Systemic and Vascular Inflammation Predict Comorbidities in Treated HIV Infection

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Background

- Although inflammation and immune dysfunction are implicated in the pathogenesis of comorbidities in people with HIV (PWH), whether an immune risk profile can predict PWH at higher risk of comorbidities is unclear.

Objectives

•To determine if inflammatory profiles comprised of biomarkers reflecting different inflammatory pathways predict co-morbidities in treated PWH

Methods

•In the UCD Infectious Diseases Cohort Study of PWH on antiretroviral therapy (ART), we measured 23 biomarkers using bead-based quantitative ELISA on the Luminex Magpix platform (Table 1)

Table 1: Custom Multiplex Biomarker panel*

Biomarkers functional group	Biomarkers analysed
Markers of systemic inflammation	hsCRP, IL-2, IL-6, TNFR1+2, TNF-α, IFN-G
Markers of coagulation	vWF, D-dimer, sCD40L
Markers of endothelial function	E-selectin, P-selectin, sICAM-1, VCAM
Markers of atherosclerosis	MPO, Lp-PLA2
Markers of immune regulation	IL-1RA
Markers of innate immune activation	MIP-1α, MCP-1, sCD163, sCD14
Markers of microbial translocation	IL-18, LBP

*TNFR, Tumour Necrosis Factor Recptor; IFN-g, Interferon gamma; MCP, Monocyte Chemoattractant Protein ; MIP-1, Monocyte Inflammatory Protein-1; MPO, myeloperoxidase, LpPLA2, Lipoprotein associated Phospholipase A2; vWF, von Willabrand Factor; LBP, lipopolysaccharide binding protein; IL, Interleukin; RA, receptor antagonisit

- Principal component analysis (PCA) was performed followed by unsupervised hierarchical clustering (HC) to partition subjects into biomarker-derived clusters
- Differences between cluster demographics was assessed using Chi-Square and Kruskal Wallis tests.
- Logistic regression was used to assess associations between clusters and prevalent comorbidities [cardiovascular (CVD), kidney (CKD), liver disease (CLD), hypertension (HTN), dyslipidemia (DysL)).
- Analysis was performed using SPSS ver.24 and R vers.3.6.

Results

- 99 PWH were included in the analysis, median (IQR) age 41 (36.8, 48.0) years, 44.5% male; 54.5% African and 8% PWID.
- 37 subjects had a history of comorbidities (CVD, n=5; CKD, n=2; CLD, n=15; HTN, n=20; DM, n=6) while 10 had multimorbidity.
- Following PCA and unsupervised HC three distinct clusters were identified.

Acknowledgments

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Results

Figure 2: Standarised Inflammatory Biomarkers grouped by Clusters

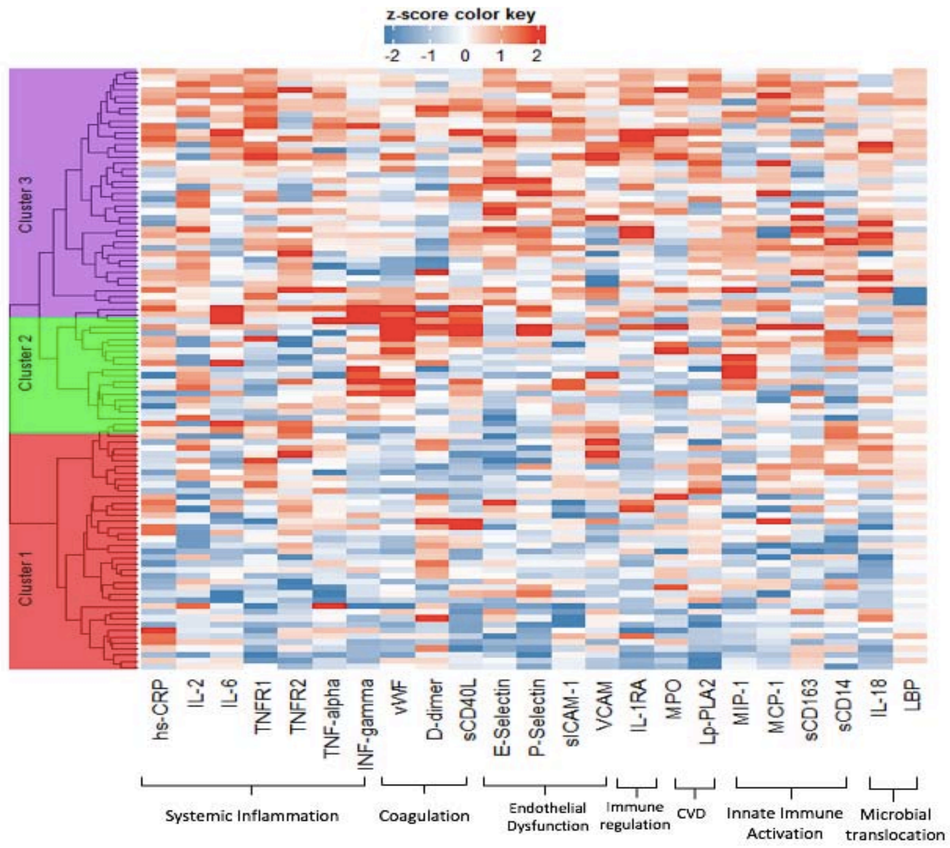


Table 1: Cluster Demographics

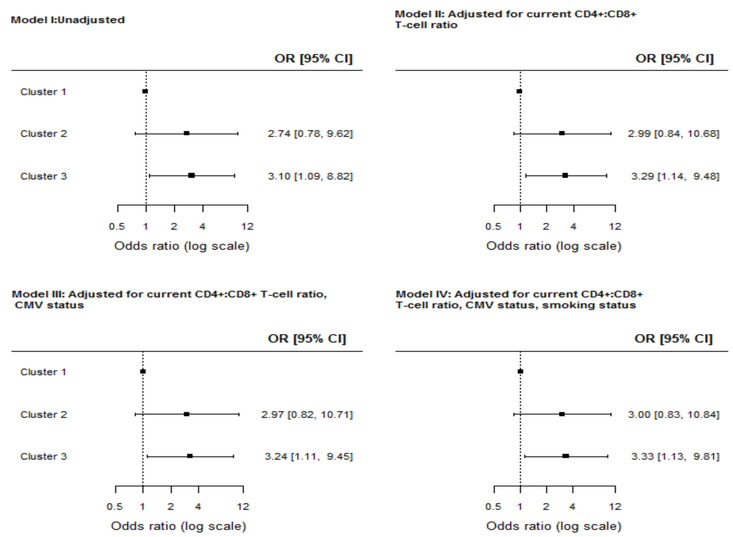
	Cluster 1 (n=35)	Cluster 2 (n=19)	Cluster 3 (n=45)	P value
Age (IQR)	40.7 (37.6, 47.9)	40.4 (34.9, 44.5)	44.3 (39.1, 49.3)	**0.047**
Male	10 (22.7%)	8 (18.2)	26 (59.1%)	**0.032**
African	26 (74.0%)	14 (73.7%)	14 (31.1%)	**0.001**
Transmission risk				0.343
Heterosexual	23 (65.7%)	13 (68.4%)	27 (60.0%)	
MSM	6 (17.1%)	2 (10.5%)	10 (22.2%)	
Smoking	6 (17.1%)	4 (21.1%)	12 (26.7%)	0.591
Nadir CD4+ count	364 (230, 526)	332 (269, 427)	363 (181, 506)	0.798
CD4/CD8 ratio	0.8 (0.5, 1.1)	0.9 (0.7. 1.3)	0.9 (0.7, 1.2)	0.353
ART duration	4.8 (1.5, 10.8)	8.2 (2.5, 10.7)	7.49 (3.7, 11.6)	0.218
CMV IgG positive	31 (88.6%)	17 (89.4%)	37 (82.3%)	0.57
HCV Ab pos.	4 (11.4%)	1 (11.1%)	8 (17.8%)	0.373
HIV RNA <40 copies/ml	34 (97.0%)	18 (94.5%)	41 (91.0%)	0.526
Comorbidity	7 (20%)	8 (42%)	22 (48.9%)	**0.027**

•Cluster 1 (n=35) was characterized by low levels of vascular, innate immune and systemic inflammation while cluster 2 and 3 by higher inflammation; Cluster 2 reflecting platelet/macrophage pathways and cluster 3, systemic, vascular and endothelial pathways as determined by V test ranking (data not shown).

Results (cont)

- Subjects in Cluster 3 were more likely **older, male** and **non-African** while other demographics did not differ significantly between clusters.
- Although both inflamed clusters, Cluster 2 and 3, had higher prevalence of comorbidities compared to cluster 1, only cluster 3 was significantly associated in logistic regression analysis (Figure 2).
- Adjusting for CD4:CD8 ratio, CMV serostatus and smoking status did not alter the strength of this association.

Figure 3: Relationship between Inflammatory Clusters and Comorbidities
(OR: odds ratio, 95% CI: 95% Confidence Interval, CMV: cytomegalovirus)



- Cluster 1, characterized by lower vascular, innate immune and systemic inflammation was associated with **reduced risk of comorbidities** (OR 0.28 [0.10, 0.74])
- This association persisted after adjustment for CD4/CD8 ratio, smoking status and CMV serostatus (OR (95%CI): 0.31[0.11, 0.86] p=0.025) and again for age, gender and ethnicity (OR 0.32 [0.11, 0.90], p=0.03).

Conclusions

- We have identified distinct inflammatory patterns in treated PWH that predict both enhanced and reduced risk of prevalent comorbidities.
- That this association persists after adjustment for selected confounders suggests alternate inflammatory pathways contributing to comorbidity pathogenesis in treat PWH.
- In this analysis with over half of participants female and African, subjects in Cluster 3 were more likely male and Caucasian which may suggest an enhanced vulnerability to comorbidities in this group.
- Further work is needed to examine this analytic approach in a larger cohort and assess utility of this method in prospective studies in identifying PWH at risk of comorbidities.

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