

Differential correlation network analysis illustrates novel biomarker interactions underlying hyperinflammation in pediatric ARDS



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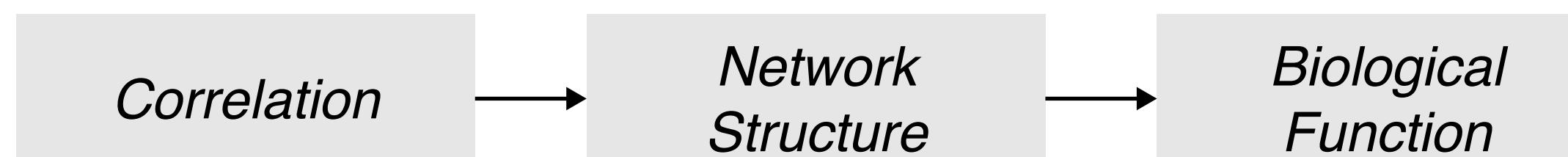
Background

Inflammatory subphenotypes derived from circulating proteins identify elevated risk of mortality, longer ICU stays, and differential treatment responses in ARDS patients with elevated inflammatory biomarkers. Despite their utility, little is understood about the biological mechanisms producing these differential effects.

Network analysis can identify significant protein-protein interactions but is scarcely employed in current ARDS studies.

In this work, we present a novel correlation-based network analysis that directly compares the correlative structure behind inflammatory subphenotypes. By measuring change in these correlations, we produce a new perspective on their biological meaning:

Standard approach:



Our approach:



Methods

1. Subphenotypes are derived from a filtered panel of N=41 plasma biomarkers of inflammation using latent profile analysis (LPA) and Spearman correlations are computed between all markers within each subphenotype;

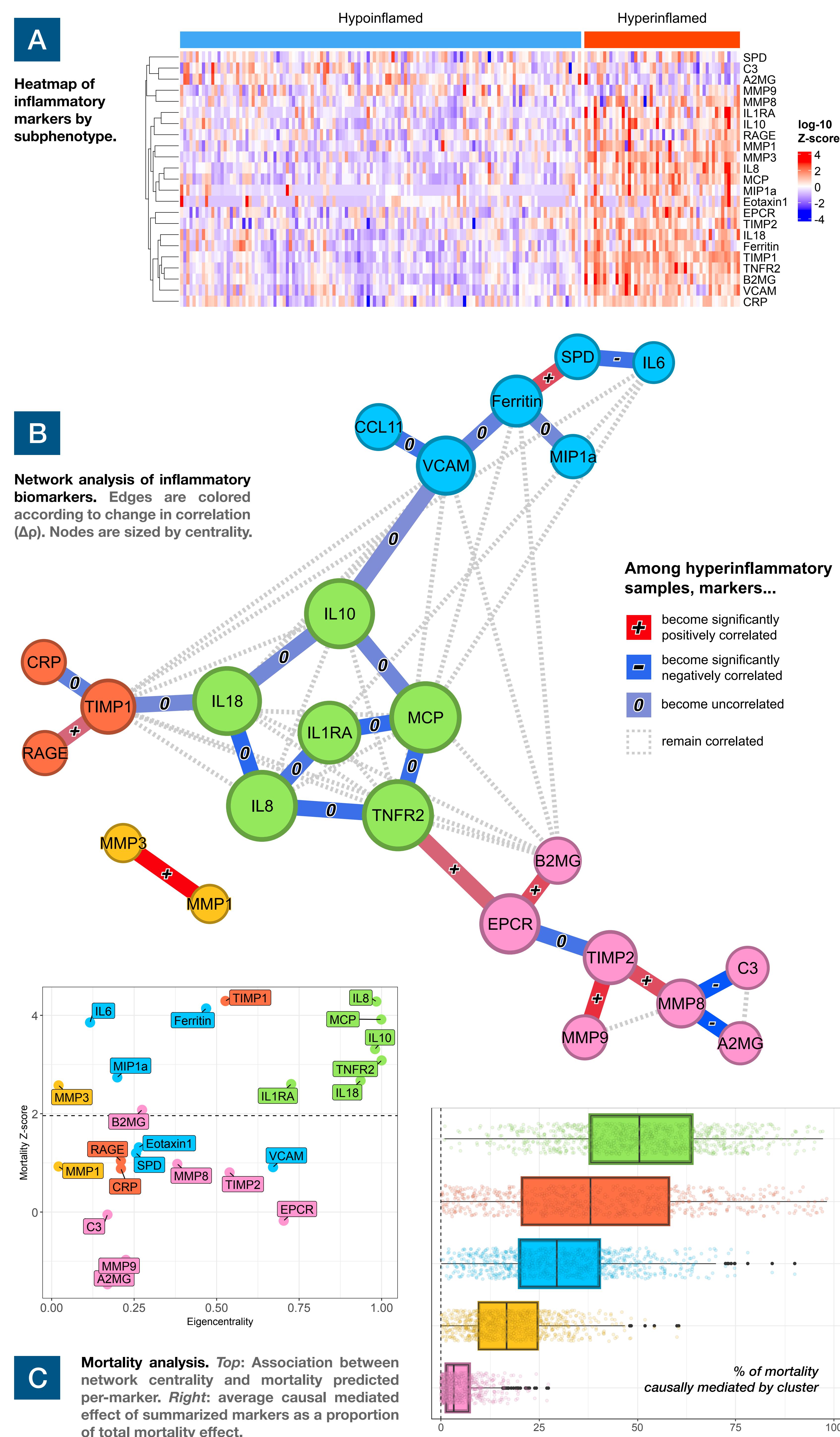
2. The delta-correlation matrix is derived from the classes' pairwise correlation matrices by subtraction:

$$\begin{matrix} \text{Hyper} & \text{Hypo} \end{matrix} - \begin{matrix} \text{Hyper} & \text{Hypo} \end{matrix} = \begin{matrix} \text{Change} \end{matrix}$$

3. Network analysis is performed on filtered **correlation changes**, and statistics are computed including eigenvector centrality and community detection by modularity;

4. Marker clusters are summarized with dimensionality reduction (PCA, UMAP) and associated with known subphenotypes and 90-day mortality;

5. Mediation analysis is performed on marker clusters using *mediation* package with bootstrapping, using quantile regression on summarized marker log-concentrations.



Results

Inflammatory subphenotypes identify significant differential outcomes (A).

- Latent profile analysis discovered 50 (27.9%) patients with hyperinflammatory subphenotype with significantly higher mortality (OR 5.07, P<0.0001).

Biomarker correlations change significantly in hyperinflamed patients (B).

- N=22 biomarkers experience $> 0.2\rho$ change in correlation between classes (permutation P < 0.05)
- Most of these markers become decorrelated (P > 0.05) in hyperinflammatory samples

Interleukin-10 signaling is central to the change in hyperinflamed correlations (B).

- The green cluster consists of markers involved in IL-10 signaling (GO:0004920) and experiences broad decorrelation in hyperinflammatory samples (Mean correlation change = -70%)

Centrality in the change network correlates with mortality association (C, left).

- Significant correlation between eigencentrality and per-marker mortality Z-score (P < 0.05)
- IL-10 module has significantly higher eigencentrality (P < 0.001) and mortality significance (P < 0.05) compared to other modules

The Interleukin-10 module most significantly mediates the mortality effect of the latent classes themselves (C, right).

- Summarized expression of the green IL-10 module significantly causally mediates 50.4% of the latent class mortality effect (P = 0.01, N=1000 simulations)

Discussion

1. Changes in biomarker relationships encode significant information about latent class subphenotypes and mortality.

- These changes may reflect differences in functional interactions specific to hyperinflammatory patients.
- Differential network analysis exposes separation between markers that otherwise typically appear similar (ex. IL6 & IL8).

2. Interleukin-10 associated markers are most significant in causal mediation of subphenotype mortality enrichment.

- IL-10 related markers were independently clustered based on inflammatory subphenotype-specific restructuring, suggesting a common functional shift specific to subphenotype.
- Expression of these markers constitutes most of the mortality enrichment of subphenotypes and can be used parsimoniously for simpler subphenotype classification.