Inflammatory clusters are associated with multimorbidity and Cardiovascular disease in People with HIV on effective treatment

0578

Padraig McGettrick[1], Willard Tinago[1], Alejandro Garcia Leon[1], Stefano Savinelli[1,3] Eoin Feeney[1,3] Eavan Muldoon[2], Tara McGinty[1,2], Aoife Cotter[1,2], John Lambert[2], Gerard Sheehan[2], Alan Landay[4], Patrick W. G. Mallon[1,3]

1. Centre for Experimental Pathogen Host Research, University College Dublin, Ireland, 2. Department of Infectious Diseases, Mater Misericordiae University Hospital, Dublin, Ireland, 3. Department of Infectious Diseases, St. Vincent's University Hospital, Dublin, Ireland, 4. Rush University Medical Center, Chicago, United States of America

Introduction

People with HIV (PWH) on antiretroviral therapy (ART) are at increased risk of comorbidities, including cardiovascular disease (CVD). Traditional CVD risk assessments under-estimate CVD risk in PWH, with underlying inflammation thought to contribute to excess, unmeasured risk. Strategies in order to identify PWH at risk of developing multimorbidity and CVD are lacking. We examined bioprofiling inflammatory pathways of participants as a novel strategy to identify those at risk of multimorbidiy and CVD.

Methods

The UCD Infectious Diseases Cohort Study recruited PWH on effective ART and analysed 27 biomarkers of systemic, innate and vascular inflammation by chemiluminescence immunoassays and 7 T-cell markers by flow cytometry: CD4+ and CD8+ T-cell senescence (CD57+,28-), activation (CD38+, HLADR+), exhaustion (PD-1+) and T-regulatory cells (CD4+, 25+, FoxP3+).

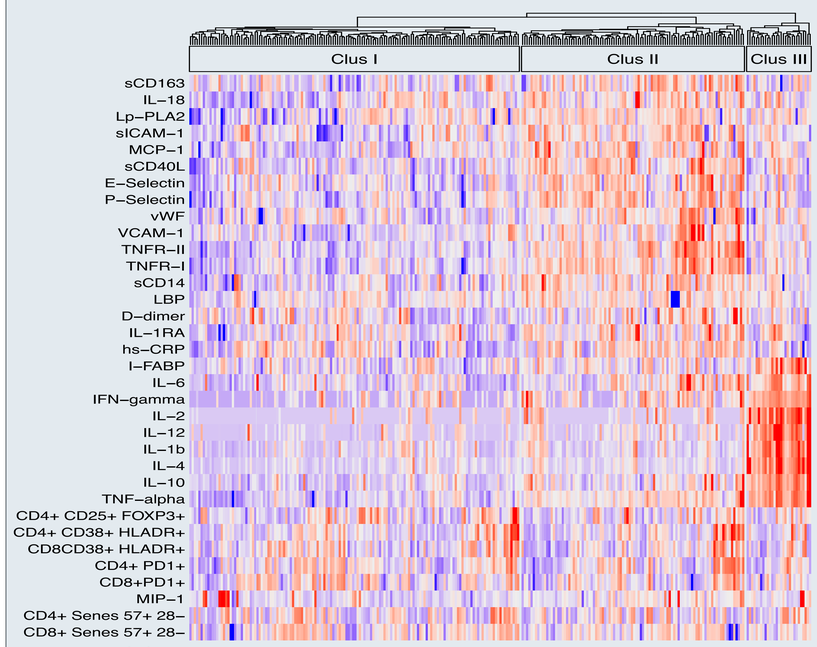
Principal component analyses was used to reduce redundancy in the biomarker dataset and identify principal components which contributed most to the inflammatory variance in the study population.

Individualized principal component derived coeffecients for study participants was then calculated which allowed partition of participants into biomarker-derived clusters using unsupervised hierarchical clustering.

Acknowledments

We wish to thank the participants of the ID Cohort study for their time and effort in contributing to this data.

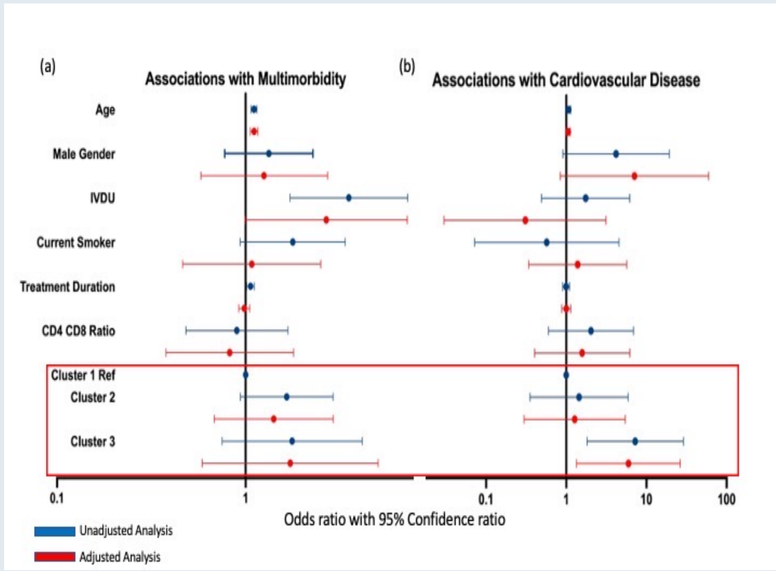
Figure 2: Characterisation of biomarker derived clusters



IVDU; Intravenous drug user, ref: reference, IL, Interleukin;MCP-1 Monocyte chemoattractant protein; vwf, von willibrand factor; VCAM1, Vascular cell adhesion molecule;TNFR, tumour necrosis factor receptor; LBP, LPS binding protein; IL-1RA, IL-1receptor antagonist; I-FABP,intestinal fatty acid binding protein; MIP-1, macrophage inflammatory protein

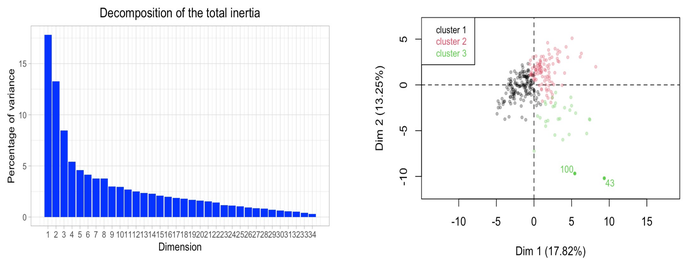
Figure 3: Aassociations between variables and (a) multimorbidity and (b) CVD

Adjusted for (a): Age ethnicity, IVDU, Smoking, Treatment duration and (b) age, gender, IVDU, smoking, total and LDL cholesterol



In a cohort of PWH on effective ART, individuals can be partitioned into groups of inflammatory profiles based on patterns of inflammation, with specific inflammatory profiles associated with both multimorbidity and Cardiovascular disease.

Figure 1: Scree plot of principal components identified from inflammatory dataset and (b) unsupervised hierarchical clustering analysis



Having identified inflammatory clusters we explored associations between clusters and:

(a) multimorbidity (2 or more of CVD, Hypertension, Dyslipidaemia, malignancy, Osteoporosis, Diabetes, Kidney, Liver, respiratory or psychiatric disease)

(b) Cardiovascular disease (myocardial infarction, angina, stroke, peripheral vascular disease).

Methods-continued

Contribution of original biomarkers to cluster formation was assessed using quantitative variable analysis

Multivariate models were assessed including variables associated with endpoints on univariate analysis ($p<0.1$). Data are reported as median unless stated.

Results

277 PWH were included in the analysis. Median age was 44 (39, 50) years old, 57.4% were male, 45% Caucasian and 25.1% were current smokers.

Following principal component analysis and unsupervised hierarchical cluster analysis, three biomarker derived clusters were identified. Cluster 1 (n=148, 53.4%) was characterized by **lower** biomarker values of systemic (TNFa, TNFR1, TNFR2, IFN-gamma, IL-6, IL-1b), vascular (P-selectin, E-selectin, VCAM, ICAM-1) and innate (sCD14, MCP-1) inflammation.

Results-continued

In contrast cluster 2 (n=100, 36.1%) was characterized by **higher** values of vascular and innate inflammation and cluster 3 (n=29, 10.5%) was characterized by **high** values of markers of T-cell activation and proliferation (IL-1b, TNFa, IL-6, IFN-gamma, IL-10, IL-12, IL-2, IL-4) and microbial translocation (IFABP). There was no significant differences in demographics, HIV or immunological indices between clusters.

77 (27.8%) individuals reported a history of multimorbidity and 13 (5%) with a history of CVD.

On univariate analysis both cluster 2 and 3 were associated with multimorbidity compared to non-inflamed cluster 1 (see figure 3a), although association failed to reach statistical significance. Cluster 3, however, was significantly associated with CVD (figure 3b).

On multivariate analysis, after adjustment for age, gender, smoking, IVDU, total and LDL cholesterol, Cluster 3 remained significantly associated with CVD [adjusted odds ratio 7.07 (95% confidence interval 1.28, 38.9), p=0.025]. .

Conclusion

In a cohort of PWH on ART, individuals can be partitioned into clusters of inflammatory patterns, with clusters characterised by higher inflammation associated with multimorbidity and more specifically CVD.

Further studies are warranted to examine the utility of bio-profiling populations to identify and stratify individuals at high risk of developing CVD for targeted preventative interventions.