Global Metabolomic and Lipidomic Profiling of Bone Marrow Plasma Identifies Distinct Signatures of Minimal Residual Disease in Multiple Myeloma Patients

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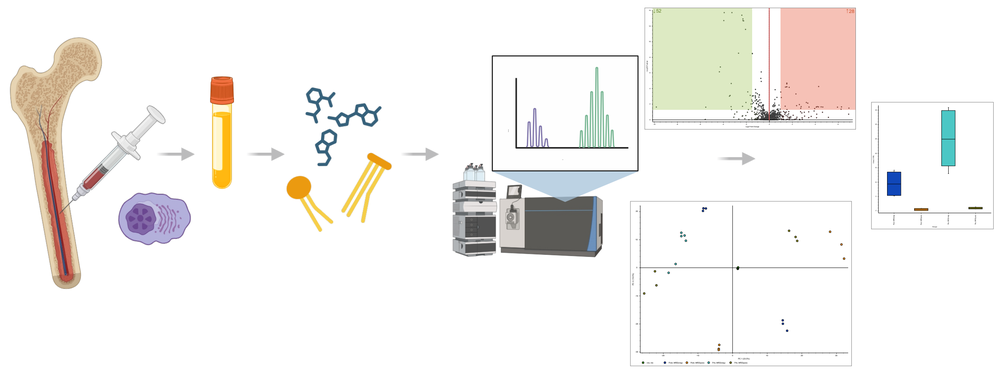
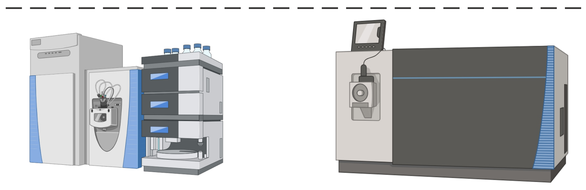
INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy, with over 188,000 new cases worldwide and nearly 121,000 deaths annually. Within the bone marrow (BM), interactions between malignant plasma cells and surrounding tissues drive disease progression. While treatments once targeted cancer cells, newer strategies harness the patient's immune system in the BM. However, relapse remains frequent due to minimal residual disease (MRD), underscoring the need for deeper BM understanding. Global metabolomics and lipidomics offer insights into metabolic and lipid signatures underlying MM, potentially revealing novel biomarkers and therapeutic targets.



METHODS

Samples and preparation: Bone marrow plasma samples (n=8) were obtained from the Oslo University Hospital Cancer Biobank, including patients at diagnosis and after first-line treatment staying minimal residual disease positive (MRD+) or achieving negative (MRD-) state. Metabolites and lipids from bone marrow plasma (BMP) samples were extracted by 100 % ice cold methanol or isopropanol (1:3, v/v), respectively. Samples were then mixed before centrifugation (10 min, 4 °C, 21 100 RCF), supernatant aliquots were mixed to create the pooled quality control (PQC). Remaining supernatant was placed in HPLC vials for analysis.



Global LC-MS Metabolomics and Lipidomics Analysis: Metabolites were separated by XRs Diphenyl column and analyzed using the Ultimate 3000 HPLC coupled to Q-Exactive Orbitrap MS (Thermo Scientific). Lipids were separated and analysed using Accucore C30 HPLC column and Vanquish Horizon UHPLC coupled to Fusion Orbitrap Tribrid.

Data processing and statistical analysis: Compound Discoverer (3.4, Thermo Scientific) was used for peak integration, alignment, SERRF QC correction, univariate and multivariate statistics and data visualisation. LipidSearch software was used for lipid identification via fragment matching. SIRIUS 6 software was used for identification of selected significant features based on isotopical, fragmentational and molecular matching.

RESULTS

We identified over one hundred metabolites (Level 1 and 2), including amino acids, purines, pyrimidines, and exogenous compounds, as well as 485 lipids in positive mode and 105 lipids in negative mode from over 20 lipid classes. PCA revealed clustering in patients before and after treatment. Univariate analysis showed multiple differentially abundant metabolites and lipids between MRD- and MRD+ post-treatment, pointing to exogenous and microbial-derived compounds.

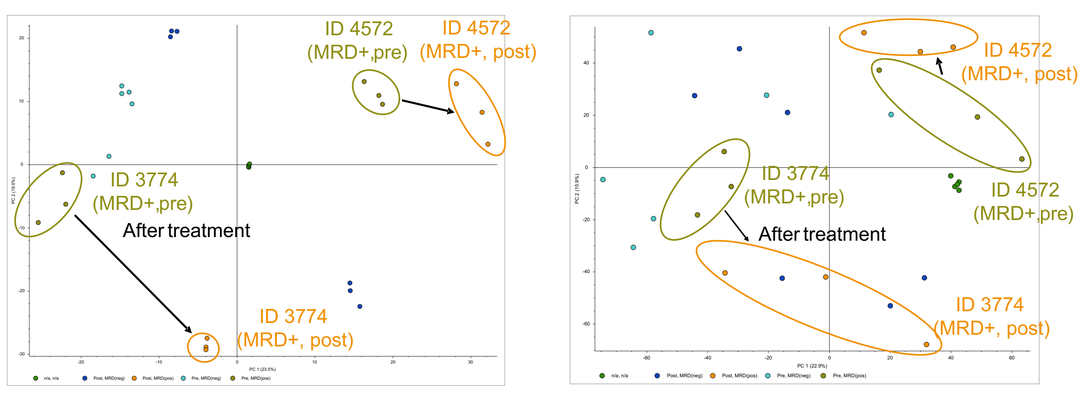


Figure 1. Principal component analysis of metabolomics and lipidomics data (positive mode) representing myeolma patients before (Pre) and after (Post) first-line treatment. Patients were stratified into those who achieved MRD negativity (MRD-) after treatment and those who remained MRD positive (MRD+). The colored elipses highlight triplicate analysis of one biological sample of one patient before and after treatment, illustrating the dynamic change of the metabolome and lipidome.

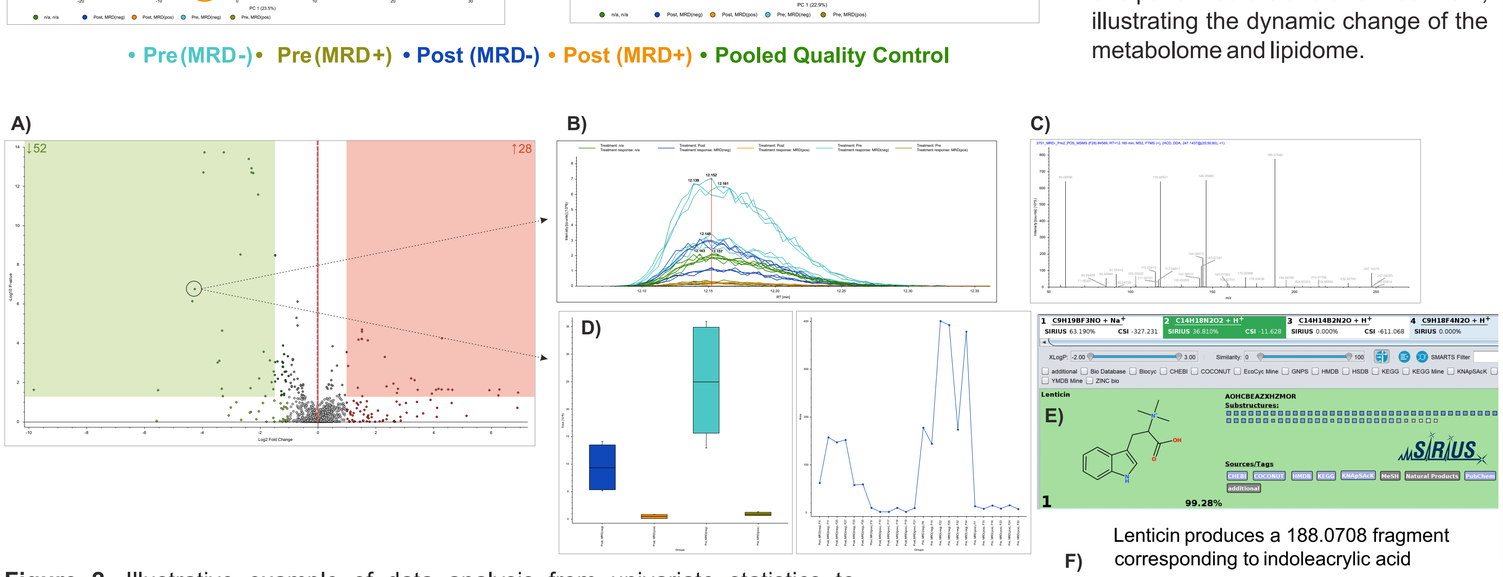


Figure 2. Illustrative example of data analysis from univariate statistics to compound identification. Univariate statistics was carried out by volcano plots (A), boxplots and trendlines (D). Significantly abundant unknown feature 247.1437 *m/z* eluting at 12.52 min (B) providing the corresponding fragmentational spectra(C) was selected. SIRIUS 6 software was used for the analysis of isotope patterns and fragmentation patterns in MS/MS spectra and search in molecular structure databases (E). The 99 % match was found for plant and microbial trypthophan-derived metabolite lenticine (also known as hypaphorine) (E, F).

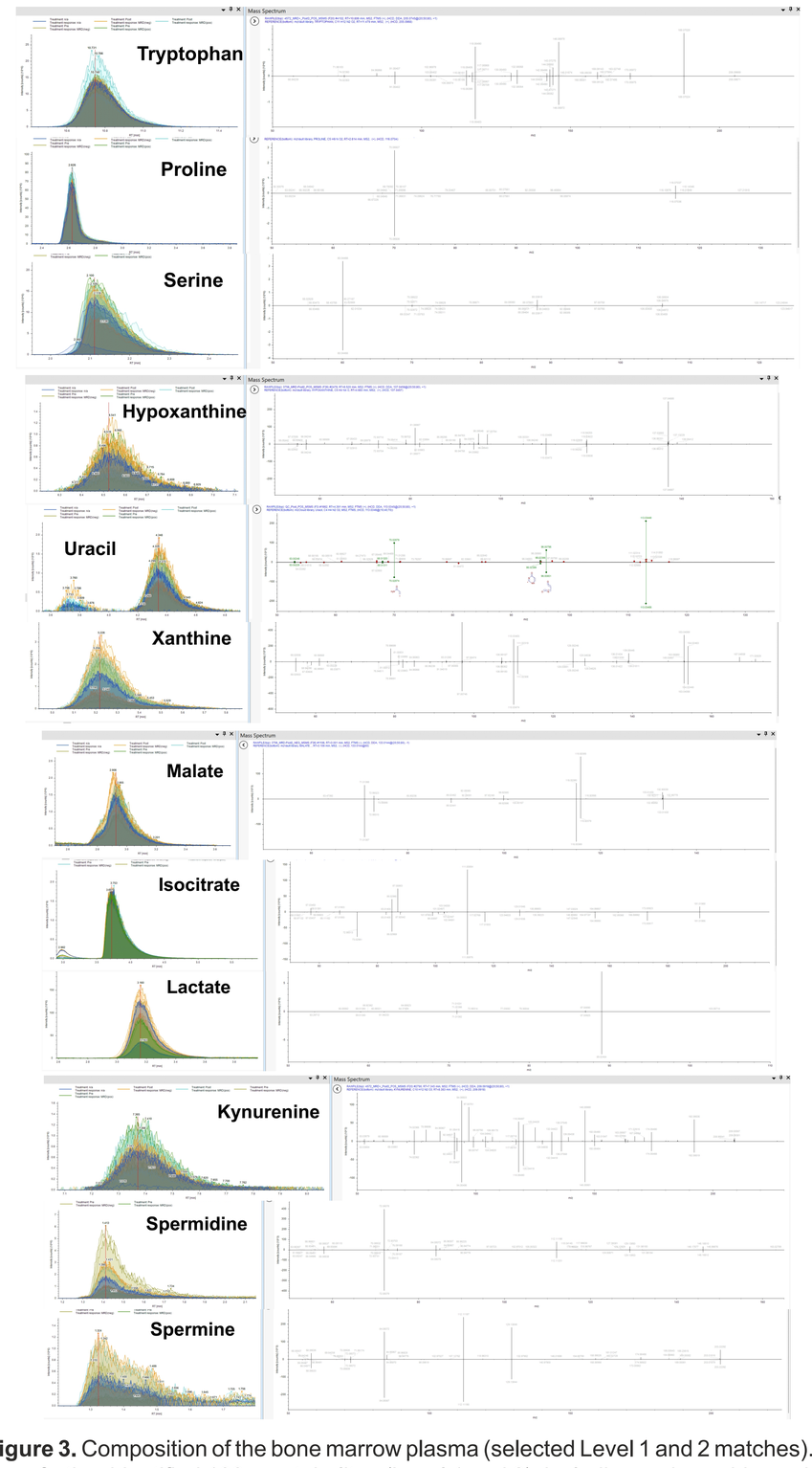


Figure 3. Composition of the bone marrow plasma (selected Level 1 and 2 matches). We have further identified 100+ metabolites (Level 1 and 2), including amino acids, purines, pyrimidines, and exogenous compounds. And by lipidomics we identified 485 lipids in positive and 105 lipids in negative mode from over 20 lipid classes identified by (grade A) fragment matching (LipidSearch).

CONCLUSION

In this pilot study we found metabolic and lipid profiles in the BM of MM patients, distinguishing MRD+ from MRD– groups. These findings highlight potential biomarkers and therapeutic targets, enabling enhanced disease monitoring, earlier intervention, and the development of more effective treatment strategies. This pilot sutdy is part of a larger cohort study where it is planned to measure 153 MM patients to validate these results.