Principal Components Analysis to Identify Biomarkers Predictive of Non-AIDS Events

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BACKGROUND

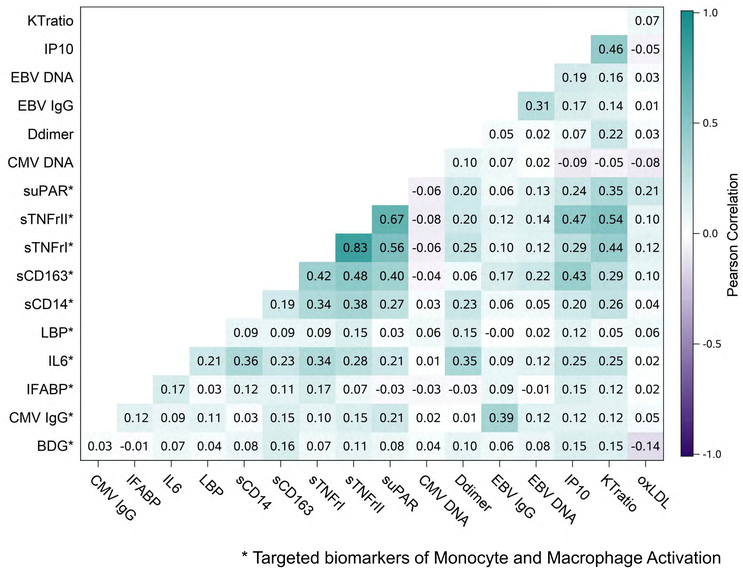
- Studies continue to generate numerous individual biomarkers due to technologic improvements and large specimen repositories
- Potential for increased risk of type I error analyzing multiple individual biomarkers: concern for false positive findings
- Statistical approaches that combine biomarkers or target a subset of biomarkers can aid in biological understanding and improve statistical efficiency
- The best high-dimensional analytic methods are not clear

METHODS

- Utilized ACTG case-control[1] study of biomarker predictors of non-AIDS clinical events for analysis
  - 143 cases and 315 matched-controls
  - ART-naïve at baseline and on suppressive ART at 1 year
  - Baseline characteristics: Median age 45 years, 85% male sex, 49% white non-Hispanic and 31% black non-Hispanic, median CD4 count 215 cells/μL, median HIV RNA 4.8 log10 copies/ml; gender not available
- 17 biomarkers previously measured[1,2,3,4] at year 1 of suppressive ART were considered for analysis [**Figure 1**]
  - Targeted subset of 10 biomarkers of monocyte and macrophage activation* was pre-specified
- Three statistical approaches:
  (1) simple, equally-weighted average of all biomarkers **(Naïve All)** and targeted biomarkers **(Naïve MM)**
  (2) optimally-weighted combination of targeted biomarkers from confirmatory factor analysis **(CFA MM)**
  (3) optimally-weighted combination of all biomarkers from principal components analysis (PCA)
- Number of principle components (PCs) determined with scree plots, % variability explained by the PCs, and interpretability of biomarkers groupings
- Biomarkers log-10 transformed, normalized (mean 0, SD 1)
- Summary scores from each method analyzed with conditional logistic regression models to evaluate risk of subsequent non-AIDS events

RESULTS

Figure 1. Correlations between biomarkers at Year 1



* Targeted biomarkers of Monocyte and Macrophage Activation

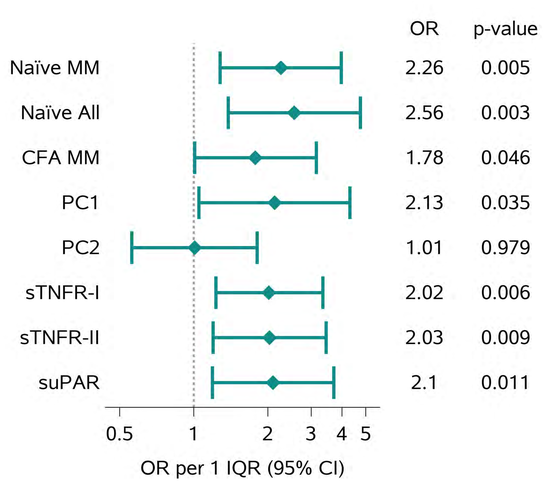
Table 1. Correlations between PC Scores and Biomarkers

	PC1	PC2
BDG*	0.08	0.21
CMV DNA	-0.14	0.19
CMV IgG*	0.11	0.63
Ddimer	0.36	0.02
EBV DNA	0.06	0.59
EBV IgG	-0.00	0.80
IFABP*	0.08	0.18
IL6*	0.52	0.18
IP10	0.48	0.35
KTratio	0.64	0.19
LBP*	0.27	0.11
oxLDL	0.24	-0.09
sCD14*	0.49	0.07
sCD163*	0.50	0.31
sTNFrI*	0.82	0.06
sTNFrII*	0.88	0.08
suPAR*	0.71	0.01

- Two principle components best described the data (vs 1 or 3 PCs)
- Each PC primarily composed of distinct biomarker subsets as shown by correlations in **Table 1.** Strongest associations:
  - PC1: IL-6, IP-10, KT Ratio, sCD14, sCD163, sTNFr-I, sTNFr-II, suPAR (consistent with *a priori* list)
  - PC2: CMV IgG, EBV IgG, EBV DNA
- In assessing predictors of non-AIDS events [**Figure 2a and 2b**]:
  - All methods performed well with this dataset
    - PCA may be preferred since unsupervised, allows multiple biomarker scores, and uses all biomarkers
  - PC1 associated with increased risk of all non-AIDS events [**Figure 2b**] and the subset of MI/Strokes [**Figure 2a**]
  - PC2 related to all non-AIDS events, but not MI/Strokes
  - Effects were similar to those reported for strongest individual predictors (sTNFr-I, sTNFr-II, suPAR)[1,2]

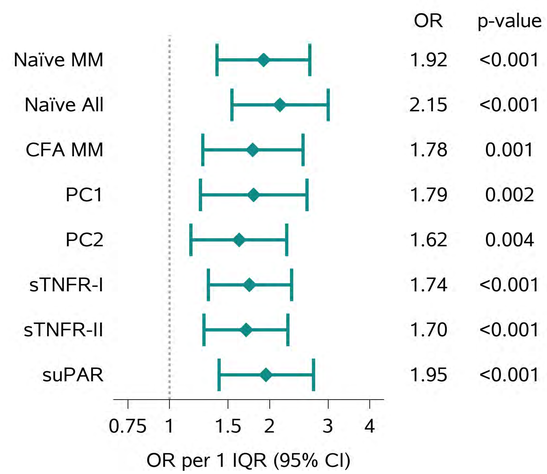
Figure 2. Odds ratios (OR) from conditional logistic regression - Biomarkers at Year 1

a. Risk of MI/strokes



MM: Monocyte and Macrophage biomarkers
CFA: Confirmatory Factor Analysis
PC: Principal Component

b. Risk of All Events



Events: 41 MI/Stroke
52 Malignancy
37 Serious Bacterial Infection
13 Deaths due to other causes (non-accidental)

CONCLUSIONS

- **PCA useful high-dimensional tool to:**
  - **Reduce number of statistical comparisons**
  - **Characterize meaningful biomarker profiles/clusters**
  - **Identify specific biomarkers to consider as endpoints in future interventional trials**
- **Naïve approach did well with this dataset, but biomarkers had strong positive associations in individual analysis**
  - **Positive or negative effects of biomarkers could exist in other applications**
  - **Numerical simulations will provide further insights**
- **In our analysis we confirmed sTNFr-I and –II and suPAR were strongest predictors of non-AIDS events**
  - **Supports sTNFr-II as primary endpoint in ACTG studies**

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[1]Tenorio AR , Zheng Y, et al. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis 2014; 210:1248–59.
[2]Hoenigl M, Moser CB, et al. Soluble Urokinase Plasminogen Activator Receptor Is Predictive of Non-AIDS Events During Antiretroviral Therapy-mediated Viral Suppression. Clin Infect Dis. 2019 Aug 01; 69(4):676-686.
[3]Hodowanec AC, et al. Increased CMV IgG Antibody Titer is Associated with Non-AIDS Events among Virologically Suppressed HIV-Positive Persons. Pathog Immun. 2019; 4(1):66-78
[4]Gianella S, Moser C, et al. Presence of asymptomatic CMV and EBV DNA in blood of persons with HIV starting antiretroviral therapy are associated with non-AIDS clinical events. AIDS. 2020 Jan 30