PHENOTYPIC CLUSTERING OF HIV-ASSOCIATED ATHEROSCLEROSIS AND AGE-RELATED OUTCOMES

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BACKGROUND

- While people with HIV have increased cardiovascular disease (CVD) risk, conventional CVD risk equations underperform in this population suggesting that the underlying mechanisms are not fully elucidated
- Machine learning involves algorithms that learn from raw data points, facilitating analysis of large datasets to identify novel phenotypes
- We used machine learning to develop phenotypic profiles of individuals with subclinical carotid atherosclerosis, and to determine whether these phenotypes differentially associate with age-related disease

METHODS

SOURCE DATA: MACS/WIHS COMBINED COHORT STUDY (MWCCS)

- The MWCCS prospectively follows people with and without HIV infection at 14 sites in the United States

STUDY POPULATION AND CAROTID ATHEROSCLEROSIS DEFINITION

- 2,670 participants free of coronary heart disease had non-invasive B-mode ultrasound of the right carotid artery performed in 2004-2006
- 425 (38% women) identified with plaque (focal intima media thickness [cIMT] >1.5 mm) were included in this analysis

STATISTICAL ANALYSIS

- Random forests and hierarchical clustering on ~80 factors assessed at time of ultrasound grouped people into phenotypically similar clusters

Domain	Variables
Demographic, behavioral	age, race/ethnicity, income, education, smoking, IDU history, crack/cocaine use, alcohol use, cohort
Clinical, cardiometabolic	BMI, waist and hip circumference, waist-to-hip ratio, SBP, DBP, pulse pressure, cholesterol (total, HDL, LDL), triglycerides, aspirin use, hypertension, diabetes, use of anti-hypertensive/lipid-lowering/diabetes medications, HgA1c, serum glucose and insulin, eGFR, family history of CVD
Carotid artery	no. of plaques, common carotid artery IMT, distensibility, echogenicity (grey scale median)
Clinical chemistry	WBC, RBC, hematocrit, mean corpuscular volume, platelets, monocytes, eosinophils, basophils, ASP, ALT, ALP, GGT, albumin, blood urea nitrogen, creatinine, bilirubin, calcium, phosphate
Gynecologic	menopause status (STRAW+10 criteria), anti-Mullerian hormone level
HIV and HCV	HIV RNA, CD4, CD8, CD4:CD8 ratio, ART meds/adherence, history of AIDS, HCV status/treatment
Inflammation, coagulation	hsCRP, IL-6, sCD14, sCD163, galectin-3, galectin-3 binding protein, D-dimer

- We assessed the association of each cluster with mortality, hospitalization rates, and cognitive decline over 13 years follow-up

  Cognitive decline estimated using demographically corrected Z-scores based on:
  1) Trail Making Test, Part A (psychomotor, info. processing speed), 0-300 seconds
  2) Trail Making Test, Part B (executive function), 0-300 seconds
  3) Symbol Digit Modalities Test (psychomotor, info. processing speed), 0-110 correct

RESULTS

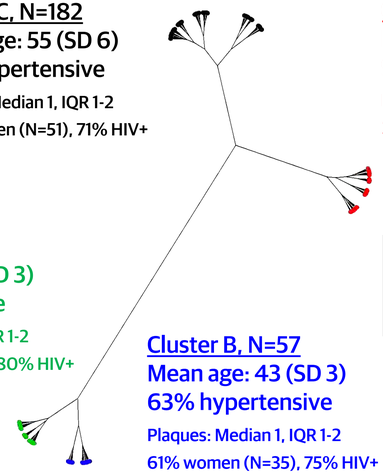
1. CLUSTERING OF PARTICIPANTS WITH CAROTID ARTERY PLAQUE (N=425)

Cluster C, N=182
Mean age: 55 (SD 6)
36% hypertensive
Plaques: Median 1, IQR 1-2
28% women (N=51), 71% HIV+

Cluster D, N=106
Mean age: 55 (SD 6)
92% hypertensive
Plaques: Median 2, IQR 1-2
26% women (N=28), 59% HIV+

Cluster A, N=80
Mean age: 42 (SD 3)
5% hypertensive
Plaques: Median 1, IQR 1-2
59% women (N=47), 80% HIV+

Cluster B, N=57
Mean age: 43 (SD 3)
63% hypertensive
Plaques: Median 1, IQR 1-2
61% women (N=35), 75% HIV+



Unrooted dendogram, in which each "leaf" represents a single participant. Distance between leaves denotes random forest-based proximity (average participant-to-participant distance), using number of plaques, common carotid artery intima-media thickness (IMT), distensibility/stiffness, and echogenicity as labels.

Summary: We identified 4 distinct clusters that differed by age and hypertension (p<0.001)
- Clusters C and D (mean age 55) on average 13 years older than A and B
- Clusters B and D much more likely to be hypertensive than A and C

2. SELECTED CHARACTERISTICS OF 4 ATHEROSCLEROSIS CLUSTERS

	Clusters				P-values		
	A (N=80)	B (N=57)	C (N=182)	D (N=106)	Over-all	A vs. B	C vs. D
Demographics							
Race/ethnicity (%)							
Black	41	56	26	42	<0.001	0.08	<0.01
Hispanic	19	19	6	5			
Income <$30,000/yr (%)	74	79	52	60	<0.001	0.55	0.27
Carotid artery							
Mean CCA-IMT (mm)	0.73 (0.08)	0.84 (0.18)	0.81 (0.18)	0.84 (0.18)	<0.001	<0.001	0.11
Mean elasticity (10^5×N/m^2)	6.52 (7.67)	7.72 (3.84)	7.67 (4.30)	10.1 (5.81)	<0.001	<0.001	<0.001
HIV-specific*							
Mean CD4+ count (cells/uL)	428 (296)	528 (318)	477 (287)	513 (325)	0.30	0.12	0.02
HIV RNA <200 cp/mL (%)	46	72	59	58	0.07	0.01	0.28
Current ART use (%)	75	74	71	74	0.92	0.73	0.33
History of AIDS (%)	28	19	38	29	0.10	0.27	0.06

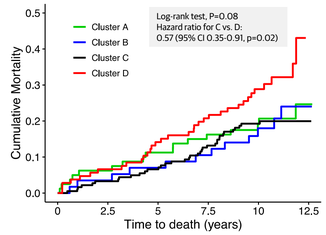
	Clusters				P-values		
	A (N=80)	B (N=57)	C (N=182)	D (N=106)	Over-all	A vs. B	C vs. D
Cardiometabolic							
Current smoking (%)	60	54	33	54	<0.001	0.48	<0.001
History of diabetes (%)	6	26	13	20	0.01	<0.01	0.12
Treated for HTN** (%)	50	44	88	51	<0.001	0.99	<0.001
Mean body mass index (kg/m^2)	24.5 (3.6)	30.9 (7.8)	24.8 (4.2)	26.8 (5.3)	<0.001	<0.001	<0.001
Mean bilirubin (mg/dL)	0.67 (0.64)	0.66 (0.48)	0.88 (0.86)	0.69 (0.41)	0.03	0.94	0.01
Biomarkers							
Median hsCRP (ug/mL) (IQR)	1.1 (0.6-3.7)	2.9 (1.1-5.3)	1.6 (0.7-4.3)	1.9 (1.0-4.6)	0.01	<0.01	0.14
Median IL-6 (pg/mL) (IQR)	0.76 (0.54-1.48)	1.26 (0.90-2.21)	0.98 (0.64-1.63)	1.06 (0.77-2.34)	0.13	0.08	0.19
Median galectin-3 (ng/mL) (IQR)	8.09 (6.87-10.47)	10.23 (9.01-12.04)	9.64 (7.63-11.00)	9.71 (8.06-11.9)	0.02	<0.01	0.39
Median D-dimer (standardized) (IQR)	-0.30 (-0.49--0.01)	-0.26 (-0.43--0.06)	-0.19 (-0.39-0.13)	-0.08 (-0.40-0.37)	0.09	0.69	0.26

*Among those with HIV. **Among those with hypertension. Pairwise comparisons compare groups of similar age. ANOVA, T-tests, or chi-square tests used to determine unadjusted P-values as appropriate.

3. ASSOCIATION OF CLUSTERS WITH AGE-RELATED OUTCOMES

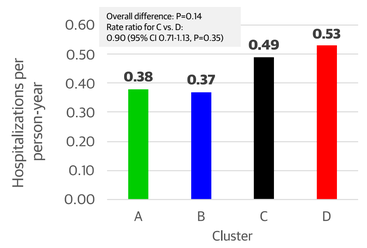
A. Cumulative all-cause mortality

Kaplan-Meier estimates and Cox proportional hazards regression



B. Hospitalization rate

Poisson regression with GEE



C. Cognitive decline

Linear mixed effects model, with random intercept by ID

	Trail Making Test, Part A		Trail Making Test, Part B		Symbol Digit Modalities Test	
	Beta	P-value	Beta	P-value	Beta	P-value
Cluster (vs. Cluster D)						
Cluster C	0.133	0.30	0.071	0.60	0.111	0.40
Cluster B	0.008	0.96	-0.062	0.73	0.111	0.52
Cluster A	0.095	0.55	0.103	0.54	0.113	0.48
Time (per 6-mo. interval)	-0.017	<0.001	-0.017	<0.001	-0.021	<0.001
Cluster * Time interaction						
Cluster C * Time	0.010	<0.001	0.013	<0.001	0.011	<0.001
Cluster B * Time	0.018	<0.001	0.018	<0.001	0.014	<0.001
Cluster A * Time	0.016	<0.001	0.012	<0.001	0.019	<0.001

Interpretation of results, using Trail Making Test, Part A (TMTA) as example

- *Cluster C has a 0.133 higher Z-score for TMTA (p=0.30) at baseline than Cluster D*
- *Each 6-month time interval after baseline is associated with a 0.017 decrease in the TMTA Z-score (p<0.001) in Cluster D*
- *Every 6 months, the TMTA Z-score for Cluster C decreases by 0.007 (i.e., [-0.017] + 0.010), which represents less decline than in Cluster D (p<0.001)*

Summary: Over 13 years of follow-up, compared with Cluster D, C had:
1. Better survival (hazard ratio 0.57, 95% CI 0.35-0.91, p=0.02)
2. Less cognitive decline (p<0.001) across 3 measures, as above

Outcomes for Cluster C similar to Clusters A and B despite older age

CONCLUSIONS

- We identified a profile of individuals with subclinical atherosclerosis (Cluster C) who, as they entered their 6th decade, seemed to represent more of a "healthy aging" phenotype than others of the same age (Cluster D)
  - Outcomes for C were more similar to those 13 years younger (A, B)
- Future work should further characterize this group and identify mechanisms underlying their apparent resiliency