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Performance comparison of a multi-protein Multiple Sclerosis Disease Activity Test for blood serum samples that were collected before versus after the MRI scan

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Ferhan Qureshi[1], Shannon Mccurdy[1], Elisa Sheng[1], Kian Jalaleddini[1], Anisha Keshavan[1], James Eubanks[1], Ati Ghoreyshi[1], Tammy Hoyt[2], John Foley[2], Tanuja Chitnis[3, 4]

[1]Octave Bioscience, Menlo Park, United States, [2]Rocky Mountain Multiple Sclerosis Clinic, Salt Lake City, United States, [3]Brigham and Women's Hospital, Boston, United States, [4]Harvard Medical School, Boston, United States

Introduction

The Multiple Sclerosis Disease Activity (MSDA) Test is a validated multi-protein assay that measures 18 protein biomarkers and utilizes an algorithm to determine a Disease Activity (DA) score [1]. In this research, we investigate the robustness of the predictive performance when serum is collected before MRI. The ability to predict disease activity using a blood based biomarker test prior to radiographic evidence or clinical manifestations would enhance the care of MS patients by enabling potential interventions.

Objectives

To determine whether the overall DA score model probabilities predict the primary disease activity endpoint used for clinical validation, T1 gadolinium lesions, with similar performance when serum was collected prior to MRI versus after MRI.

Methods

- We re-examine the serum samples and concurrent MRI reports (within 60 days of the blood draw date) used to clinically validate the MSDA Test. We divide the serum-MRI paired data into two groups: serum before MRI and serum after MRI, depending on whether the serum collection occurred before the MRI or on or after the MRI.
- Serum was assayed using the MSDA Test. The presence or absence of T1 gadolinium (Gd+) lesions was determined from the MRI report. Predictive performance is measured by the Area Under the receiver operating Curve (AUC) for the DA score model probability from the MSDA Test and the presence or absence of Gd+ lesions.
- We synthesized data with varying equivalence margins to select a margin, Δ, corresponding to a Type I error of α=0.05 and power, 1-β, of approximately 0.80. We tested for noninferiority of the AUC for serum before MRI compared to serum after MRI using the observed data and Δ selected from the simulation study.

		Serum Before MRI (N=53)		**Serum After MRI** (N=135)	
		mean	stddev	mean	stddev
MRI lag (days)[1]		13.7	12.1	-9	10
Age (years)		40.2	13.4	43.4	13.4
MSDA Score		4.7	2	4.8	2.2
		count	%	count	%
Gd+:	No	32	60.4	80	59.3
	Yes	21	39.6	55	40.7
Sex:	Female	35	66	99	73.3
	Male	18	34	36	26.7
Site:	AUB	26	49.1	33	24.4
	BWH	6	11.3	55	40.7
	RMMSC	10	18.9	42	31.1
	UMASS	11	20.8	5	3.7

[1]MRI date - serum date; negative lag indicates serum was collected after the MRI

Table 1: Serum-MRI paired data summary statistics, grouped by serum before MRI and serum after MRI, depending on whether the serum collection occurred before the MRI or on or after the MRI.

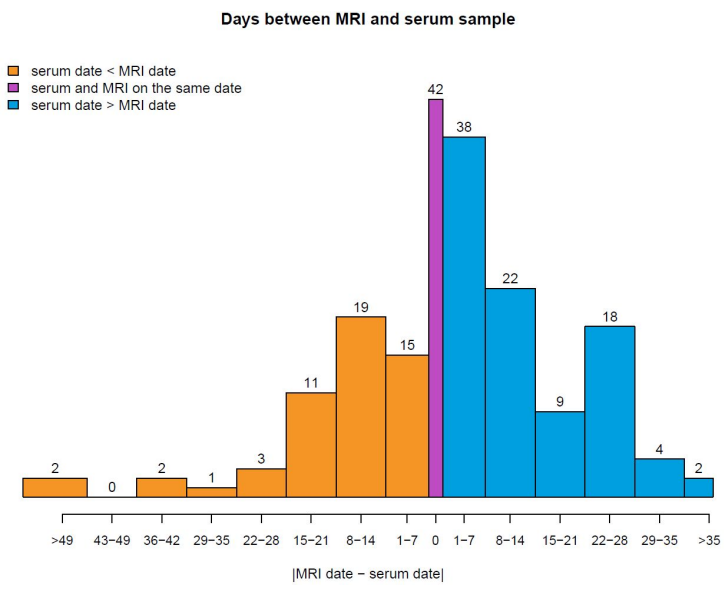

Figure 1: Distribution of days between the MRI and serum sample dates for the N=188 serum-MRI paired datapoints.

Results

- The observed AUC was similar for the serum before MRI group (SB_AUC = 0.754, bootstrapped 90% CI = [0.630, 0.870]) compared to serum after MRI group (SA_AUC = 0.788, bootstrapped 90% CI = [0.721, 0.850]).
- We selected an equivalence margin of Δ = 0.161 to correspond to a Type I error of α = 0.05 and power of 1 - β = 0.809 for the noninferiority test of H0: SB_AUC - SA_AUC ≤ -Δ versus H1: SB_AUC - SA_AUC > -Δ in simulated data.
- We rejected H0 in the observed data, concluding SB_AUC is no worse than SA_AUC - Δ.

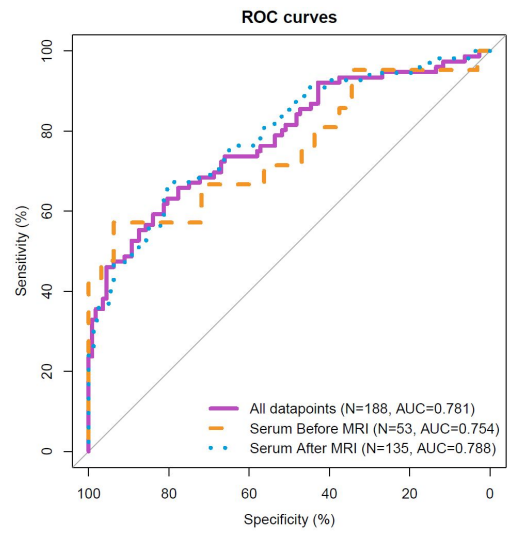

Figure 2: ROC curves for all serum-MRI paired datapoints (N=188), only datapoints with serum before MRI (N=53) and only datapoints with serum on or after MRI (N=135).

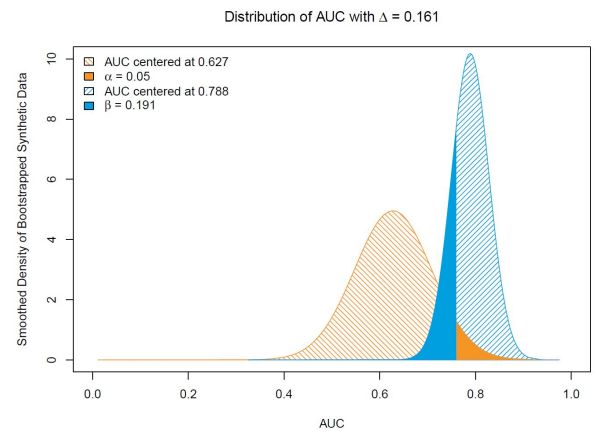

Figure 3: Smoothed density of bootstrapped AUC using synthetic data corresponding to an equivalence margin Δ = 0.161. The value of Δ was selected based on a manual search to obtain β of approximately 0.20 from two bootstrapped AUC distributions centered at 0.788 and 0.788 - Δ, where the critical value is the 95%ile from the latter distribution

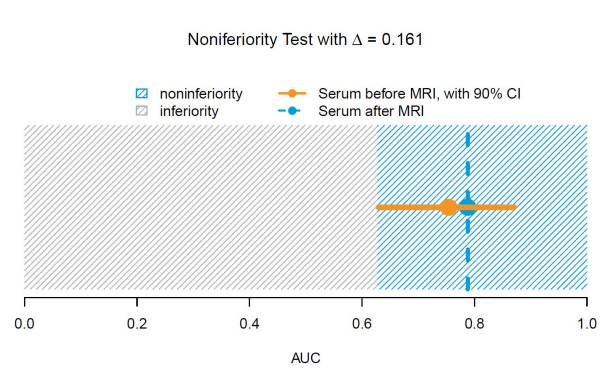

Figure 4: Noninferiority of AUC for the serum before MRI group compared to the serum after MRI group is shown by the 90% CI falling within the noninferiority region.

Conclusions

- The results indicate blood serum collection before MRI (within 60 days) does not affect the efficacy of the MSDA test as a quantitative measurement tool for evaluation of disease activity.
- Similarly high predictive performance in the serum before MRI group indicates the biomarkers underlying the MSDA test may be able to pick up on disease activity before MRI.
- Our methodology is useful for powering future studies of predictive performance.
- Future work aims to study the extent of equivalence with greater lags between paired serum-MRI data and/or narrower equivalence margins

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References: [1] Chitnis T, Foley J, Ionete C, et al. Clinical Validation of a Multi-protein, Serum-based Assay for Disease Activity Assessments in Multiple Sclerosis. Clinical Immunology. Aug 2023. https://doi.org/10.1016/j.clim.2023.109688