



The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS**Integrative Multi-Omic Analysis for Prognosis Stratification in Acute Myeloid Leukemia**

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Acute myeloid leukemia (AML) is a heterogeneous hematopoietic malignancy with a dismal prognosis. European LeukemiaNet (ELN) is crucial for tailoring AML treatment individually. Various AML models correlated survival and clinical drug response with immune cell differentiation state by deconvoluting transcriptomics. However, few comprehensive molecular subtyping models integrate multi-omic profiles for prognostic and drug response prediction. Thus, this study aimed to integrate DNA methylation, genomics, transcriptomics and ex vivo drug sensitivity screening of AML patients and explore their roles in facilitating AML molecular stratification and redefining prognosis.

Firstly, data on 90 patients with AML (non-promyelocytic leukemia) were retrieved from The Cancer Genome Atlas (TCGA) for consensus clustering by 10 advanced consensus clustering algorithms. The optimal three distinct subtypes, UAMOCS1, UAMOCS2, and UAMOCOS3, were identified to achieve the best clustering effect. Multi-omics were orchestrated together for UAMOCS shaping. The UAMOCS can significantly distinguish overall survival (median 18 vs. 27 vs. 45 months, $P = 0.0048$) among the three distinct subtypes with the integrated contribution of transcriptomic profiles and DNA methylation and mutation data. Also, the activity of AML-specific transcription factors and chromatin remodeling makers showed a diverse pattern among the three subtypes, epigenetically contributing to UAMOCS shaping.

Next, the nearest template prediction, a model-free method, was applied to further validate this predictive model. Similar subtyping under this model is generated robustly by imitating 50 subtype-specific genes and capable of identifying survival in both the "ihCAMs-AML" (Figure 1) and GSE37642. The main validation cohort was a real-world *de novo* AML cohort (acute promyelocytic leukemia excluded), "ihCAMs-AML" (N=98), aged 14-70 years, with a median follow-up of 28 (1-55) months. The samples were simultaneously available for methylome (N=31, 850K Methylation Chip), DNA mutation (N=96, targeted deep sequencing), transcriptome (N=98, bulk RNA-seq), and ex vivo drug screening (N=66, 17 drugs under 100% peak plasma concentration) profiling analysis.

Clinical relevance showed that traditional cytogenetic stratification was strongly correlated with our system. UAMOCS1, acting as an "immune activator", is characterized by enriching of AML myelodysplasia-related (AML-MR) gene mutations (especially RUNX1 mutation, $P = 0.00839$), unstable chromosome (deletions on 7q), increased abundance of immune cells with immune escaping marker and poor risk. UAMOCS2 was defined as an intermediate immune burden and a "monocytic-like" phenotype with intermediate survival, corresponding to its inclining result toward M4/M5. UAMOCS3 was an "immune desert" group supposed to be the most favorable subset among the three groups.

The ex vivo drug screening result implied that UAMOCS also provide values in distinguishing drug response. UAMOCS1 hardly benefited from commonly used chemotherapeutic drugs compared with the other two distinct subtypes. Pharmacogenomics database GDSC (the Genomics of Drug Sensitivity in Cancer) among AML cell lines was used to evaluate potential drug targets for overcoming drug resistance. Receptor tyrosine kinase signaling inhibitors (SB505124 and EphB4) might be sensitive to UAMOCS1.

Taken together, UAMOCS model was generated that can classify AML patients independently and help develop precise chemotherapeutic strategy for patients with AML in the future.

Disclosures No relevant conflicts of interest to declare.

Figure 1

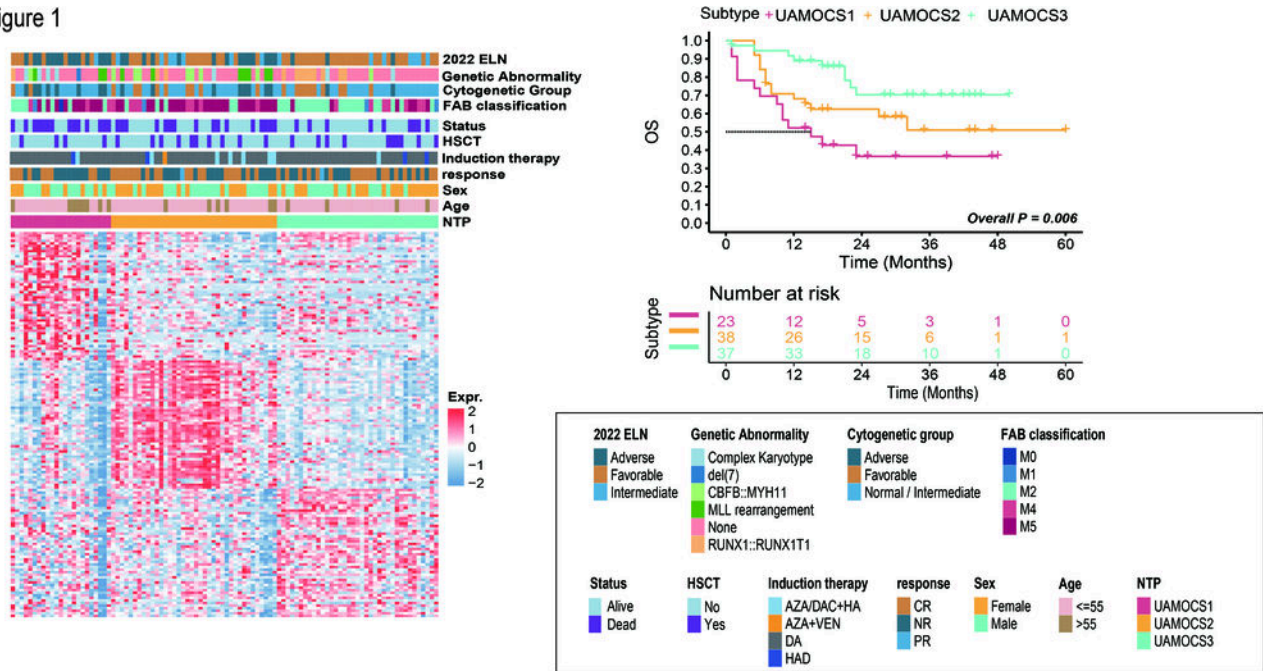


Figure 1 Legend: Characteristics of ihCAMs-AML as an externally validated cohort classified by UAMOCS. The left heatmap showed transcriptomic profiling and its basic clinical characteristics for UAMOCS subtyping using the nearest template prediction method in the ihCAMs-AML cohort. The right survival plot showed the overall survival of the three subtypes classified by the UAMOCS in the ihCAMs-AML cohort. Note: CR: complete remission; NR: no remission; PR: partial remission; AZA+VEN: Azacitidine + Venetoclax; DA: Daunorubicin + Cytarabine; HAD: Homoharringtonine + Daunorubicin + Cytarabine; HSCT: hematopoietic stem cell transplantation

Figure 1

<https://doi.org/10.1182/blood-2023-173211>