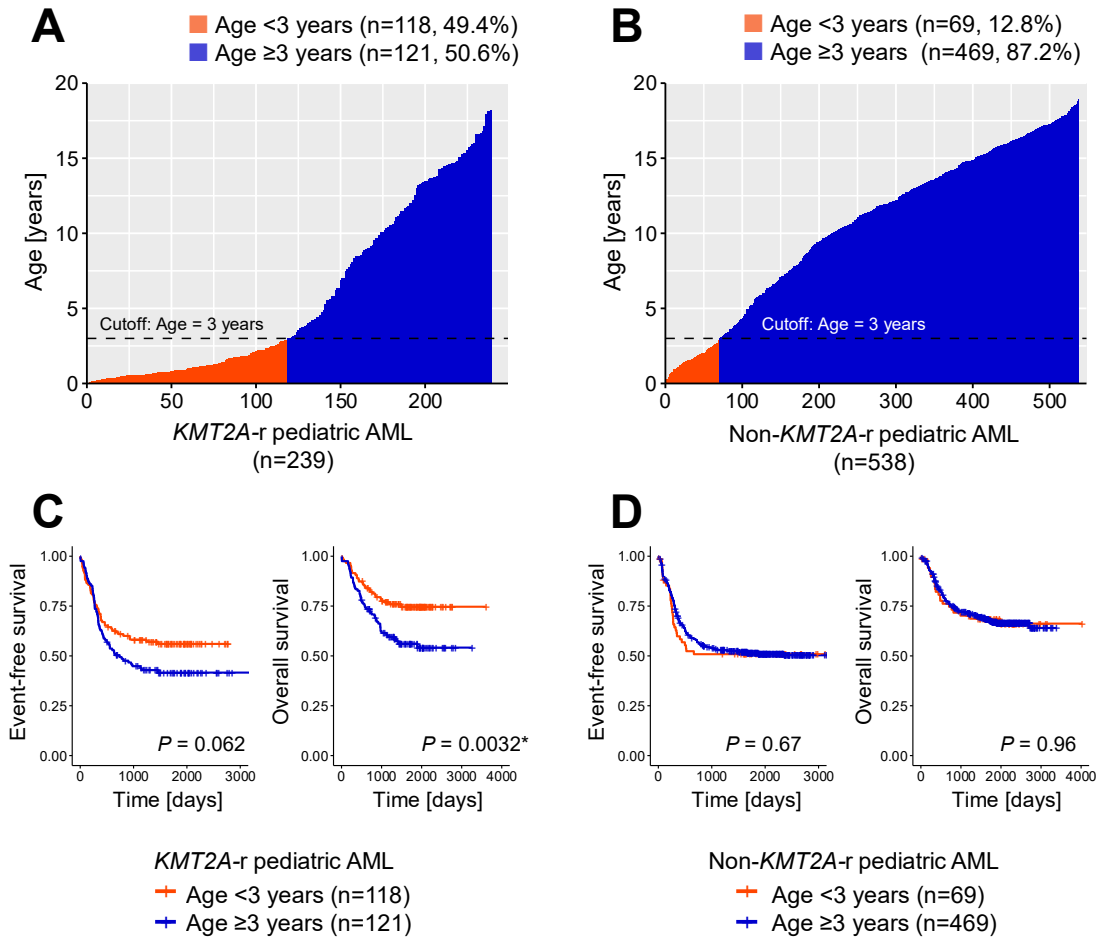
Abbreviations: WBC, white blood cells; FAB, French-American-British classification; NOS, not otherwise specified; *FLT3*-ITD, *FLT3* internal tandem duplications.
*$P < 0.05$; **$P < 0.01$

Supplementary Table 4. Results of multivariate analysis for event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML

	EFS			OS		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Age (+1 year)	1.04	1.00 – 1.08	0.044 *	1.07	1.03 – 1.12	0.0013 **
WBC (+10^4/μL)	1.02	1.00 – 1.03	0.049 *	1.02	1.00 – 1.04	0.030 *
KMT2A ::*MLLT3*	0.75	0.40 – 1.43	0.39	0.95	0.40 – 2.25	0.91
KMT2A ::*MLLT10*	1.55	0.80 – 2.98	0.19	2.01	0.83 – 4.88	0.12
KMT2A ::*ELL*	1.01	0.46 – 2.21	0.98	1.62	0.60 – 4.39	0.34
KMT2A ::*MLLT4*	2.30	1.02 – 5.17	0.044 *	2.57	0.95 – 6.93	0.062
KMT2A ::*MLLT1*	1.19	0.48 – 2.93	0.71	0.75	0.21 – 2.64	0.65
Other *KMT2A* fusions	1.44	0.80 – 2.59	0.23	2.51	1.19 – 5.29	0.015 *
Non-signaling mutations	0.89	0.53 – 1.47	0.64	0.62	0.31 – 1.24	0.18
KRAS G12 mutations	2.23	1.29 – 3.86	0.0043 **	2.17	1.15 – 4.11	0.017 *
KRAS G13 mutations	1.18	0.65 – 2.14	0.58	1.66	0.83 – 3.32	0.15
Other *KRAS* mutations	1.51	0.74 – 3.06	0.26	0.80	0.27 – 2.35	0.69
FLT3-ITD	1.76	0.67 – 4.60	0.25	2.56	0.84 – 7.86	0.10

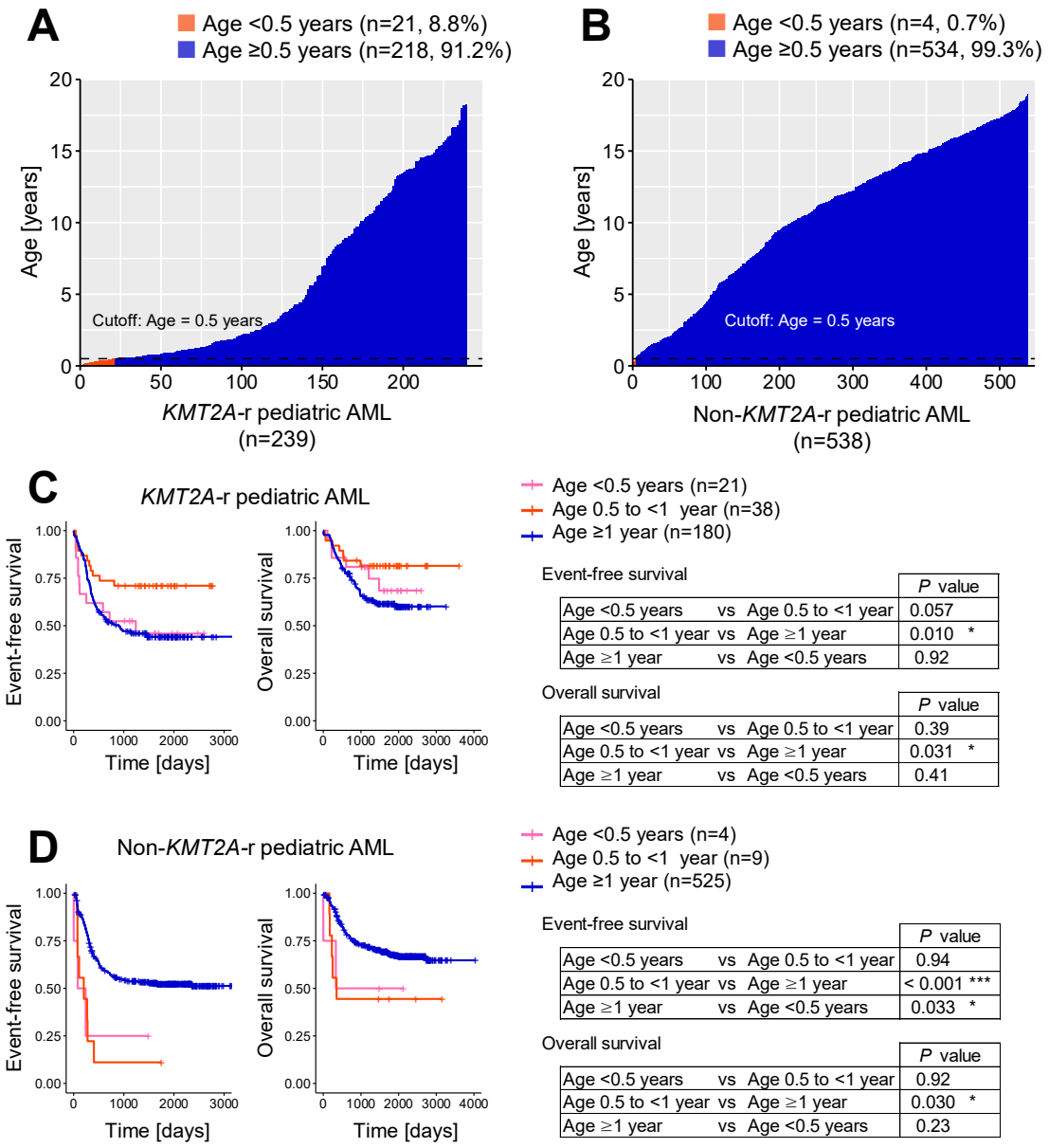
Abbreviations: CI, confidence interval; WBC, white blood cells; *FLT3*-ITD, *FLT3* internal tandem duplications.
*$P < 0.05$; **$P < 0.01$

Supplementary Figure 1. Comparison of *KMT2A*-r and non-*KMT2A*-r AML cases (Cutoff: Age = 3 years)



(A, B) Age distribution of *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML cases (n = 538). Patients divided by age groups using a cutoff at 3 years (<3 years vs. ≥3 years). **(C)** Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the age group (<3 years vs. ≥3 years). **(D)** EFS and OS in non-*KMT2A*-r AML based on the age group (<3 years vs. ≥3 years).
***P* < 0.01

Supplementary Figure 2. Comparison of *KMT2A*-r and non-*KMT2A*-r AML cases (Cutoff: Age = 0.5 years)



Event-free survival

			P value	
Age <0.5 years	vs	Age 0.5 to <1 year	0.057	
Age 0.5 to <1 year	vs	Age ≥1 year	0.010	*
Age ≥1 year	vs	Age <0.5 years	0.92	

Overall survival

			P value	
Age <0.5 years	vs	Age 0.5 to <1 year	0.39	
Age 0.5 to <1 year	vs	Age ≥1 year	0.031	*
Age ≥1 year	vs	Age <0.5 years	0.41	

Event-free survival

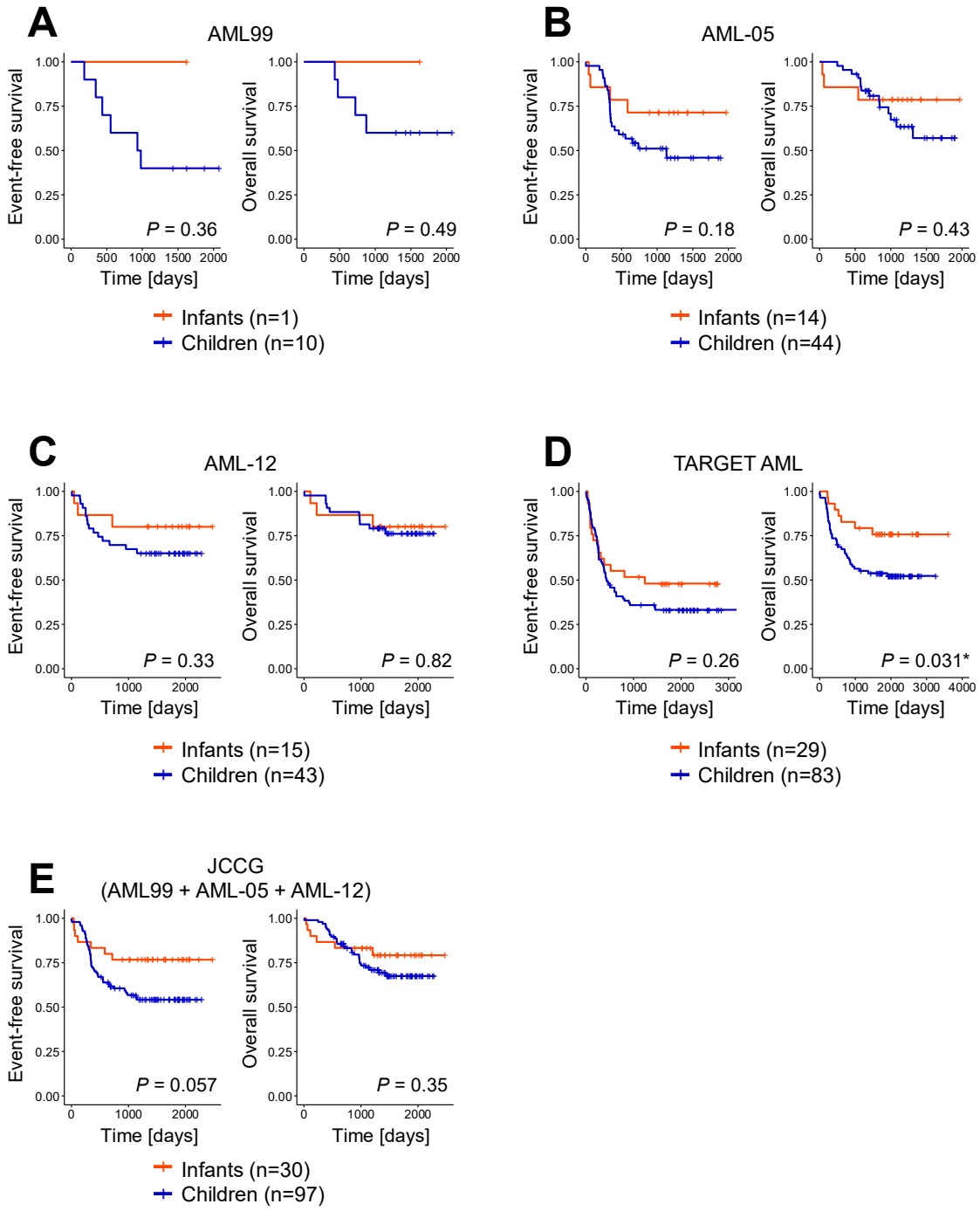
			P value	
Age <0.5 years	vs	Age 0.5 to <1 year	0.94	
Age 0.5 to <1 year	vs	Age ≥1 year	< 0.001	***
Age ≥1 year	vs	Age <0.5 years	0.033	*

Overall survival

			P value	
Age <0.5 years	vs	Age 0.5 to <1 year	0.92	
Age 0.5 to <1 year	vs	Age ≥1 year	0.030	*
Age ≥1 year	vs	Age <0.5 years	0.23	

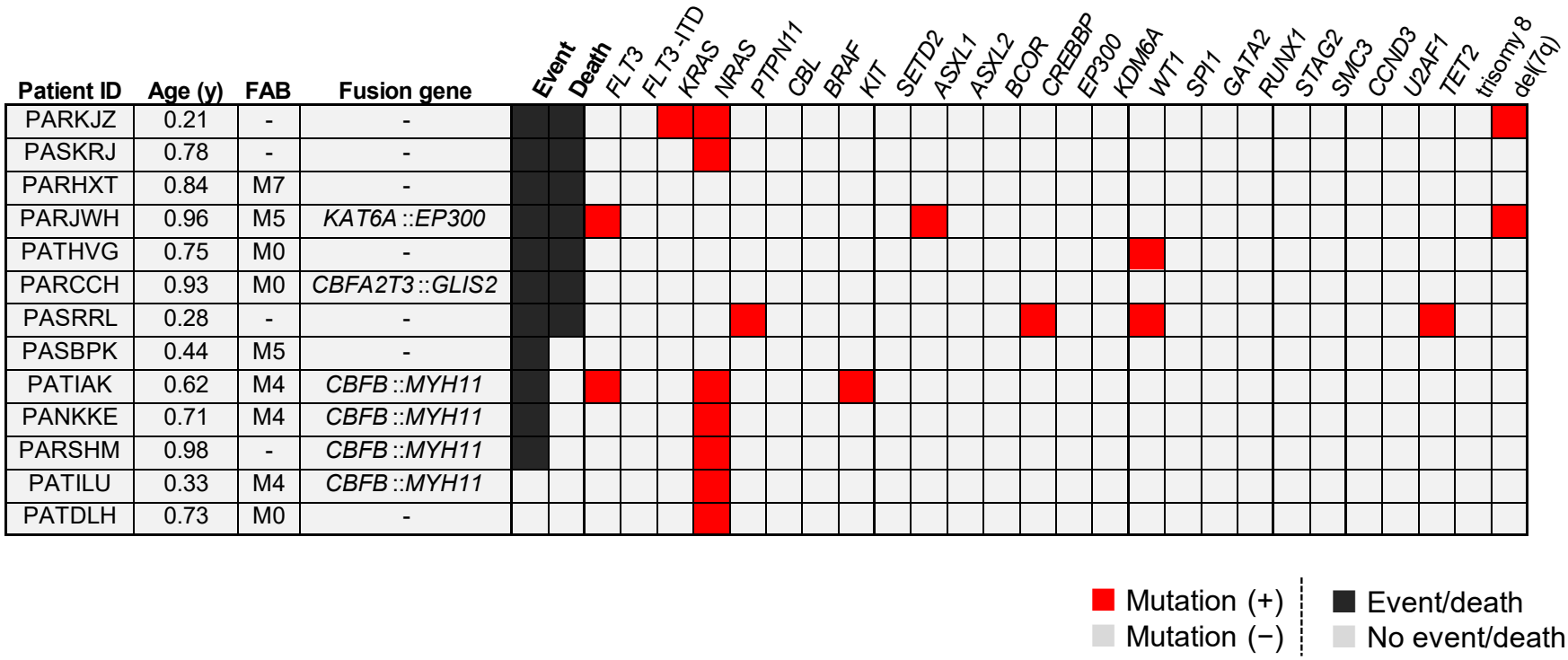
(A, B) Age distribution of *KMT2A*-r AML (n = 239) and non-*KMT2A*-r AML cases (n = 538). Patients divided by age groups using a cutoff at 0.5 years (<0.5 years vs. ≥0.5 years). **(C)** Event-free survival (EFS) and overall survival (OS) in *KMT2A*-r AML based on the age group (<0.5 years, 0.5 to <1 year and ≥1 year). **(D)** EFS and OS in non-*KMT2A*-r AML based on the age group (<0.5 years, 0.5 to <1 year and ≥1 year). Pairwise log-rank test results are shown in both C and D.
*$P < 0.05$; ***$P < 0.001$

Supplementary Figure 3. Comparison of prognosis between infants and children in each cohort



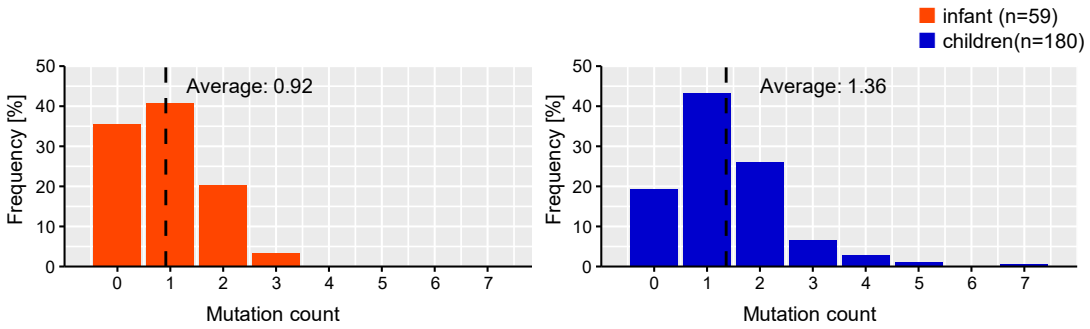
Event-free survival (EFS) and overall survival (OS) between infants and children in *KMT2A*-r AML, stratified by cohorts. Analyses were conducted in the following order: **(A)** AML99, **(B)** AML-05, **(C)** AML-12, **(D)** TARGET AML cohort, and **(E)** Japan Children's Cancer Group (JCCG; AML99 + AML-05 + AML-12).
*$P < 0.05$

Supplementary Figure 4. Clinical and genetic characteristics of infants with non-*KMT2A*-rearranged AML



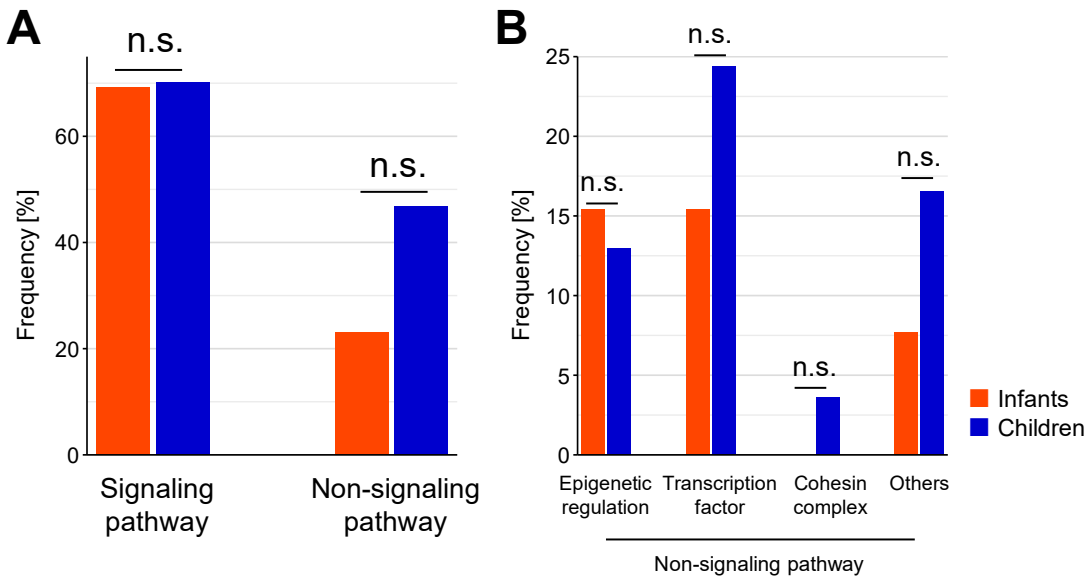
Overview of the patient characteristics and gene mutation landscape in infants and children with non-*KMT2A*-r AML.
Abbreviations: FAB, French-American-British classification; *FLT3*-ITD, *FLT3* internal tandem duplications.

Supplementary Figure 5. Comparison of mutation counts between infants and children with *KMT2A*-r AML



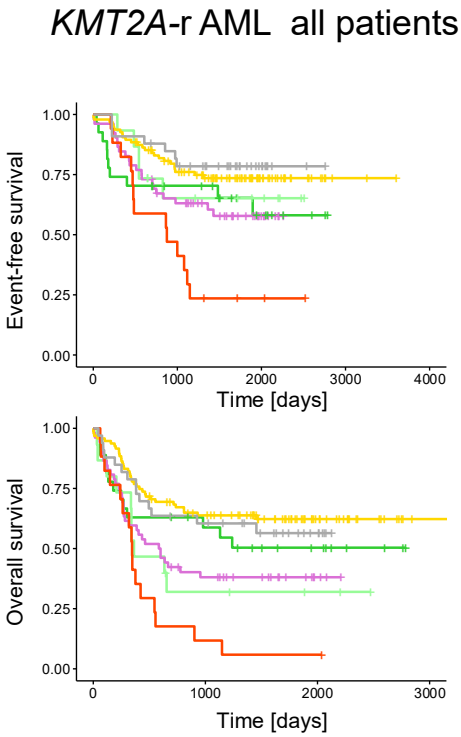
Number of mutated genes between infants and children were compared. Genes with at least one detected mutation are mutation-positive genes, and the number of mutation-positive genes is used as the x-axis. The number of mutation-positive genes per patient was calculated, and the relative frequency was visualized for infants and children, and the dashed line represents the mean value.

Supplementary Figure 6. Comparison of gene mutations in infants and children with non-*KMT2A*-r AML



Comparison of positive mutation rates classified by function between infants and children with non-*KMT2A*-r AML.

Supplementary Figure 7. Comparison of prognosis according to *KMT2A* rearrangement patterns



P values (Event-free survival)

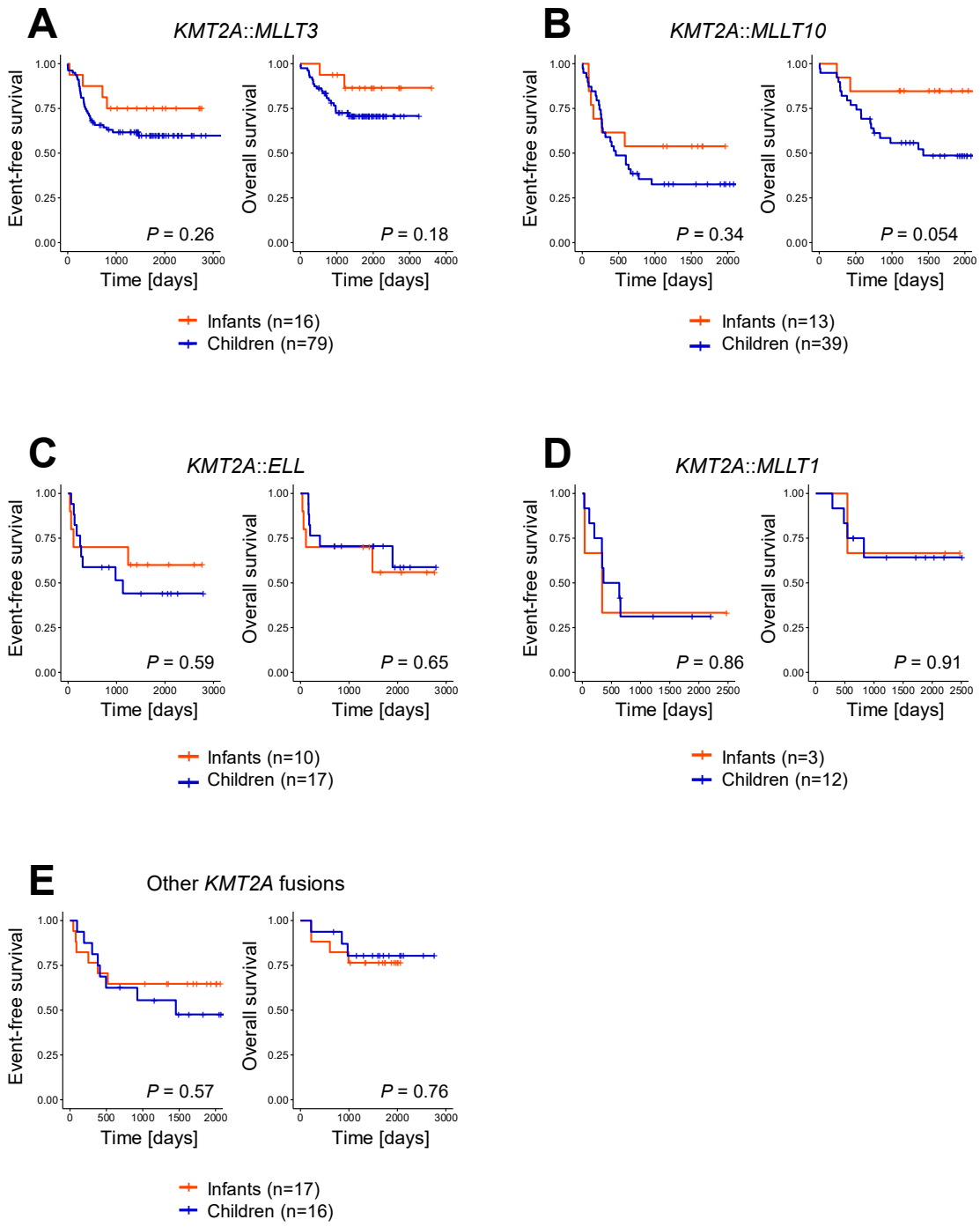
	MLLT3	*MLLT10*	*ELL*	*MLLT4*	*MLLT1*
MLLT10	0.0092 **				
ELL	0.32	0.37			
MLLT4	< 0.001 ***	0.062	0.020 *		
MLLT1	0.037 *	0.73	0.38	0.29	
Others	0.63	0.15	0.63	0.0014 **	0.15

P values (Overall survival)

	MLLT3	*MLLT10*	*ELL*	*MLLT4*	*MLLT1*
MLLT10	0.13				
ELL	0.25	0.96			
MLLT4	< 0.001 ***	0.10	0.13		
MLLT1	0.61	0.71	0.71	0.13	
Others	0.71	0.14	0.23	0.0013 **	0.45

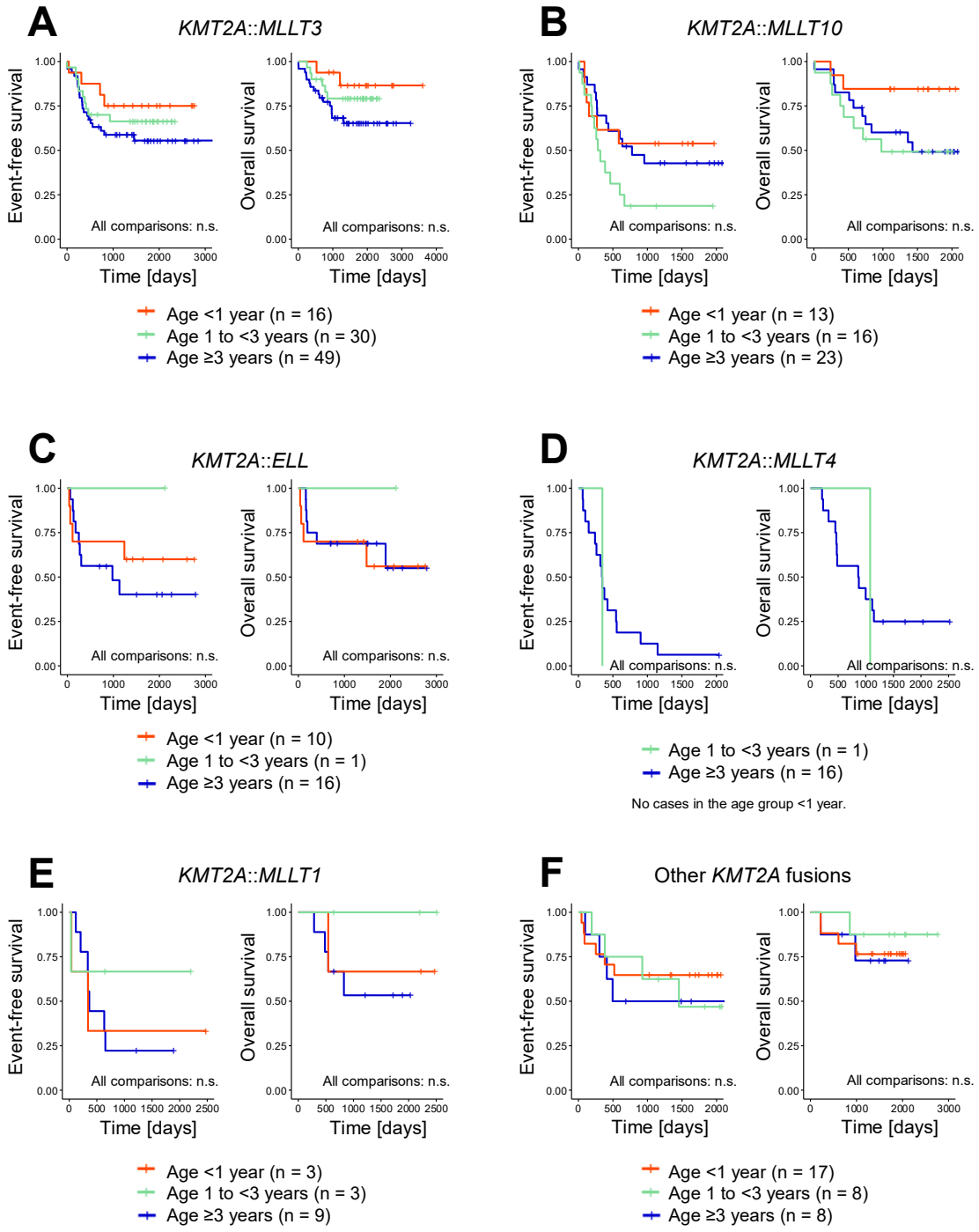
Event-free survival (EFS) and overall survival (OS) according to *KMT2A* rearrangement patterns in patients with *KMT2A*-r AML. The result of pair wised log-rank test is also presented.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Supplementary Figure 8. Comparison of the impact of the *KMT2A* fusion pattern on prognosis in infants and children with AML



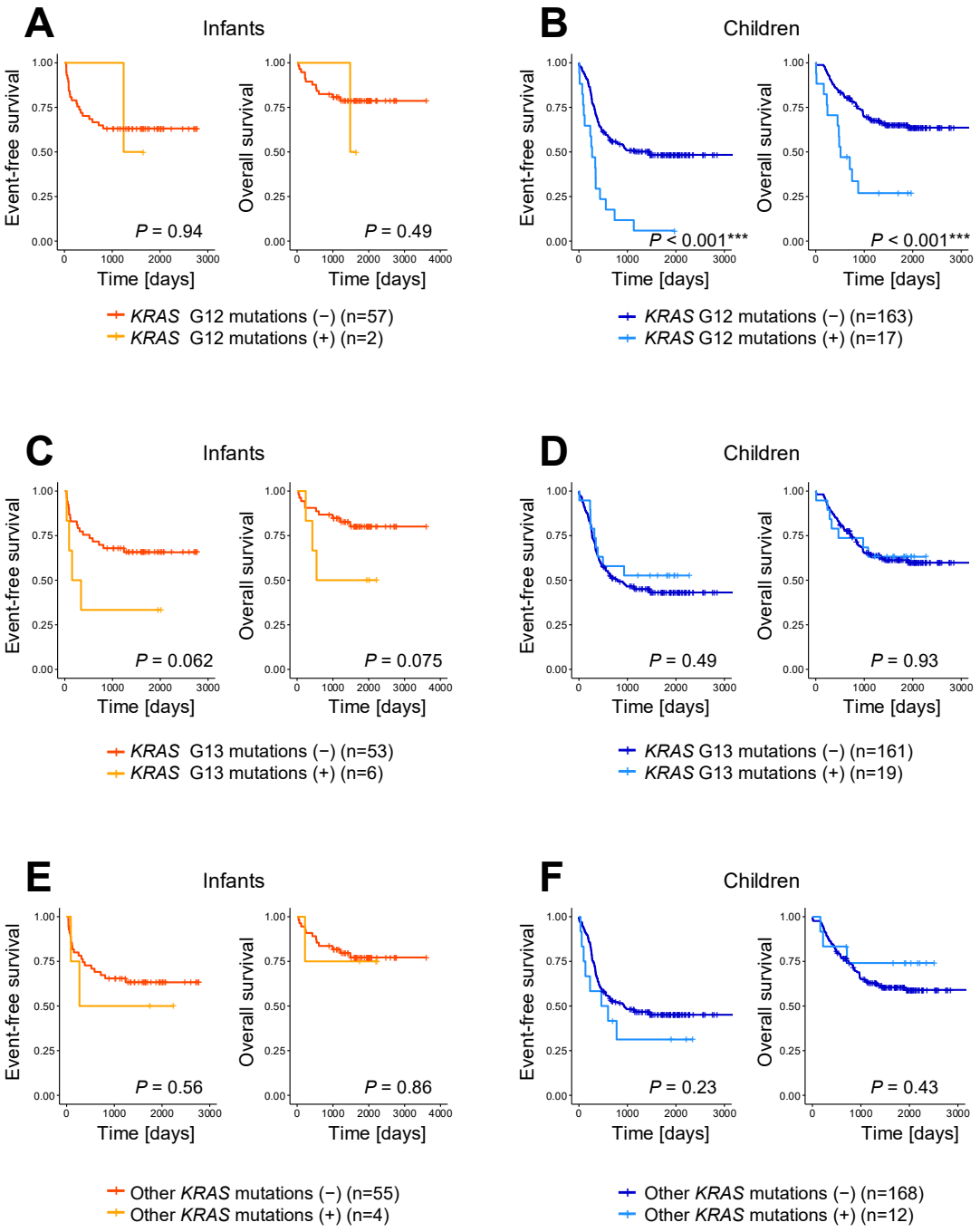
Event-free survival (EFS) and overall survival (OS) between infants and children, stratified by *KMT2A* rearrangement subtype. Analyses were conducted in the following order: **(A)** *KMT2A*::*MLLT3*, **(B)** *KMT2A*::*MLLT10*, **(C)** *KMT2A*::*ELL*, **(D)** *KMT2A*::*MLLT1*, and **(E)** other *KMT2A* fusions.

Supplementary Figure 9. Comparison of the impact of *KMT2A* fusion patterns on prognosis in AML patients stratified by age groups: <1 year, 1 to <3 years, and ≥3 years



Event-free survival (EFS) and overall survival (OS) by three age group (<1 year, 1 to <3 years, and ≥3 years), stratified by *KMT2A* rearrangement subtype. Analyses were conducted in the following order: **(A)** *KMT2A*::*MLLT3*, **(B)** *KMT2A*::*MLLT10*, **(C)** *KMT2A*::*ELL*, **(D)** *KMT2A*::*MLLT4*, **(E)** *KMT2A*::*MLLT1*, and **(F)** other *KMT2A* fusions.

Supplementary Figure 10. Impact of codon-specific *KRAS* mutations on prognosis



(A) Event-free survival (EFS) and overall survival (OS) in infants with *KMT2A*-r AML based on the presence of the *KRAS* G12 mutations. **(B)** EFS and OS in children with *KMT2A*-r AML based on the presence of the *KRAS* G12 mutations. **(C)** EFS and overall survival OS in infants with *KMT2A*-r AML based on the presence of the *KRAS* G13 mutations. **(D)** EFS and OS in children with *KMT2A*-r AML based on the presence of the *KRAS* G13 mutations. **(E)** EFS and OS in infants with *KMT2A*-r AML based on the presence of the other *KRAS* mutations. **(F)** EFS and OS in children with *KMT2A*-r AML based on the presence of the other *KRAS* mutations.
****P* < 0.001