Predictive Value of Microbiome and Metabolomic Biomarkers in Myeloid Neoplasms

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Introduction

Myeloid neoplasms (MN), including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and acute myeloid leukemia (AML), are hematologic malignancies marked by genetic heterogeneity and immune dysregulation. While somatic mutations and inflammation are key pathophysiologic drivers, growing evidence highlights the gut microbiome as a critical environmental factor influencing disease phenotype, progression, and treatment outcomes.

Aim

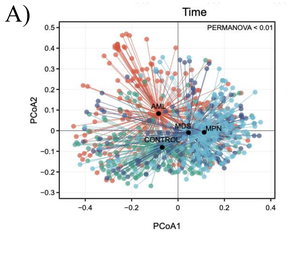
This study aimed to define microbiome signatures across MN subtypes and assess its relationship with host immunity, treatments and clinical outcomes.

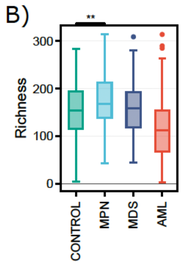
Methods

A total of 321 newly diagnosed MN patients and 180 healthy controls (HCs) were enrolled, with samples collected at diagnosis and, for high-risk MDS and AML, longitudinally during and after treatment. Shotgun metagenomic sequencing was performed on stool and bone marrow (BM) samples, alongside plasma and fecal metabolomics and BM RNA sequencing. Microbial species, virulence factors (VFs), antibiotic resistance genes (ARGs), and host gene expression were quantified and integrated through statistical and machine learning approaches.

Results

We identified distinct microbiome signatures across MN subtypes, with AML showing the most pronounced dysbiosis and lowest alpha-diversity, both associated with poor overall survival (figures A and B).

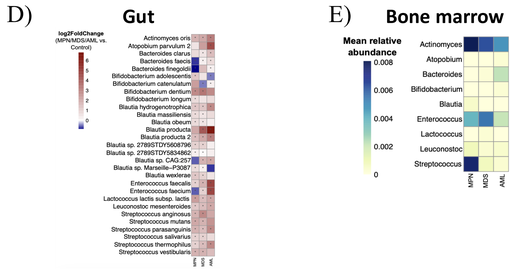




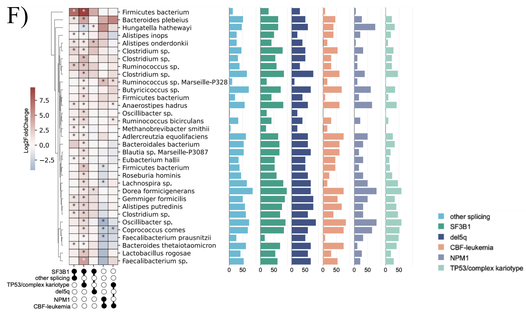
Enrichment of pathobionts (e.g., Eggerthella lenta, Enterococcus faecium) and depletion of commensal butyrate-producers (e.g., Faecalibacterium prausnitzii) were observed (figures C).



Notably, enriched gut species and their VFs were also detected in the BM, suggesting microbial translocation across a disrupted intestinal barrier and supporting a gut–BM–immune axis (figures D and E).



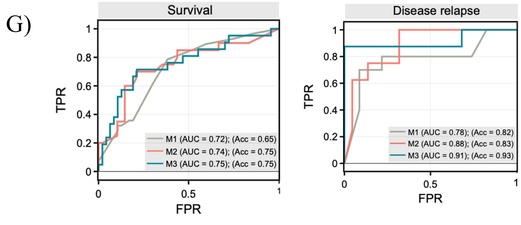
Microbiome composition further correlated with disease genotype, notably with TP53-mutated/complex karyotype MN showing marked depletion of commensals (figure F).



In high-risk MDS and AML, treatment type significantly influenced microbiome composition: intensive chemotherapy (IC) led to greater loss of microbial diversity than hypomethylating agents ± Venetoclax, and was associated with increased ARG burden in the gut.

Resistome analysis revealed four resistotypes, with resistotype 3, characterized by E. faecium enrichment, prevalent in IC-treated AML patients and those with recent antibiotic exposure.

Machine learning models integrating clinical, genomic, microbiome, and resistome data significantly improved prediction of survival, AML evolution, treatment response, infection, and relapse (figure G).



Conclusions

These findings support the integration of gut microbiome profiling into personalized risk stratification strategies in MDS and AML.

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