Integrative clinical and molecular characterization of an acute promyelocytic leukemia-like subgroup with high early death risk in newly diagnosed acute myeloid leukemia: a multicenter study

Authors

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Table S1. Univariate and multivariate analysis of predictors of early death within APL-like AML and 'Other AML'

	APL-like AML (n=237)				Other AML (n=505)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P*-value[a]	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value[a]	HR (95%CI)	*P*-value
Male	0.489 (0.225, 1.062)	**0.071**	0.432 (0.197, 0.950)	**0.037**	3.695 (1.235, 11.052)	**0.019**		
Age ≥ 60years	2.604 (1.264, 5.366)	**0.009**	3.031 (1.446, 6.352)	**0.003**	5.830 (2.326, 14.614)	**< 0.001**	3.979 (1.526, 10.373)	**0.005**
ECOG > 2	7.779 (3.838, 15.766)	**< 0.001**			9.805 (3.910, 24.586)	**< 0.001**	5.819 (2.214, 15.293)	**< 0.001**
WBC > 50×10^9/L	1.669 (0.810, 3.439)	0.165			1.023 (0.393, 2.662)	0.963		
Hemoglobin < 60g/L	1.975 (0.810, 4.816)	0.134			1.100 (0.322, 3.752)	0.879		
Platelets < 50×10^9/L	2.275 (1.071, 4.831)	**0.032**			1.010 (0.413, 2.471)	0.983		
LDH > 2ULN	1.927 (0.923, 4.021)	**0.081**			1.413 (0.588, 3.394)	0.440		
Albumin < 35g/L	3.388 (1.595, 7.196)	**0.002**	3.999 (1.846, 8.661)	**< 0.001**	1.909 (0.791, 4.606)	0.150		
Overt DIC at diagnosis	4.826 (2.079, 11.204)	**< 0.001**	3.736 (1.557, 8.966)	**0.003**	1.363 (0.456, 4.076)	0.580		
Prolonged PT > 3sec	5.606 (2.743, 11.458)	**< 0.001**			4.404 (1.022, 18.982)	**0.047**		
Prolonged APTT > 10sec	1.658 (0.504, 5.456)	0.405			4.466 (1.309, 15.241)	**0.017**		
FIB < 1g/L	0.935 (0.223, 3.917)	0.926			21.854 (2.912, 164.030)	**0.003**	27.161 (3.014, 244.767)	**0.003**
D-D > 3mg/L	6.720 (2.351, 19.208)	**< 0.001**			1.506 (0.547, 4.143)	0.428		
INR ≥ 1.5	5.824 (2.867, 11.830)	**< 0.001**			5.033 (1.475, 17.176)	**0.010**		
MBE/MTE before induction	9.838 (4.802, 20.156)	**< 0.001**	9.995 (4.626, 21.594)	**< 0.001**	11.579 (1.548, 86.628)	**0.017**		
Infection at diagnosis	0.937 (0.459, 1.913)	0.859			4.647 (1.786, 12.092)	**0.002**	3.166 (1.189, 8.430)	**0.021**
Blast ≥ 75%	1.569 (0.769, 3.203)	0.216			0.534 (0.155, 1.843)	0.321		
CD13 positive	0.593 (0.279, 1.259)	0.174			1.816 (0.243, 13.568)	0.561		
CD33 positive	20.645 (0.000, >10000)	0.615			21.376 (0.000, >10000)	0.544		
CD117 positive	0.380 (0.187, 0.770)	**0.007**			0.704 (0.206, 2.403)	0.576		
CD11b positive	1.306 (0.601, 2.835)	0.500			2.862 (1.186, 6.906)	**0.019**		
CD14 positive	1.065 (0.324, 3.504)	0.917			4.024 (1.462, 11.074)	**0.007**	3.989 (1.381, 11.518)	**0.011**
CD15 positive	1.068 (0.460, 2.479)	0.878			1.830 (0.748, 4.478)	0.185		
CD7 positive	0.434 (0.104, 1.821)	0.254			0.366 (0.107, 1.249)	0.109		
CD38positive	0.838 (0.402, 1.749)	0.638			2.071 (0.607, 7.066)	0.245		
CD56 positive	2.827 (1.397, 5.719)	**0.004**			3.229 (1.320, 7.900)	**0.010**		

Table S1. (Continued)

	APL-like AML (n=237)				Other AML (n=505)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P*-value[a]	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value[a]	HR (95%CI)	*P*-value
CD64 positive	1.225 (0.604, 2.484)	0.575			1.716 (0.714, 4.124)	0.227		
CD2 positive	2.141 (0.292, 15.703)	0.454			2.781 (0.645, 11.989)	0.170		
CD4 positive	1.984 (0.978, 4.025)	**0.058**			2.634 (1.051, 6.603)	**0.039**		
KMT2A-r	0.684 (0.093, 5.017)	0.709			0.731 (0.098, 5.459)	0.760		
CBF-AML	1.747 (0.417, 7.321)	0.446			0.959 (0.321, 2.869)	0.940		
Other fusion	3.864 (1.174, 12.711)	**0.026**			0.047 (0.000, 933.054)	0.544		
NPM1	0.778 (0.348, 1.739)	0.540			0.788 (0.264, 2.358)	0.670		
DNMT3A	1.408 (0.683, 2.900)	0.354			0.601 (0.176, 2.052)	0.417		
IDH1/2	0.478 (0.206, 1.109)	**0.085**			0.883 (0.259, 3.011)	0.842		
FLT3-ITD	1.127 (0.557, 2.280)	0.739			0.324 (0.075, 1.397)	0.131		
CEBPA	0.585 (0.140, 2.452)	0.464			0.194 (0.026, 1.452)	0.110		
TET2	1.982 (0.949, 4.136)	**0.069**			1.149 (0.267, 4.953)	0.852		
NRAS/KRAS	1.507 (0.674, 3.370)	0.317			2.318 (0.960, 5.593)	**0.061**		
PTPN11	0.878 (0.307, 2.511)	0.809			1.828 (0.536, 6.236)	0.336		
WT1	1.400 (0.426, 4.606)	0.580			0.259 (0.035, 1.935)	0.188		
ELN-2022 (Adverse vs other)	2.403 (0.986,5.859)	**0.054**			1.607 (0.618, 4.182)	0.331		
Induction regimen (Intensive vs VEN-HMAs)	0.545 (0.242, 1.227)	0.143			1.980 (0.573, 6.840)	0.280		

Bold typing indicates statistical signifcance.

APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; LDH, lactate dehydrogenase; ULN, upper limit of normal; DIC, disseminated intravascular coagulation; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; D-D, D-dimer; INR, international normalized ratio; MBE, major bleeding event; MTE, major thrombotic event; CBF, core binding factor; ELN, European LeukemiaNet; VEN, venetoclax; HMAs, hypomethylating agents.

[a] Variables with *P*-value < 0.10 in univariate analysis were included in multivariate analysis.

Figure S1

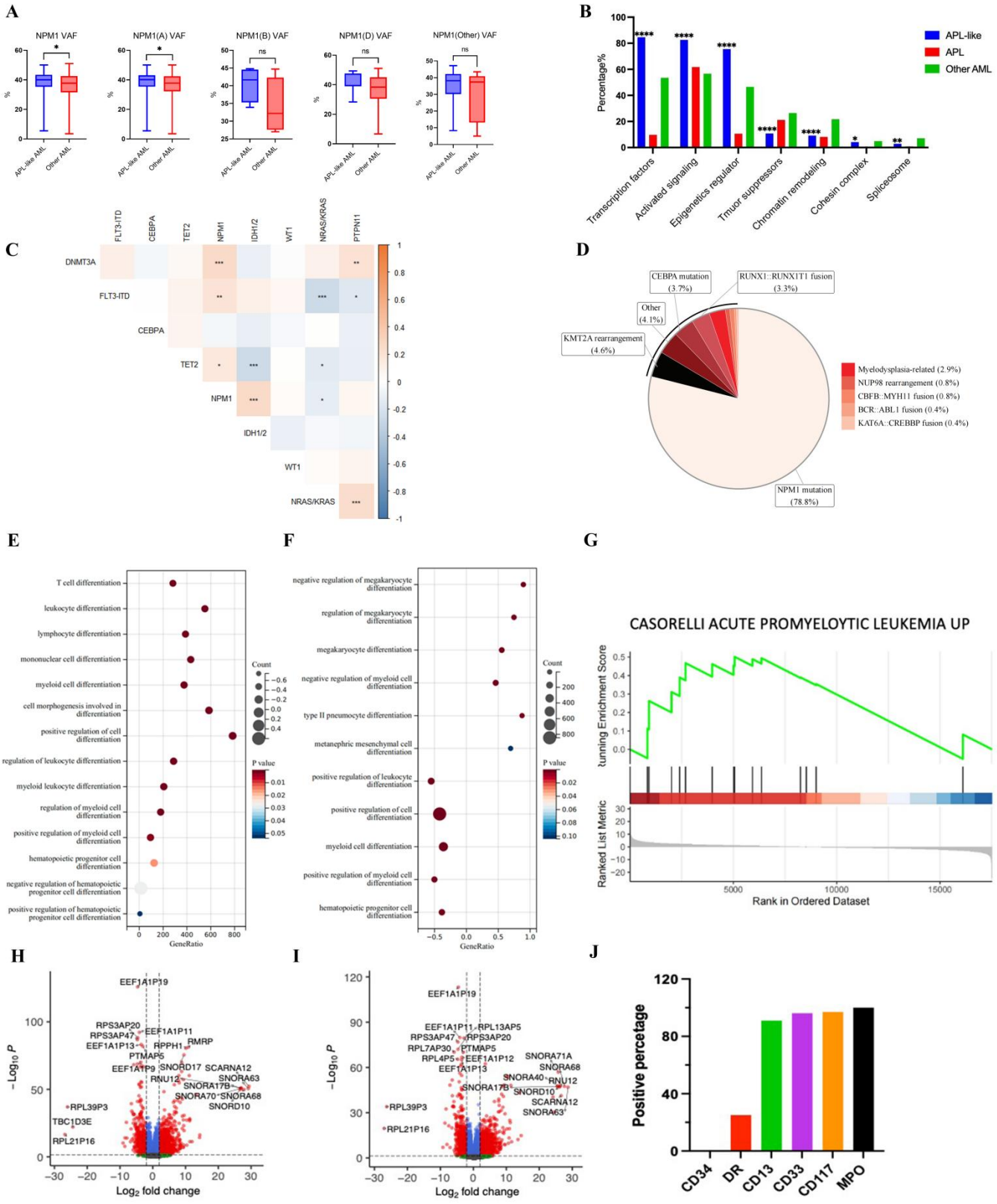

Figure S1. Molecular characteristics of APL-like AML. (**A**) Variant allele frequency (VAF) of *NPM1*, *NPM1* subtype A, *NPM1* subtype B, *NPM1* subtype D and *NPM1* other subtypes in *NPM1*^{mut} APL-like AML in comparison to *NPM1*^{mut} 'Other AML'. ns, not significant. (*P < .05, ** P < .01, *** P < .001, **** P < .0001). (**B**) Frequency of mutations classified by functional pathways in APL-like AML, APL and 'Other AML'. APL-like AML shows a higher incidence of mutations in genes involved in transcription factors,

activated signaling and epigenetics regulator than non APL-like subtypes (*$P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$). (**C**) Corplot of the genomic landscape of 241 APL-like AML patients. The correlations between different mutations of genes are represented by colors from strong positive correlations of orange to strong negative correlations of blue (*$P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$). (**D**) The pie chart showing the distribution of APL-like AML by molecular subgroups. *NPM1* mutations accounted for a proportion of 78.8% (190/241) of APL-like AML. Other molecular subtypes were also identified. (**E**) Gene Ontology (GO) analysis of differentially expressed genes between 52 APL-like AML samples and BeatAML database cohort. (**F**) GO analysis of differentially expressed genes between 52 APL-like AML samples and healthy donors from GSE133281. (**G**) Gene set enrichment analysis (GSEA) of acute promyelocytic leukemia (APL) gene set in 52 APL-like AML samples. (**H**) Volcano plot for differentially expressed genes (DEGs) between Ga and other BeatAML samples. (**I**) Volcano plot for DEGs between Gb and other BeatAML samples. (**J**) Bar chart illustrating immunophenotypic features of 38 samples with available information from Gb of BeatAML database.

Figure S2

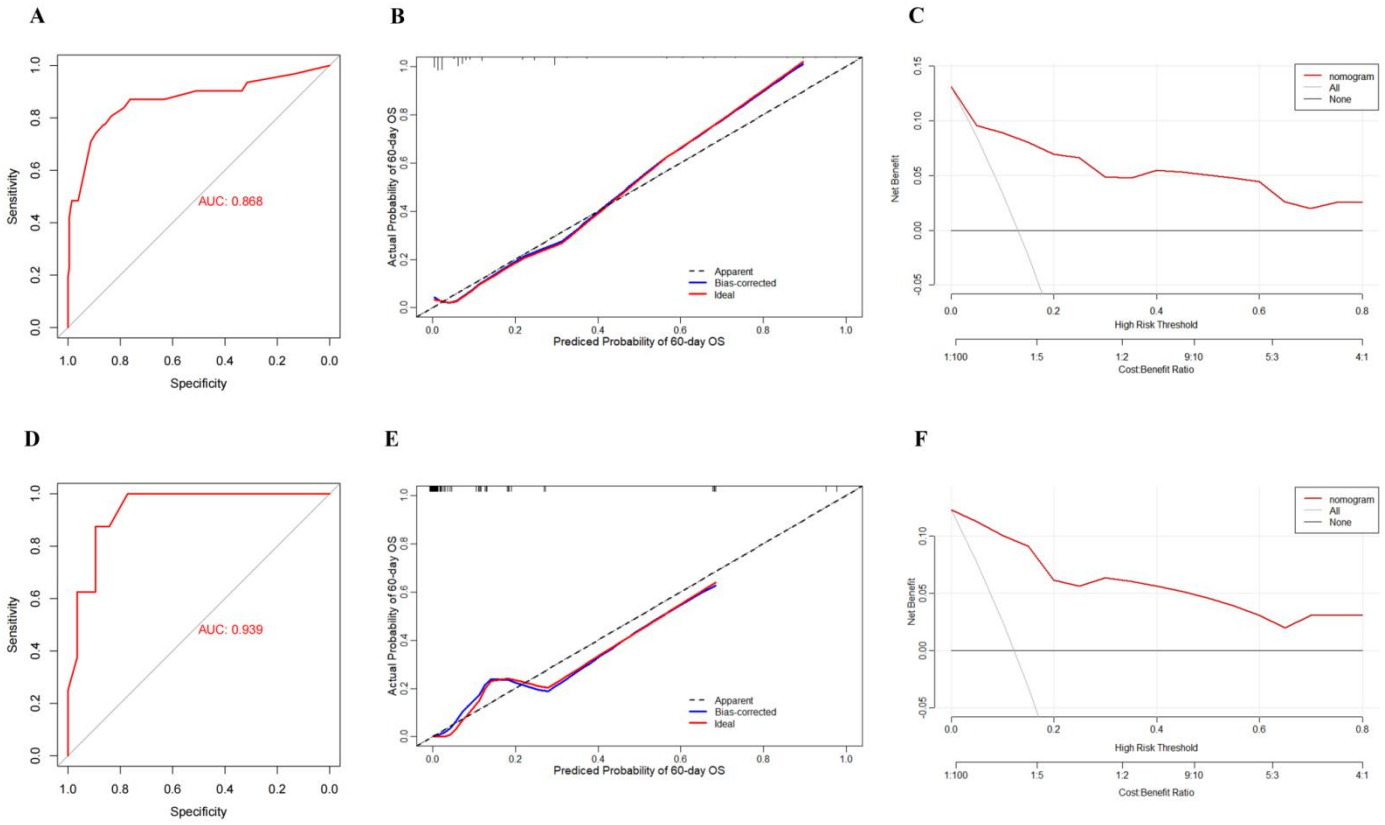

Figure S2. Performance of nomogram for predicting 60-day overall survival (OS) of APL-like AML. (**A**) The Receiver Operating Characteristic (ROC) curve analysis of the nomogram for predicting 60-day OS in the development cohort. (**B**) The calibration curve for the consistency between predicted and actual 60-day OS probability of APL-like AML in the development cohort. (**C**) Decision curve analysis (DCA) of the nomogram for predicting 60-day OS of APL-like AML in the development cohort. (**D**) The ROC curve analysis of the nomogram for predicting 60-day OS in the validation cohort. (**E**) The calibration curve for the consistency between predicted and actual 60-day OS probability of APL-like AML in the validation cohort. (**F**) DCA curve of the nomogram for predicting 60-day OS of APL-like AML in the validation cohort.