XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026
Palazzo degli Affari

XIX Congress of the Italian Society of Experimental Hematology ABSTRACT N. P060

Acute Leukemias

INTEGRATION OF GENOMIC AND CLINICAL DATA IN ACUTE MYELOID LEUKEMIA: ACTUAL PERFORMANCE OF THE SANGER MULTISTAGE PROGNOSTIC MODEL

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Introduction: Acute myeloid leukemia (AML) shows remarkable biological heterogeneity, with diverse genomic lesions driving variable clinical trajectories. Although the Sanger AML multistage model by Gerstung et al. (Nature Genetics, 2017) predicts disease transitions through multiple clinical states, its real-world performance has not been externally validated. We aimed to assess its predictive accuracy in a contemporary AML cohort and to explore the clinical-molecular determinants of treatment response.

Methods:

We retrospectively analyzed 73 AML patients (median age 61 years, range 19–81) diagnosed and treated between 2019 and 2024. Genomic profiling was performed by NGS panels covering recurrently mutated AML genes. Clinical variables, cytogenetic risk, and mutational profiles were used to compute individualized predictions through the Sanger AML multistage online tool. Observed clinical outcomes were classified at 12 and 36 months into three major groups: patients in continuous complete remission (CR), relapsed, and refractory. Agreement between predicted and observed outcomes was measured by weighted Cohen's kappa.

Results: Among 73 patients, 23 (32%) achieved durable CR, 21 (29%) relapsed, and 29 (39%) were refractory or died without remission. CR patients were significantly younger (median 51 years) and mostly treated with intensive chemotherapy (78%), while refractory cases were older (median 63 years) and frequently harbored TP53 mutations (24%) or complex karyotypes (43%). Relapsed patients showed intermediate profiles, with partial enrichment of FLT3-ITD (19%) and adverse-risk cytogenetics (40%), as reported in Table 1.

TP53 mutation emerged as the strongest independent adverse factor (HR 8.07, 95% CI 2.23–29.13, p=0.0014), conferring more than eightfold increased risk of death and a median OS of 1 month compared with 14 months in TP53 wild-type. FLT3-ITD mutations correlated with higher CR achievement (43% vs 14%, p=0.037).

At 12 months, 65 evaluable patients yielded moderate agreement between model predictions and actual outcomes (weighted κ=0.57, SE=0.10, 95% CI 0.38–0.77), with best accuracy among refractory and continuously remitted patients. Misclassifications mainly involved elderly or non-intensively treated cases. At 36 months, concordance declined to κ=0.34 (SE=0.06, 95% CI 0.23–0.46), as relapsed and long-term survivors were less reliably predicted. Alive-vs-dead concordance confirmed this trend (κ=0.55 at 12 months; κ=0.39 at 36 months). Overall, the model captured early mortality well but underestimated relapse probability, reflecting evolving treatment paradigms.

Conclusions: TP53 mutation remains the dominant adverse determinant in AML. The Sanger multistage model retains good short-term but limited long-term accuracy, emphasizing the need for retraining with contemporary therapeutic datasets and integration of dynamic molecular variables for individualized prognostication.

	CR patients (23) [range] – (%)	Relapsed patients (21) [range] – (%)	Refractory patients (29) [range] – (%)	p
Sex, male/female	11/12 (48/52)	14/7 (67/33)	15/14 (52/48)	0.416
Age at diagnosis, years	51 [19-74]	64 [24-77]	63 [31-81]	0.003
Type of AML:				
Primary	16 (70)	15 (71)	13 (45)	0.2
Secondary/therapy-related	7 (30)	6 (29)	16 (55)	
ECOG PS				
0-2	22 (96)	20 (95)	24 (83)	0.148
3-4	1 (4)	1 (5)	5 (17)	
Complex/high risk karyotype	*Available for 22*	*Available for 20*	*Available for 23*	
No	19 (86)	12 (60)	13 (57)	0.07
Yes	3 (14)	8 (40)	10 (43)	
Risk status according to ELN 2022:				
Favorable	3 (13)	6 (29)	6 (21)	0.18
Intermediate	9 (39)	3 (14)	2 (7)	
Adverse	17 (48)	12 (57)	21 (72)	
AML approach at diagnosis:				
Intensive chemotherapy	18 (78)	8 (38)	14 (48)	0.007
Non-intensive treatment	5 (22)	13 (62)	11 (52)	
Palliative care	0 (0)	0 (0)	4 (0)	
HSCT in CR1				
No	8 (35)	17 (81)	29 (100)	<0.001
Yes	15 (65)	4 (19)	0 (0)	
Median follow-up, months	18 [1-61]	4 [13-61]	2 [1-16]	
Gene mutations with significance				
FLT3-ITD	10 (43)	4 (19)	4 (14)	0.037
TP53	0 (0)	0 (0)	7 (100)	0.003