haematologica
Journal of the Ferrata Storti Foundation

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

by Mingkai Shu, Wenjing Ding, Linlin Wang, Zheng Wang, Lijun Wang, Mingqing Zhu, Dandan Liu, Hongjie Shen, Yun Wang, Xueqing Dou, Xiao Ma, Yang Zhang, Yang Xu, Ying Wang, Shengli Xue, Jianhong Fu, Huiying Qiu, Xiaowen Tang, Yue Han, Jinyan Huang, Depei Wu, Haiping Dai, Lijun Wen and Suning Chen

Received: July 7, 2025.
Accepted: November 19, 2025.

Citation: Mingkai Shu, Wenjing Ding, Linlin Wang, Zheng Wang, Lijun Wang, Mingqing Zhu, Dandan Liu, Hongjie Shen, Yun Wang, Xueqing Dou, Xiao Ma, Yang Zhang, Yang Xu, Ying Wang, Shengli Xue, Jianhong Fu, Huiying Qiu, Xiaowen Tang, Yue Han, Jinyan Huang, Depei Wu, Haiping Dai, Lijun Wen and Suning Chen. 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. Haematologica. 2025 Nov 27. doi: 10.3324/haematol.2025.288377 [Epub ahead of print]

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.
E-publishing of this PDF file has been approved by the authors.
After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval; the final version of the manuscript will then appear in a regular issue of the journal.
All legal disclaimers that apply to the journal also pertain to this production process.

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:

Mingkai Shu[1,2*], Wenjing Ding[3*], Linlin Wang[4], Zheng Wang[5], Lijun Wang[1,2], Mingqing Zhu[1,2], Dandan Liu[1,2], Hongjie Shen[1,2], Yun Wang[1,2], Xueqing Dou[1,2], Xiao Ma[1,6], Yang Zhang[7], Yang Xu[1,2], Ying Wang[1,2], Shengli Xue[1,2], Jianhong Fu[1,2], Huiying Qiu[1,2], Xiaowen Tang[1,2], Yue Han[1,2], Jinyan Huang[8], Depei Wu[1,2], Haiping Dai[1,2#], Lijun Wen[1,2#], Suning Chen[1,2#]

*MS and WD contributed equally to this study.

#Corresponding authors

Affiliations:

[1]National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Suzhou, People's Republic of China

[2]Institute of Blood and Marrow Transplantation, Collaborative Innovation Center of Hematology, Soochow University, Suzhou, People's Republic of China

[3]Weifang People's Hospital, Shandong Second Medical University, Weifang, People's Republic of China

[4]Yancheng No.1 People's Hospital, Affiliated Hospital of Medical School, Nanjing University, Yancheng Clinical College of Xuzhou Medical University, Yancheng, People's Republic of China

[5]Suzhou Jsuniwell Medical Laboratory, Suzhou, People's Republic of China

[6]Suzhou Hongci Hospital, Suzhou, People's Republic of China

[7]Department of Hematology, Canglang Hospital of Suzhou, People's Republic of China

[8]Biomedical big data center, the First Affiliated Hospital, Zhejiang University, Hangzhou, People's Republic of China

Corresponding authors:

Suning Chen

National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, Jiangsu, People's Republic of China.

Email: chensuning@suda.edu.cn

Lijun Wen

National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, Jiangsu, People's Republic of China.

Email: sudawlj@163.com

Haiping Dai

National Clinical Research Center for Hematologic Diseases, Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, Jiangsu, People's Republic of China.

Email: daihaiping8@126.com

Keywords:

APL-like, coagulation abnormality, transcriptomic analysis, early death

Data availability statement

The data reported in the study is available from the corresponding author on reasonable request.

Acknowledgements

All the samples used in this study were from the Hematologic Biobank, the National Clinical Research Center for Hematologic Diseases, Jiangsu Biobank of Clinical Resources, Coordination Service Platform, The First Affiliated Hospital of Soochow University. We would like to thank all the patients who participated in the study, their supporters, investigators and clinical research staff from the study centers.

Funding

This study was supported by grant from the National Key R&D Program of China (2022YFC2502701), the National Natural Science Foundation of China (82170158, 81970142), the Open Project of Jiangsu Biobank of Clinical Resources (SBK202003001, SBK202003003), the NHC Key Laboratory of Thrombosis and Hemostasis, The First Affiliated Hospital of Soochow University (KJS2420).

Author contributions

SC, MS, WD and LW* contributed to research design. MS and WD conducted collection of data, performed statistical analysis and prepared the manuscript. LLW, ZW, LW#, YW@ and XD helped collection of data. MZ, DL and HS reviewed morphology, flow cytometry and molecular data. XM, YZ, YX, YW&, SX, JF, HQ, XT, YH and DW collected samples and treated the patients. JH supported the RNA-seq data analysis. HD, LW*, and SC contributed to the revision of the manuscript and supervision of the study. All authors approved the manuscript and had final responsibility for the decision to submit for publication. (*refers to the author of Lijun Wen; # refers to the author of Lijun Wang; @ refers to the author of Yun Wang; & refers to the author of Ying Wang).

Competing interests disclosure

The authors declare no competing interests.

To the editor:

Acute promyelocytic leukemia (APL)-like is a subset of non-APL acute myeloid leukemia (AML) that has gained increasing attention, displaying a CD34 and HLA-DR double negativity immunophenotype that resembles APL. While previous studies of APL-like AML (APLL) focused on *NPM1* mutation,[1-3] further elucidation of APLL molecular characterization has not been extensively elucidated. Moreover, clinical outcomes of APLL, particularly early outcomes, have not been clearly presented. Therefore, on the basis of the largest APLL cohort to date, we demonstrate a unique APLL subgroup of AML with distinct molecular profiles and elevated risk of early death (ED).

In this multicenter study, we screened consecutive patients diagnosed with AML between January 2017 and November 2022. A cohort of 871 newly diagnosed AML patients with complete clinical data were included in this study. APLL was defined as AML with an immunophenotype of CD34 and HLA-DR double negativity on the basis of 20% threshold in flow cytometry analysis, along with the absence of retinoic acid receptor α / β / γ *(RARA/RARB/RARG)* rearrangement. ED was defined as death from any cause within 60 days after initial diagnosis. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University and was conducted in accordance with the principles of the Declaration of Helsinki.

241 (27.7%) patients were defined as APLL according to immunophenotypic features, 123 (14.1%) as APL by detection of *PML::RARA* fusion and 507 (58.2%) as 'Other AML'. The clinicopathologic characteristics of study cohort are summarized in Table 1. Of 241 APLL patients, 131 (54.4%) were male, with a median age of 50 years (IQR: 38-58). 108 (44.8%) APLL patients experienced overt DIC at diagnosis, a propotion significantly higher than the 15.8% in 'Other AML' ($P < 0.001$). Similarly, the prevalence of major bleeding/thrombotic events (MBE/MTE) before induction within APLL was significantly higher than 'Other AML' (9.5% vs 0.6%, $P < 0.001$).

APLL exhibited a significantly higher blast burden (71.3% vs 59.0%, $P < 0.001$) than 'Other AML' and distinct immunophenotypic features beyond the double

negativity. For genomic alterations, *NPM1* mutation predominated in APLL and was significantly more common than in 'Other AML' (78.8% vs 24.4%, $P < 0.001$; Figure 1A). Besides, *NPM1*-mutated APLL presented significantly higher *NPM1* mutation variant allele frequency than *NPM1*-mutated 'Other AML' (Figure S1A; 40.1% vs 37.7%, $P = 0.016$). Regarding mutations of various signaling pathways, APLL exhibited dominant prevalence in functional pathways including transcription factors, activated signaling and epigenetics regulator (Figure S1B). Within APLL, co-mutation analysis (Figure S1C) demonstrated overlapping mutations of *NPM1* with *IDH1/2* ($P < 0.001$), *DNMT3A* ($P < 0.001$), *FLT3-ITD* ($P = 0.002$) and *TET2* ($P = 0.012$). *NPM1* mutations were mutually exclusive with *NRAS/KRAS* mutations ($P = 0.044$). Apart from the central role of *NPM1* mutations, there were a series of additional molecular subtypes within APLL (Figure S1D), including AML with *KMT2A* rearrangement (4.6%), core binding factor AML (4.1%), AML with *CEBPA* mutation (3.7%), etc.

RNA-Seq analysis was performed to explore transcriptomic characteristics of APLL. The Gene Ontology analysis of differentially expressed genes (DEGs) indicated up-regulation of myeloid cell differentiation pathways comparing 'Other AML' patients and healthy donors (Figure S1E,F). Besides, the Gene set enrichment analysis revealed that APL gene set was up-regulated in APLL (Figure S1G). Next, unsupervised hierarchical clustering of the gene expression profile was performed. It was indicated that 34 of 52 (65.4%) APLL samples were clustered together, suggesting a potential distinct entity (Figure 1B). Based on the distribution of APLL samples within the cluster, we interpreted it as two parts. 31 of 34 (91.2%) APL-like samples were clustered as a consecutive part of Ga. For the rest of the cluster (Gb), whose data was primarily from BeatAML database, we found that DEGs of Gb against other BeatAML data were similar to those of Ga compared to other AML (Figure S1H,I). This indicated that Gb exhibited similar gene expression profiles to Ga. The analysis of 38 patients with available information from Gb demonstrated that these patients also presented APL-like immunophenotypic features (Figure S1J). We assumed that patients from Gb met the criteria of APLL and the whole cluster represented an APLL cluster, further indicating that APLL might be a distinct entity

from transcriptomic aspect.

Regarding early outcomes of APLL, at a median time of 17 days (range: 2-56) from initial diagnosis, ED occurred in 31 of 237 (13.1%) APLL patients, the rate of which was significantly higher than 'Other AML' (20/505, 3.9%; $P < 0.001$) and APL (7/123, 5.7%; $P = 0.031$) (Figure 2A). Among 31 ED cases of APLL, 22 (71.0%) died of MBE/MTE, which was in line with that of APL (5/7, 71.4%). In contrast, the ED causes of 'Other AML' were primarily attributed to infections (15/20, 75.0%; Figure 2B). This distribution was significantly different from that in APLL ($P = 0.001$).

Multivariate analysis identified 5 predictive factors for ED of APLL (Table S1): male (HR: 0.432, 95%CI: 0.197-0.950, $P = 0.037$), age ≥ 60 years (HR: 3.031, 95%CI: 1.446-6.352, $P = 0.003$), albumin < 35g/L (HR: 3.999, 95%CI: 1.846-8.661, $P < 0.001$), overt DIC at diagnosis (HR: 3.736, 95%CI: 1.557-8.966, $P = 0.003$) and MBE/MTE before induction (HR: 9.995, 95%CI: 4.626-21.594, $P < 0.001$). All these factors were independent of 'Other AML' except for age ≥ 60 years.

Utilizing regression coefficients from multivariate analysis, we developed a nomogram to accurately predict risks of ED in APLL, as is shown in Figure 2C. The assigned points for each variable were as follows: 38.0 for female, 49.2 for age ≥ 60 years, 62.2 for albumin < 35g/L, 57.8 for overt DIC at diagnosis and 100.0 for MBE/MTE before induction. An external cohort of 65 APLL patients from Suzhou Hongci Hospital was collected as our validation cohort and performance analysis presented acceptable efficacy in both development and validation cohorts (Figure S2). Next, 157.8 was determined as the optimal cutoff point for discriminating low- and high-risk groups of APLL. Based on this stratification standard, high-risk group exhibited an inferior ED rate in both development (55.0% vs 4.6%, $P < 0.001$; Figure 2D) and validation cohort (53.8% vs 1.9%, $P < 0.001$; Figure 2E).

Univariate analysis was then conducted to uncover predictors of ED among high-risk APLL patients (Figure 2F). Surprisingly, we found that venetoclax (VEN) plus hypomethylating agents (HMA) regimen was a risk factor of ED among these patients (HR: 3.022, 95%CI: 1.263-7.243, $P = 0.013$), while low-intensity chemotherapy played a protective role (HR: 0.300, 95%CI: 0.101-0.888, $P = 0.030$).

In this large-cohort multicenter study, we focused on investigation of molecular profiles and early outcomes of APLL. Transcriptomic analysis of APLL has barely been reported. Here, on the basis of largest APLL RNA-Seq samples to date, we identified up-regulation of APL-related gene sets and myeloid cells differentiation pathway in APLL samples, indicating similar molecular biology of APLL compared with APL. However, 65.4% APL-like samples were clustered together and were distinct to classic APL and other AML clusters, suggesting a potential unique subtype. The supplementary information from BeatAML database, particularly immunophenotypic features, further supported that the cluster was posssibly a specific cluster of APLL. These findings suggest that while APLL may exhibit some similarities with APL on molecular pathogenesis, it is likely a distinct entity and the differentiation mechanism may be distinguished from classic APL.

In our APLL cohort, the ED rate reached 13.1%, significantly higher than that of APL and 'Other AML', indicating APLL is a unique subgroup with elevated ED risks. 71.0% of APLL ED cases were attributed to MBE/MTE, which is not only comparable to that of our APL group (71.4%), but also basically aligns with some of recent findings of APL.[4,5] Moreover, we firstly elucidated the predictors of ED within APLL. Overt DIC at diagnosis was identified as a risk factor for ED in APLL. A recent investigation by Paterno et al[6] identified DIC as one of the predictors of early mortality within non-APL AML. In our study, we confirmed it was a risk factor that was independent of 'Other AML'. MBE/MTE before induction similarly contributed to risks of ED in APLL. In contrast, infection at diagnosis was an independent risk factor of ED in 'Other AML', demonstrating distinct patterns of ED in two subgroups. Together, it can be concluded that coagulation dysfunction specifically plays a central role in APLL patients' inferior early outcomes.

A surprising finding of our analysis is that options of induction regimens might impact ED of high-risk APLL patients, as VEN-HMA regimen increased ED risks within these patients. While VEN-HMA regimen has been a standard induction regimen for elderly or unfit AML patients,[7-9] it has been noted that the regimen also triggered tumor lysis syndrome (TLS), especically under standard "ramp-up" dosage

among AML with *IDH1/2* or *NPM1* mutations.[10-12] This might be associated with our finding, as the potential TLS could further impair poor fitness status and deteriorate coagulation dysfunction in high-risk APLL patients. A recent study revealed that reduced venetoclax exposure could alleviate 8-week mortality rate in AML cohort while having no impact on long-term survival.[13] Studies are also emerging on modification of VEN dosage to reduce adverse events of patients.[14,15] Therefore, further prospective study may be critical for appropriate induction regimens options and dosage among high-risk APLL patients.

In conclusion, we reveal that APLL is a distinct subgroup of AML, with first elucidation of its unique transcriptomic profile and risk-stratification model of elevated risk of ED. These findings facilitate understanding and advance guideline of this subset. Nevertheless, due to the limitation of retrospective nature of the study, biological research of APLL pathogenesis and optimal management on APLL await exploration in the future.

References

1. Mason EF, Kuo FC, Hasserjian RP, Seegmiller AC, Pozdnyakova O. A distinct immunophenotype identifies a subset of NPM1-mutated AML with TET2 or IDH1/2 mutations and improved outcome. Am J Hematol. 2018;93(4):504-510.

2. Mason EF, Hasserjian RP, Aggarwal N, Seegmiller AC, Pozdnyakova O. Blast phenotype and comutations in acute myeloid leukemia with mutated NPM1 influence disease biology and outcome. Blood Adv. 2019;3(21):3322-3332.

3. Chen EC, Shimony S, Luskin MR, Stone RM. Biology and Management of Acute Myeloid Leukemia With Mutated NPM1. Am J Hematol. 2025;100(4):652-665.

4. Voso MT, Guarnera L, Lehmann S, et al. Acute promyelocytic leukemia: long-term outcomes from the HARMONY project. Blood. 2025;145(2):234-243.

5. Zhao Y, Yu X, Yan L, et al. Study on clinical features of early death in older patients with acute promyelocytic leukemia. Ann Hematol. 2025;104(1):183-192.

6. Paterno G, Palmieri R, Tesei C, et al. The ISTH DIC-score predicts early mortality in patients with non-promyelocitic acute myeloid leukemia. Thromb Res. 2024;236:30-36.

7. Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345-1377.

8. Bhansali RS, Pratz KW, Lai C. Recent advances in targeted therapies in acute myeloid leukemia. J Hematol Oncol. 2023;16(1):29.

9. Döhner H, DiNardo CD, Appelbaum FR, et al. Genetic risk classification for

adults with AML receiving less-intensive therapies: the 2024 ELN recommendations. Blood. 2024;144(21):2169-2173.

10. Wei AH, Loo S, Daver N. How I treat patients with AML using azacitidine and venetoclax. Blood. 2025;145(12):1237-1250.

11. Rowe M, Babushok D, Carroll M, et al. Tumor Lysis Syndrome in Acute Myeloid Leukemia Patients Treated With a Venetoclax Based Regimen. Eur J Haematol. 2025;114(4):626-635.

12. Diao S, Nichols ED, DiNardo C, et al. Incidence of tumor lysis syndrome in patients with acute myeloid leukemia undergoing low-intensity induction with venetoclax. Am J Hematol. 2021;96(3):E65-E68.

13. Willekens C, Bazinet A, Chraibi S, et al. Reduced venetoclax exposure to 7 days vs standard exposure with hypomethylating agents in newly diagnosed AML patients. Blood Cancer J. 2025;15(1):68.

14. Kantarjian HM, DiNardo CD, Kadia TM, et al. Acute myeloid leukemia management and research in 2025. CA Cancer J Clin. 2025;75(1):46-67.

15. Sastow D, Levavi H, Wagner N, Pratz K, Tremblay D. Ven the dose matters: Venetoclax dosing in the frontline treatment of AML. Blood Rev. 2024;68:101238.

Table 1. Clinicopathologic characteristics of APL-like AML, APL and 'Other AML'

Parameter	APL-like AML (n=241)	APL (n=123)	Other AML (n=507)	*P*-value (APL-like AML vs APL)	*P*-value (APL-like AML vs Other AML)	*P*-value (APL vs Other AML)
Age (years), median (IQR)	50.0 (38.0, 58.0)	35.0 (28.0, 48.0)	42.0 (32.0, 53.0)	< **0.001**	< **0.001**	**0.002**
Sex (Male), n (%)	131 (54.4)	62 (50.4)	241 (47.5)	0.475	0.081	0.567
ECOG score, n (%)				0.814	< **0.001**	< **0.001**
0-2	206 (85.5)	104 (84.6)	477 (94.1)			
3-4	35 (14.5)	19 (15.4)	30 (5.9)			
Complete blood count, median (IQR)						
WBC, x 10^9/L	48.61 (15.51, 103.23)	4.17 (1.29, 20.81)	20.75 (5.13, 64.19)	< **0.001**	< **0.001**	< **0.001**
Hemoglobin, g/L	80.0 (70.0, 97.0)	90.0 (73.0, 113)	80.0 (65.0, 98.0)	**0.001**	0.415	< **0.001**
Platelets, x 10^9/L	49.0 (27.5, 94.5)	25.0 (14.0, 47.0)	39.0 (20.0, 76.0)	< **0.001**	**0.008**	< **0.001**
Biochemistry, median (IQR)						
LDH, U/L	489.1 (284.7, 857.3)	335.0 (210.0, 575.0)	427.8 (257.5, 666.0)	< **0.001**	**0.005**	**0.008**
Albumin, g/L	36.00 (32.35, 40.00)	41.90 (37.08, 44.55)	35.20 (32.05, 38.55)	< **0.001**	0.148	< **0.001**
Coagulation, n (%)						
Overt DIC[a]	108 (44.8)	110 (89.4)	80 (15.8)	< **0.001**	< **0.001**	< **0.001**
MBE/MTE before induction[b]	23 (9.5)	16 (13.0)	3 (0.6)	0.312	< **0.001**	< **0.001**
Morphology, median (IQR)						
BMB or BMAP, %	71.3 (49.0, 85.0)	84.0 (75.5, 90.3)	59.0 (40.5, 77.5)	< **0.001**	< **0.001**	< **0.001**
Immunophenotype, n (%)						
CD13 positive	187 (77.6)	114 (92.7)	463 (91.3)	< **0.001**	< **0.001**	0.626
CD33 positive	237 (98.3)	121 (98.4)	487 (96.1)	0.981	0.097	0.209
CD117 positive	180 (74.7)	91 (74.0)	451 (89.0)	0.884	< **0.001**	< **0.001**
CD11b positive	57 (23.7)	19 (15.4)	116 (22.9)	0.069	0.815	0.072
CD4 positive	73 (30.3)	26 (21.1)	88 (17.4)	0.063	< **0.001**	0.328
CD7 positive	31 (12.9)	2 (1.6)	164 (32.3)	< **0.001**	< **0.001**	< **0.001**
CD56 positive	74 (30.7)	11 (8.9)	89 (17.6)	< **0.001**	< **0.001**	**0.019**
Fusion genes, n (%)						
KMT2A-r	11 (4.6)	0 (0)	34 (6.7)	**0.019**	0.250	0.001
CBF-AML	10 (4.1)	0 (0)	104 (20.5)	**0.019**	< **0.001**	< 0.001

Table 1. (Continued)

Parameter	APL-like AML (n=241)	APL (n=123)	Other AML (n=507)	*P*-value (APL-like AML vs APL)	*P*-value (APL-like AML vs Other AML)	*P*-value (APL vs Other AML)
Other fusion	7 (2.9)	123 (100)	20 (3.9)	< **0.001**	0.476	< **0.001**
Somatic mutations, n (%)						
NPM1	190 (78.8)	0 (0)	124 (24.4)	< **0.001**	< **0.001**	< **0.001**
DNMT3A	75 (31.1)	2 (1.6)	116 (22.9)	< **0.001**	**0.016**	< **0.001**
IDH1/2	87 (36.1)	0 (0)	84 (16.6)	< **0.001**	< **0.001**	< **0.001**
FLT3-ITD	117 (48.5)	43 (35.0)	129 (25.4)	**0.014**	< **0.001**	**0.034**
CEBPA	25 (10.4)	0 (0)	106 (20.9)	< **0.001**	< **0.001**	< **0.001**
TET2	55 (22.8)	3 (2.4)	46 (9.1)	< **0.001**	< **0.001**	**0.014**
NRAS/KRAS	47 (19.5)	10 (8.1)	135 (26.6)	**0.005**	**0.034**	< **0.001**
PTPN11	35 (14.5)	0 (0)	46 (9.1)	< **0.001**	**0.025**	< **0.001**
WT1	17 (7.1)	23 (18.7)	84 (16.6)	< **0.001**	< **0.001**	0.572
ELN-Risk 2022, n (%)				-	< **0.001**	-
Favorable	104 (43.9)	-	237 (48.2)			
Intermediate	110 (46.4)	-	151 (30.7)			
Adverse	23 (9.7)	-	104 (21.1)			
Induction regimen, n (%)				-	**0.009**	-
“3+7” regimen	91 (39.6)	-	258 (51.3)			
LIC	74 (32.2)	-	120 (23.9)			
VEN-HMA	65 (28.3)	-	125 (24.9)			
FLT3 inhibitor in induction, n (%)	22 (9.6)	-	12 (2.4)	-	< **0.001**	-

Bold typing indicates statistical signifcance.

APL, acute promyelocytic leukemia; AML, acute myeloid leukemia; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; LDH, lactate dehydrogenase; DIC, disseminated intravascular coagulation; MBE, major bleeding event; MTE, major thrombotic event; BMB, bone marrow blast; BMAP, bone marrow abnormal promyelocyte; CBF, core binding factor; ELN, European LeukemiaNet; LIC, low-intensity chemotherapy; VEN, venetoclax; HMA, hypomethylating agent.

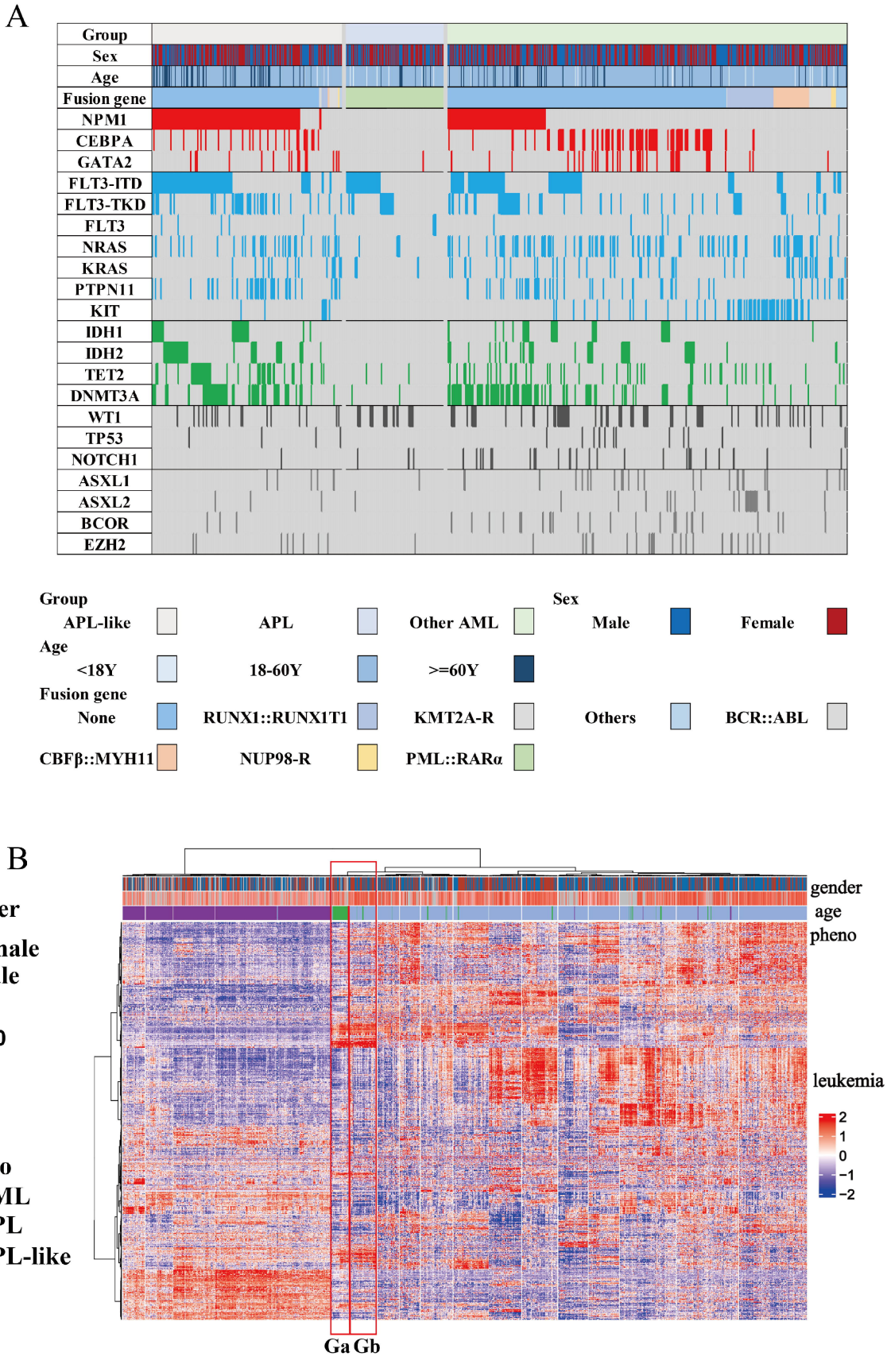
[a]Overt DIC was retrospectively evaluated according to the 2018 revision of International Society on Trombosis and Haemostasis (ISTH) guidelines.

[b]Major bleeding events (MBE) and major thrombotic events (MTE) were defined by > Grade 2 events of the revised WHO bleeding scale and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, respectively.

Figure legends

Figure 1. Genomic and transcriptomic landscape of APL-like AML. (**A**) Mutational landscape of APL-like AML, APL and ‘Other AML’. The upper panel shows the classification of the study, sex, age and fusion gene for each patient. The mutational landscape of common genes is displayed as the principal part of the figure. (**B**) Unsupervised hierarchical clustering of the gene expression pattern identifies a cluster in which 34 of 52 (65.4%) APL-like AML samples were involved. The cluster is interpreted as Ga and Gb. 31 of 34 (91.2%) APL-like AML were interpreted as Ga. Gb is mainly composed of cases from BeatAML database. Top: Gender, age and phenotype of each sample. Columns indicate cases, and rows indicate genes.

Figure 2. Details and predictive nomogram of early death (ED) within APL-like AML. (**A**) Pie charts showing the 60-day survival and ED rate of APL-like AML, APL and ‘Other AML’. ED, early death; APLL, APL-like AML. (**B**) Pie charts showing the distribution of ED causes within APL-like AML, APL and ‘Other AML’. APLL, APL-like AML; MBE, major bleeding event; MTE, major thrombotic event; DS, differentiation syndrome. (**C**) The ED predictive nomogram of APL-like AML patients. DIC, disseminated intravascular coagulation. MBE, major bleeding event; MTE, major thrombotic event. (**D**) Kaplain-Meier curves for 60-day survival of the high- and low-risk APL-like AML categorized by the scoring of the nomogram in the development cohort. (**E**) Kaplain-Meier curves for 60-day survival of the high- and low-risk APL-like AML categorized by the scoring of the nomogram in the external validation cohort. (**F**) The forest plot for univariate analysis results of predictors of ED in high-risk APL-like AML patients. DIC, disseminated intravascular coagulation; LIC, low-intensity chemotherapy; VEN, venetoclax; HMA, hypomethylating agent.


A
Group
Sex
Age
Fusion gene
NPM1
CEBPA
GATA2
FLT3-ITD
FLT3-TKD
FLT3
NRAS
KRAS
PTPN11
KIT
IDH1
IDH2
TET2
DNMT3A
WT1
TP53
NOTCH1
ASXL1
ASXL2
BCOR
EZH2
Group
APL-like
APL
Other AML
Sex
Male
Female
Age
<18Y
18-60Y
>=60Y
Fusion gene
None
RUNX1::RUNX1T1
KMT2A-R
Others
BCR::ABL
CBFβ::MYH11
NUP98-R
PML::RARα
B
gender
female
male
age
100
50
0
pheno
AML
APL
APL-like
gender
age
pheno
leukemia
2
1
0
−1
−2
Ga
Gb

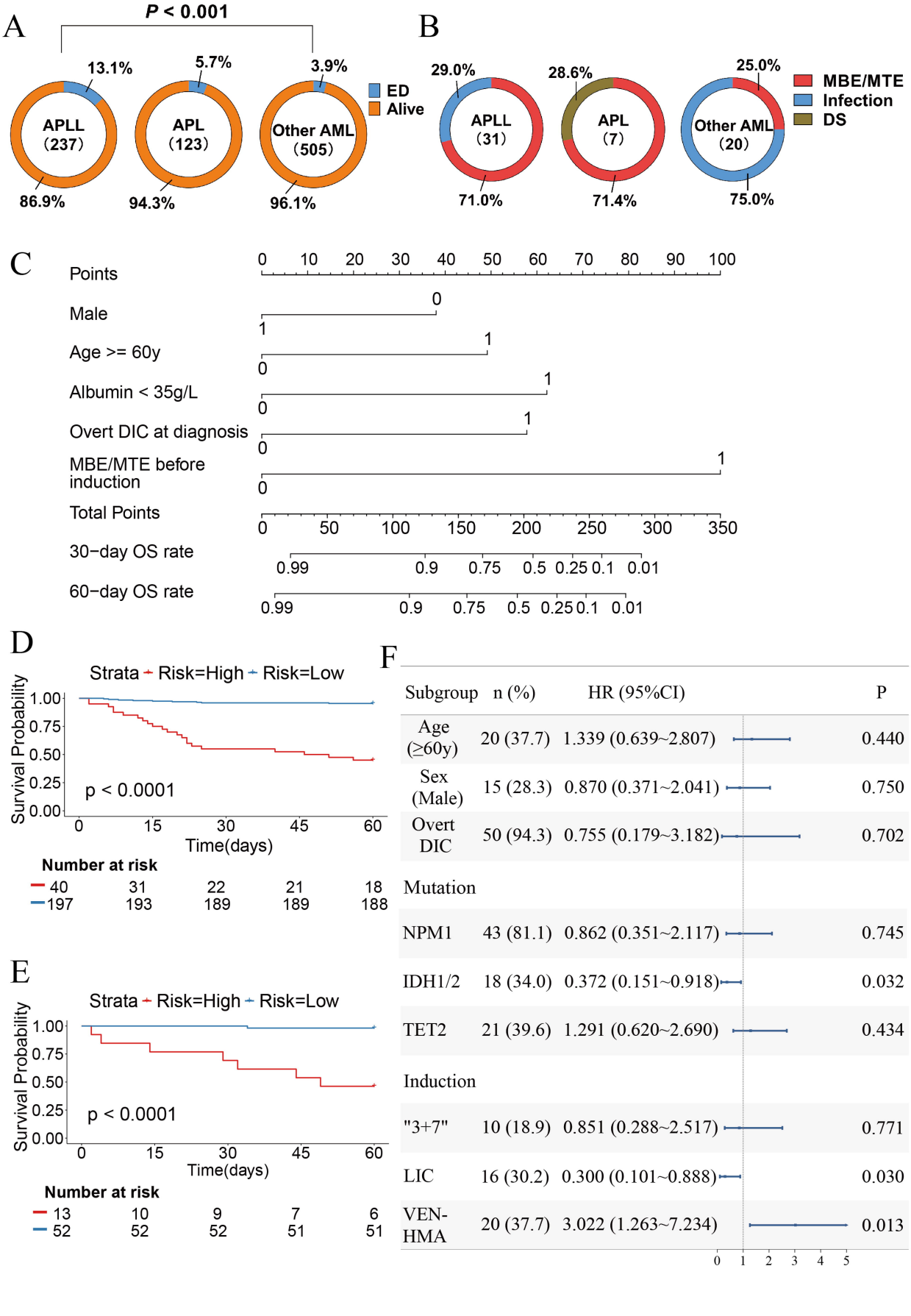

A
P < 0.001
13.1%
5.7%
3.9%
APLL (237)
APL (123)
Other AML (505)
86.9%
94.3%
96.1%
ED
Alive
B
29.0%
28.6%
25.0%
APLL (31)
APL (7)
Other AML (20)
71.0%
71.4%
75.0%
MBE/MTE
Infection
DS
C
Points
0 10 20 30 40 50 60 70 80 90 100
Male
Age >= 60y
Albumin < 35g/L
Overt DIC at diagnosis
MBE/MTE before induction
Total Points
0 50 100 150 200 250 300 350
30−day OS rate
0.99 0.9 0.75 0.5 0.25 0.1 0.01
60−day OS rate
0.99 0.9 0.75 0.5 0.25 0.1 0.01
D
Strata Risk=High Risk=Low
Survival Probability
1.00 0.75 0.50 0.25 0.00
p < 0.0001
0 15 30 45 60
Time(days)
Number at risk
40 31 22 21 18
197 193 189 189 188
E
Strata Risk=High Risk=Low
Survival Probability
1.00 0.75 0.50 0.25 0.00
p < 0.0001
0 15 30 45 60
Time(days)
Number at risk
13 10 9 7 6
52 52 52 51 51
F
Subgroup n (%) HR (95%CI) P
Age (≥60y) 20 (37.7) 1.339 (0.639~2.807) 0.440
Sex (Male) 15 (28.3) 0.870 (0.371~2.041) 0.750
Overt DIC 50 (94.3) 0.755 (0.179~3.182) 0.702
Mutation
NPM1 43 (81.1) 0.862 (0.351~2.117) 0.745
IDH1/2 18 (34.0) 0.372 (0.151~0.918) 0.032
TET2 21 (39.6) 1.291 (0.620~2.690) 0.434
Induction
"3+7" 10 (18.9) 0.851 (0.288~2.517) 0.771
LIC 16 (30.2) 0.300 (0.101~0.888) 0.030
VEN-HMA 20 (37.7) 3.022 (1.263~7.234) 0.013
0 1 2 3 4 5

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

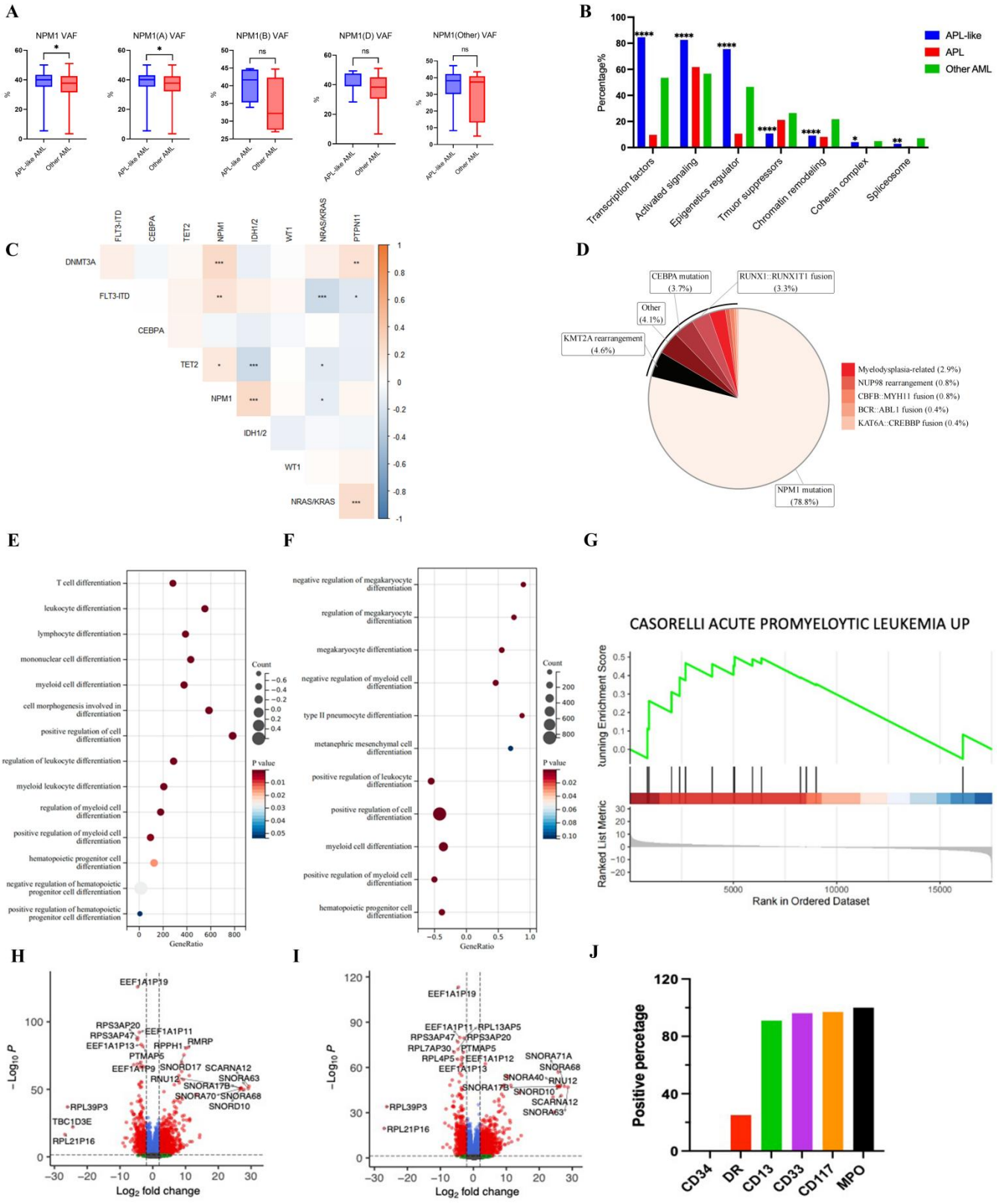


Figure S1. Molecular characteristics of APL-like AML. (**A**) Variant allele frequency (VAF) of *NPM1*, *NPM1* subtype A, *NPM1* subtype B, *NPM1* subtype D and *NPM1* other subtypes in *NPM1*^{mut} APL-like AML in comparison to *NPM1*^{mut} 'Other AML'. ns, not significant. (*P < .05, ** P < .01, *** 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

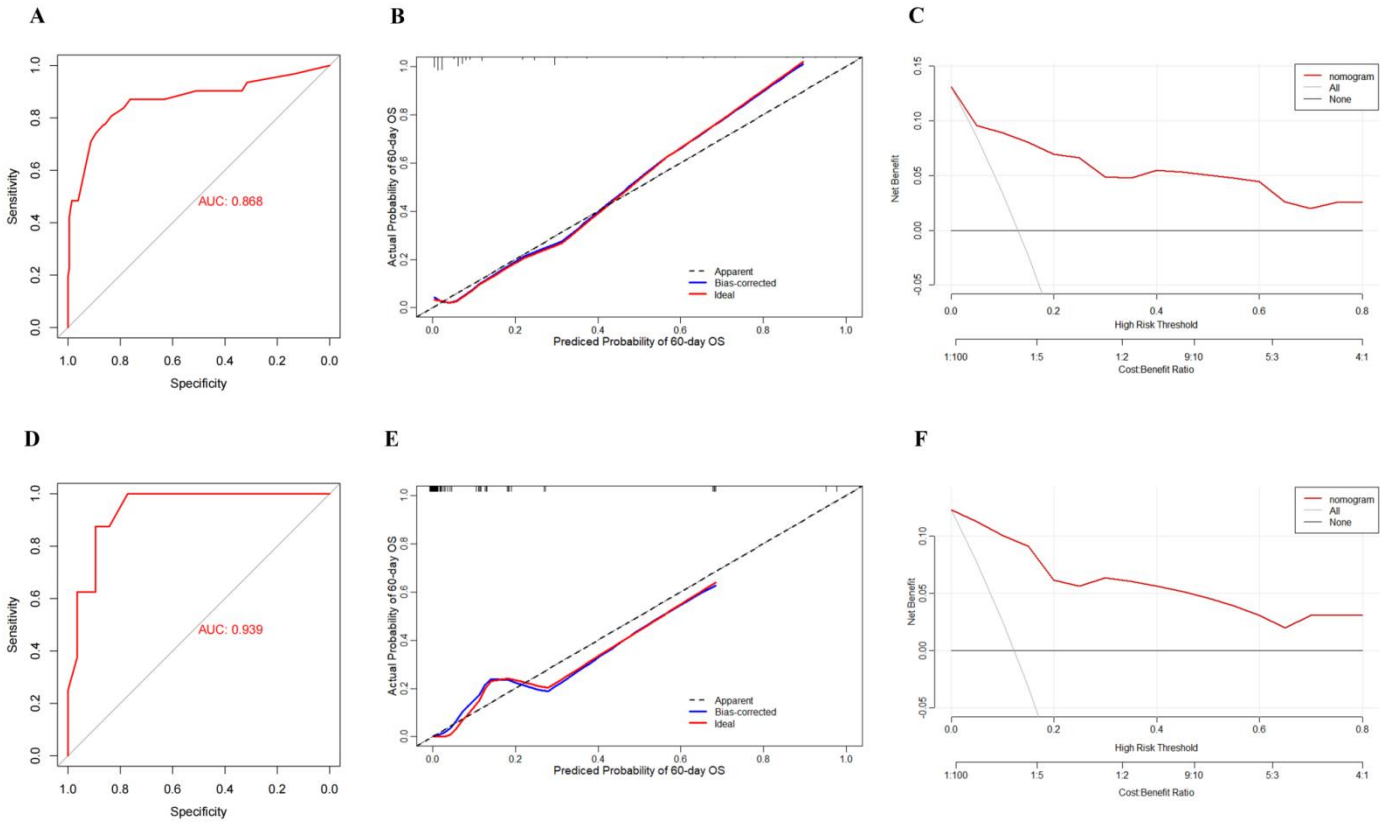


Figure S2. Performance of nomogram for predicting 60-day overall survival (OS) of APL-like AML. (**A**) The Receiver Operating Characteristic (ROC) curve analysis of the nomogram for predicting 60-day OS in the development cohort. (**B**) The calibration curve for the consistency between predicted and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