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POSTER ABSTRACTS

613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Validation and Retraining of the Stellae-123 Gene Expression Signature Improved Risk Stratification in Taiwanese Acute Myeloid Leukemia Patients

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The European Leukemia Net (ELN) recommendations provide valuable guidance in treatment decisions of patients with acute myeloid leukemia (AML). However, the genetic complexity and heterogeneity of AML are not fully covered, despite the critical role of gene expression analysis in risk stratification. Addressing this gap, the Stellae-123 score, an AI-based model that captures gene expression patterns, has demonstrated promising results in predicting survival of AML patients in four western cohorts. This study aims to assess the applicability of Stellae-123 in a Taiwanese cohort.

Our cohort included 233 *de novo* AML patients, who were diagnosed and treated at the National Taiwan University Hospital and received standard induction therapy with 7+3 chemotherapy (or 5+2 in elder fit patients). All patients had sufficient bone marrow samples for DNA and RNA sequencing at diagnosis. The median age of the cohort was 41 years. Among the patients, ELN-2022 risk groups were distributed as follows: favorable (53.4%), intermediate (27.6%), and adverse (19%).

Appling the original Stellae-123 model, which derived gene expression signatures from the BeatAML cohort RNA-seq data, our patients were categorized into low-, intermediate-, and high-risk groups, each representing 33% of the cohort. Overall, there were no differences in clinical features among these risk groups. The Stellae-123 risk groups partially aligned with the ELN risk groups, with more ELN low-risk patients in the Stellae-123 low-risk group and a higher proportion of ELN-high risk patients in the Stellae-123 high-risk group. Intriguingly, aside from mutations listed in ELN-2022, the Stellae-123 high-risk group had significantly less *NRAS* mutations than others.

Cumulative hazards predicted by Stellae-123 model yielded a c-index of 0.612 for overall survival (OS), and the three risk groups had significantly different OS ($p<0.001$). We next postulated that since Stellae-123 relies on molecular features derived from the leukemic cells, it might serve as a biomarker of biological risk to predict relapse-free survival (RFS). The c-index calculated by Stellae-123 to predict RFS was 0.607, suggesting a reasonable ability to discriminate between different risk levels for RFS. Recognizing the potential variation between the original training cohort and the Taiwanese population, we addressed this concern by retraining the Stellae-123 model using Taiwanese RNAseq data. As a result, the model retraining led to significant improvements in the cross-validated c-indexes, with values of 0.656 (OS) and 0.636 (RFS), leading to an even more robust risk stratification ($p<0.001$, Figure 1A).

As we noticed overlapping grouping between Stellae-123 and ELN-2022 in both pretrained and retrained models, we explored if Stellae-123's prognostic power was independent of ELN risk status by conducting a multivariable analysis. Remarkably, in both the pretrained and retrained Stellae-123 models, whether calculated as continuous values or categorized into three groups, they consistently demonstrated discriminative power in predicting OS and RFS, irrespective of age and ELN-2022 risk, suggesting that Stellae-123 could offer additional valuable information in predicting patient outcomes.

Considering recent data showing that incorporating age helped improve the prognostication performance of ELN-2022 and that age was an independent risk factor for inferior outcome in our cohort, we examined how age could complement current risk stratification. Serial model testing revealed significant improvement of the prognostic models when age and transcriptomic data, especially the locally retrained Stellae-123 model, were combined with ELN-2022, evident by drastically declined Akaike Information Criterion (AIC) values. Time-dependent ROC curve analysis confirmed the potential of incorporating Stellae-123 and age to complement current risk stratification system (Figure 1B).

In summary, we showed that the Stellae-123 predicted both OS and relapse risk in AML patients from Taiwan. Furthermore, we demonstrated that model retraining could improve prognostication by adapting the Stellae-123 to the particularities of Taiwanese patients. Given the remarkable extrapolation of the signature, it's suggested gene expression profile be incorporated in the risk stratification of AML patients who are candidates to intensive therapy.

Disclosures Mosquera Orgueira: *AstraZeneca:* Consultancy; *Janssen:* Consultancy. **Hou:** *Astellas Pharma Ltd:* Current Employment.

Figure 1A

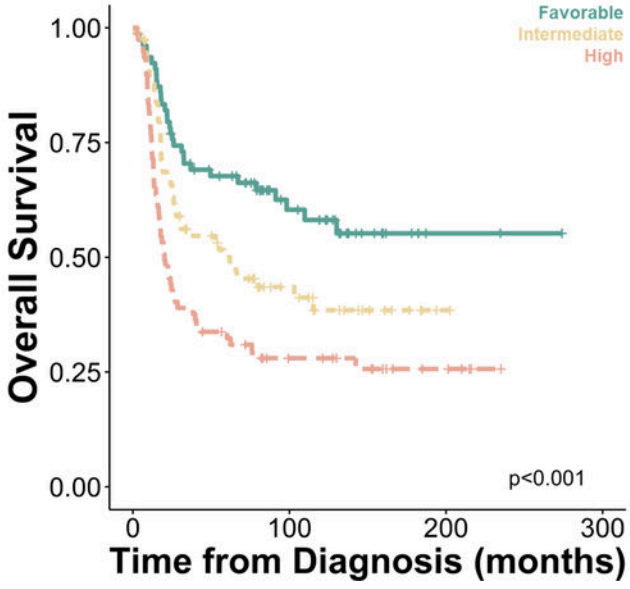

Figure 1B

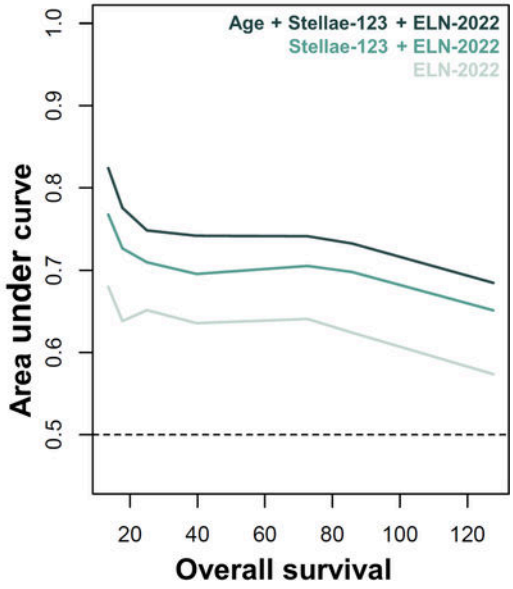

Figure 1

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