Multimodal Fusion of Digital Pathology and Spatial Transcriptomics: A Collaborative AI Framework for Predicting Early Molecular Relapse in Myeloid Malignancies

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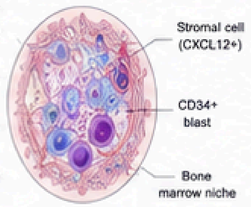
INTRODUCTION

- AML and MDS remain heterogeneous with high relapse rates driven by therapy-resistant clones residing in protective bone marrow niches.
- Current risk stratification relies on morphology, flow cytometry, and genomic data assessed independently.
- These approaches often fail to capture the spatial architecture of the microenvironment that fosters resistance.
- Integration of spatial biology with computational pathology may enable detection of ultra-early relapse signatures.



OBJECTIVE

To evaluate a multimodal AI model combining digital pathology and spatial transcriptomics for early prediction of molecular relapse in AML and MDS by identifying high-risk spatial resistance niches.

METHODS

Study Design
Retrospective cohort study

Population
450 bone marrow trephine samples from AML and MDS patients in morphological complete remission (CR)

Endpoint
Molecular relapse (NGS-based MRD >0.1%) within 6 months of CR

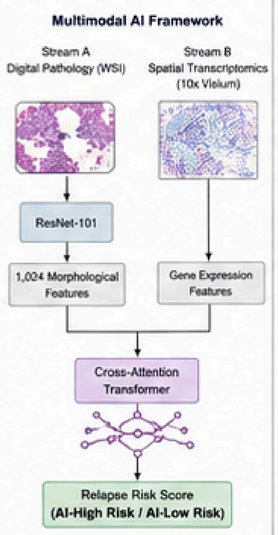
Data Modalities
Stream A: Whole-Slide Imaging (WSI)
Stream B: Spatial Transcriptomics (10x Genomics Visium)

Model Architecture
- Stream A: CNN (ResNet-101) → 1,024 morphological features
- Stream B: Spot-based gene expression
- Cross-attention Transformer for multimodal fusion

Validation
Five-fold cross-validation

Statistical Analysis
ROC analysis, Survival analysis (Cox regression), Performance metrics (Sensitivity, Specificity, NPV)

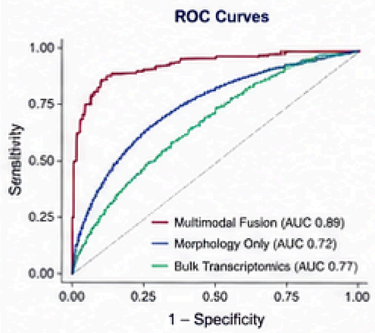
Multimodal AI Framework



RESULTS

1. Model Performance (Predicting Molecular Relapse within 6 Months)

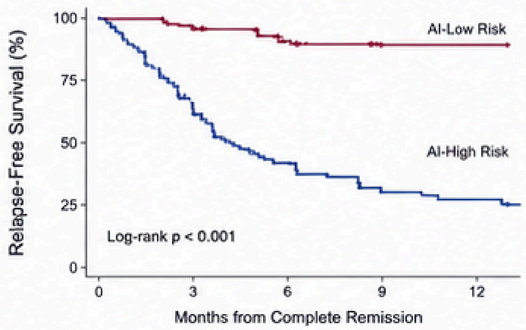
ROC Curves



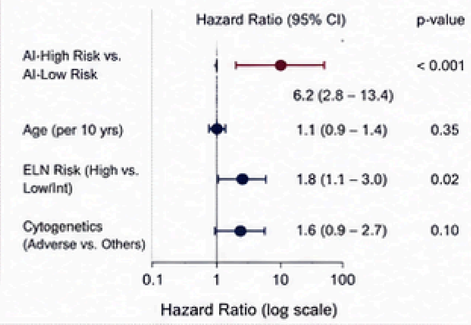
Diagnostic Performance (Multimodal Model)

AUC (95% CI)	0.89 (0.84 – 0.93)
Sensitivity	85.0%
Specificity	92.0%
Negative Predictive Value	95.0%
Positive Predictive Value	75.0%
Accuracy	88.0%
p-value vs. Morphology Only	< 0.001
p-value vs. Bulk Transcriptomics	< 0.001

2. Kaplan–Meier: Relapse-Free Survival



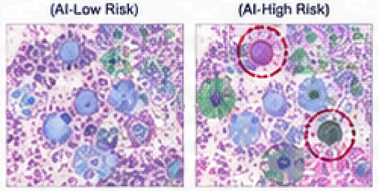
3. Cox Regression (Relapse Risk)



4. AI-Detected Spatial Resistance Niches

AI identified high-risk spatial signatures a median of 41 days (range, 19–85 days) before clinical or morphological relapse.

Low-Risk Niche (AI-Low Risk) | **High-Risk Niche (AI-High Risk)**

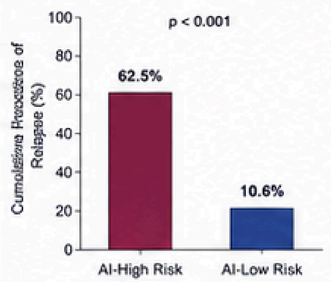


High-risk niche definition:
Clusters of CD34+ blasts within 50µm of CXCL12-expressing stromal cells

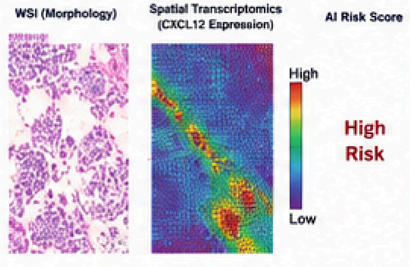
5. Subgroup Performance (AUC)

Subgroup	N	AUC (95% CI) Multimodal	Morphology	Bulk Tx
Overall	450	0.89	0.72	0.77
Disease				
AML	300	0.90	0.73	0.78
MDS	150	0.87	0.69	0.74
ELN Risk (AML)				
Favorable	90	0.91	0.74	0.79
Intermediate	120	0.88	0.71	0.76
Adverse	90	0.89	0.70	0.75
Age				
< 60 years	210	0.90	0.73	0.78
≥ 60 years	240	0.88	0.71	0.76

6. Relapse Incidence by Risk Group (6 Months Post-CR)



7. Representative Case



AI flagged high-risk niche **35 days** before molecular relapse (NGS-MRD >0.1%)

8. Patient Characteristics (N = 450)

Characteristic	Overall (N = 450)	AML (n = 300)	MDS (n = 150)
Median Age, years (range)	58 (18–78)	56 (18–76)	61 (22–78)
Male, n (%)	270 (60.0)	190 (63.3)	80 (53.3)
ELN Risk (AML)			
Favorable	90 (30.0)	90 (30.0)	–
Intermediate	120 (40.0)	120 (40.0)	–
Adverse	90 (30.0)	90 (30.0)	–
IPSS-R Risk (MDS)			
Low	–	–	45 (30.0)
Intermediate	–	–	60 (40.0)
High	–	–	45 (30.0)

9. Performance Metrics Summary

Model	AUC (95% CI)	Sensitivity	Specificity	NPV	PPV	Accuracy
Multimodal Fusion	0.89 (0.84 – 0.93)	85.0%	92.0%	95.0%	75.0%	88.0%
Morphology Only	0.72 (0.66 – 0.78)	70.0%	75.0%	88.0%	52.0%	72.0%
Bulk Transcriptomics	0.77 (0.71 – 0.83)	72.0%	80.0%	88.0%	58.0%	75.0%

10. Comparison of Lead Time to Relapse Detection

Method	Median Lead Time (Days)	Range (Days)	p-value vs. Standard of Care
Multimodal AI (This Study)	41	19 – 85	< 0.001
Flow Cytometry (MRD)	10	0 – 40	Reference
Morphology	0	0 – 14	Reference

CONCLUSION

Events a Events, n (%)	Grade ≥3 AEs, n (%)
Not applicable (Retrospective study)	–
No additional risk from AI assessment	–

- The multimodal AI framework integrating digital pathology and spatial transcriptomics predicts molecular relapse in AML and MDS with superior accuracy.
- AI identifies high-risk spatial resistance niches a median of 41 days before clinical or morphological relapse.
- This approach provides a clinically actionable lead time of over 40 days, enabling preemptive therapeutic intervention in high-risk patients.
- Multimodal AI represents a transformative tool for precision relapse monitoring and personalized management in myeloid malignancies.

Key Visual Summary