Clinical Phenotypes from Blood Serum Protein Concentration

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INTRODUCTION

Novel techniques for measurement of disease activity (DA) and disease progression (DP) through serum proteomics can improve the management of multiple sclerosis (MS). A multivariate proteomic Multiple Sclerosis Disease Activity (MSDA) test that measures the concentrations of 18 biomarkers has been analytically and clinically validated [1, 2]. Due to the complexity of the treatment paradigm for MS (e.g., Disease Modifying Therapy (DMT) diverse mechanisms of action) and heterogeneity in the biological pathways contributing to MS pathophysiology, identifying distinct clusters of biomarker profiles can enable proteomic-based MS subtyping and support clinical interpretability of MSDA test results.

PURPOSE

To identify distinct clinical phenotypes in MS patients as defined by unsupervised clustering of serum protein concentration samples. We aim to measure differences in clinical variables of interest such as DA Score, age, disease duration, sex, active/stable status and current DMT across cluster groups.

METHODS

A total of **220** patient samples collected from a matched serum-MRI study from Rocky Mountain Multiple Sclerosis Clinic were assayed in the MSDA test to generate an overall MSDA score reflecting DA status. We used unsupervised clustering techniques to identify groups of protein profiles to identify clinical phenotypes associated with over or under-expression of all **20** proteins available on our custom assay panel. We examined distributions of MSDA scores and other key clinical variables across clusters. The algorithm that determines the overall DA Score consists of the following 18 proteins: NfL, MOG, CD6, CXCl13, CXCL9, CDCP1, CCl20, OPG, IL-12B, APLP1, TNFRSF10A, SERPINA9, PRTG, FLRT2, TNFSF13B, OPN, CNTN2 and GFAP. Two additional proteins that are not used in the MSDA algorithm but are included on the assay panel were measured as well: GH and VCAN.

Active/Stable status is a composite endpoint that combined both clinical and radiographic evidence of disease activity. Patients who had any number of Gd+ lesions, New & Enlarging T2 (N/E T2) lesions or evidence of a clinical relapse were defined as Active. For this study, the administration of steroids was used as a surrogate for evidence of clinical relapse. In some cases, steroids were administered prior to the blood draw which can potentially alter the profile of proteomic biomarkers. Determination of N/E T2 lesions to establish active status for 2 patients included comparison to prior MRIs for which the duration of time exceeded 2 years.

Table 1: Cohort Characteristics

Total number of patients	220
Number of females	175
Number of stable patients	196
Median age with [25th, 75th] percentiles (y)	49 [40, 59]
Median disease duration with [25th,75th] percentiles (y)	13 [6, 20]
Number of patients on [Natalizumab, Ocrelizumab, Glatiramer Acetate, Fumarate, Other, None]	[151, 10, 10, 29, 5, 15]

RESULTS

Figure 1: We used Agglomerative Clustering (with euclidean affinity and ward linkage) on log of protein concentrations, and after optimizing the distance threshold for the most even distribution of cluster sizes as well stability of the clusters, we found 6 distinct clusters in the 20-dimensional protein space.

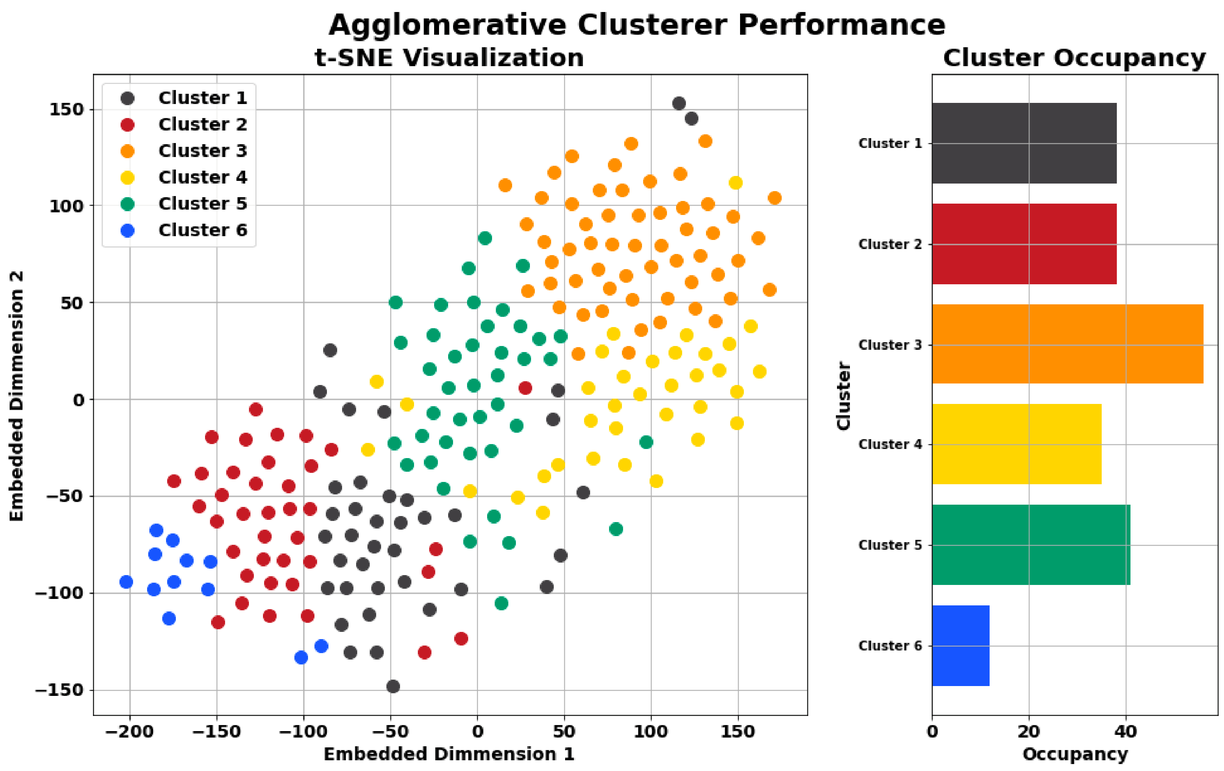
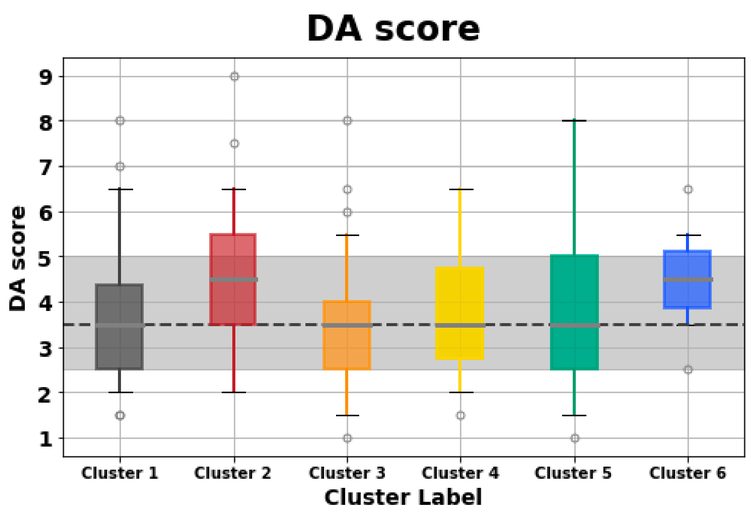


Figure 2: The following plot shows the distribution of MSDA scores across clusters, as well as their median and 25th and 75th percentiles.

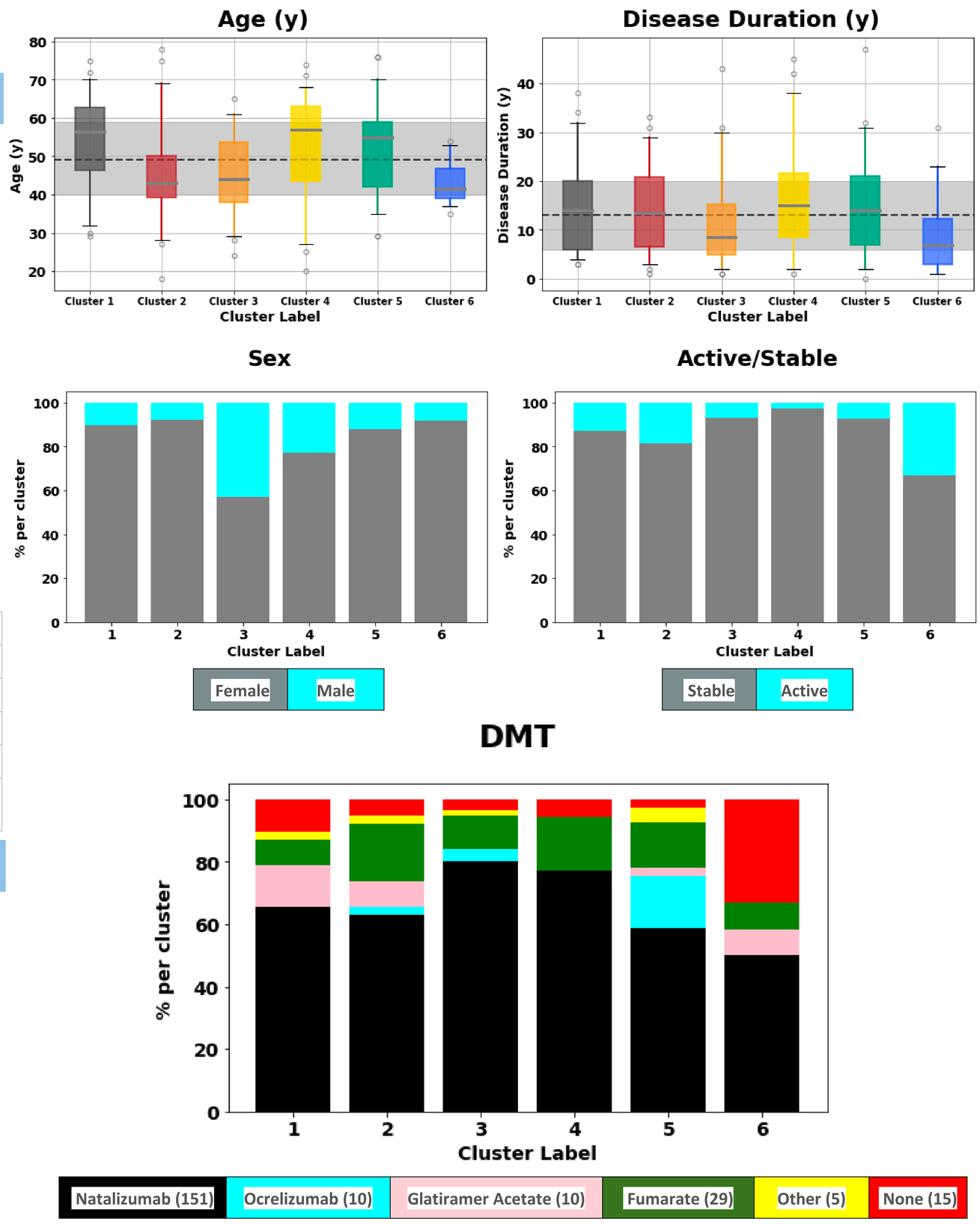


CONCLUSIONS

We find evidence for six pheno-clusters in protein concentration data which map into differences in MSDA scores, as well as several clinical variables including age, disease duration, sex and active/stable status. Cluster 6 had the highest overall DA scores and correspondingly the highest percentage of active patients. These pheno-clusters will be further evaluated in a cohort of >500 patients that have been analyzed in a real-world setting for further exploration of variables of interest including disease pathway scores, the impact of duration of DMT, and for comparisons of DMTs with diverse mechanisms of action.

RESULTS (continued)

Figures 4-8: The following plots show the distribution of various categorical and continuous clinical variables across clusters, as well as their median and 25th and 75th percentiles for continuous variables.



Disease activity is highly correlated with active/stable state of patients.
(pearson r = 0.85, p = 3.28e-05 between MSDA median and % active in each cluster)

What do we learn from protein signatures of the clusters?

From the emergent clusters, we can learn insights otherwise not accessible.

Cluster 6 is capturing younger patients with higher MSDA scores, low disease duration, highest active percentage, and highest percentage of "no DMT". This cluster is capturing patients who are not on therapies with high sensitivity. **This particular protein signature could be promising for MS diagnosis.**

Two other clusters emerge that are associated with the **most common high efficacy therapies:**

Cluster 3 has the highest percentage and absolute number of **Natalizumab** patients. This cluster's patients are mostly stable and have lower MSDA scores. This cluster is capturing younger patients with lower disease duration. And interestingly, it is the cluster with highest male percentage.

Cluster 5 is capturing most of the **Ocrelizumab** patients. This cluster's patients are older, have medium disease duration, and have a slightly higher MSDA score, compared to Natalizumab-heavier clusters.

REFERENCES AND DISCLOSURES

References: [1] Hu W. et al. 2021. Analytical Validation of a Multivariate Proteomic Serum Based Assay for Disease Activity Assessments in Multiple Sclerosis, P010 ACTRIMS 2021 [2] Chitnis T. et al. 2021. Clinical Validation Study Results of a Multivariate Proteomic Serum Based Assay for Disease Activity Assessments in Multiple Sclerosis, P574 ECTRIMS 2021

Disclosures: Ati Ghoreyshi, Anisha Keshavan and Ferhan Qureshi are employees of Octave Bioscience. Victor Gehman was an employee of Octave Bioscience at the time the study was performed. Tammy Hoyt has nothing to disclose. John Foley has received research support from Biogen, Novartis, Adamas, Octave, Genentech, and Mallinckrodt. He received speakers' honoraria and acted as a consultant for EMD Serono, Genzyme, Novartis, Biogen, and Genentech. He has equity interest in Octave. He is the founder of InterPro Biosciences.

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