

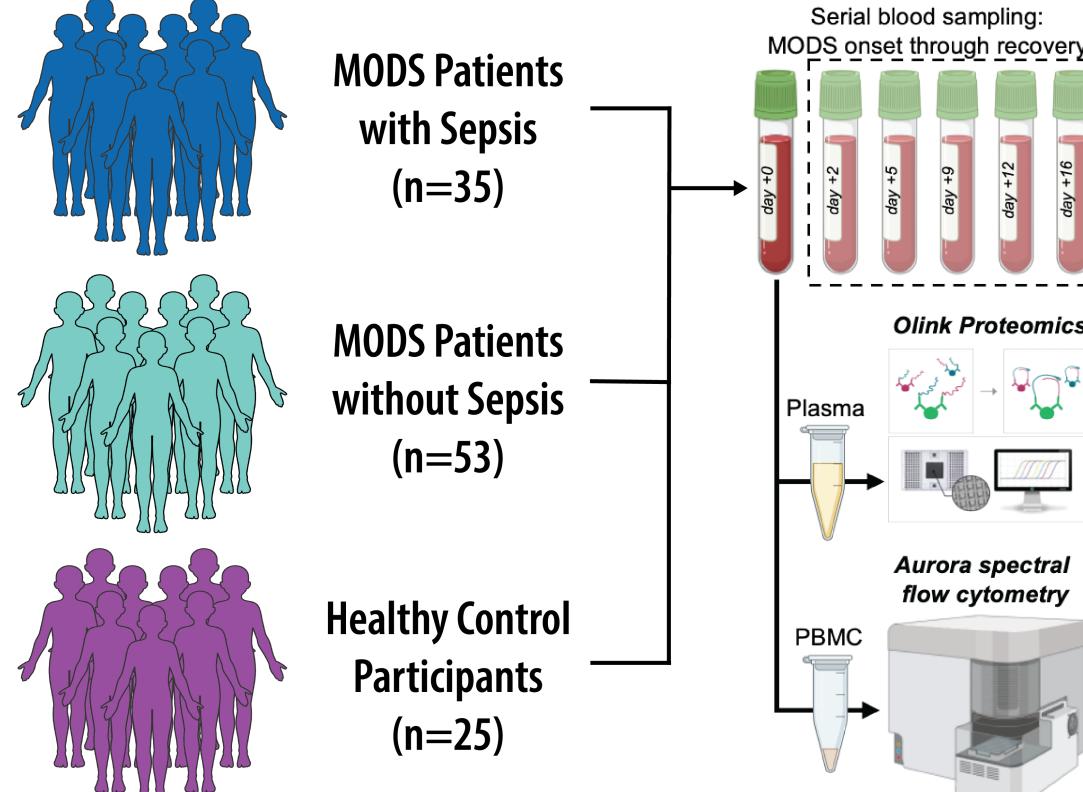
A Prognostic Proteomic Signature of Immune Dysregulation Is Present at Onset of Multiple Organ Dysfunction Syndrome in Pediatric Patients With and Without Sepsis

Robert B. Lindell, Samir Sayed, Jose S. Campos, Montana Knight, Andrea A. Mauracher, Ceire A. Hay, Peyton Conrey, Julie C. Fitzgerald, Nadir Yehya, Stephen T. Famularo, Teresa Arroyo, Richard Tustin III, Hossein Fazelinia, Edward M. Behrens, David T. Teachey, Scott L. Weiss, Mark W. Hall, Athena F. Zuppa, Deanne Taylor, Rui Feng, E. John Wherry, Nuala J. Meyer, Sarah E. Henrickson

BACKGROUND

- Sepsis is a leading cause of death of hospitalized children.
- Mortality is often related to development of multiple organ dysfunction syndrome (MODS).
- We designed a longitudinal MODS multiomics cohort to identify severity-associated MODS subphenotypes defined by targetable mechanisms of immune dysregulation.
- We hypothesized that:
 - the plasma proteome at MODS onset would reflect disease severity, and
 - mechanisms of immune dysregulation would differ between MODS patients with and without sepsis.

STUDY DESIGN



Schematic of patient cohorts and sampling pipeline.

- MODS onset defined by modified Proulx criteria.
- Single-center ancillary to PARADIGM study of pediatric MODS.

RESULTS

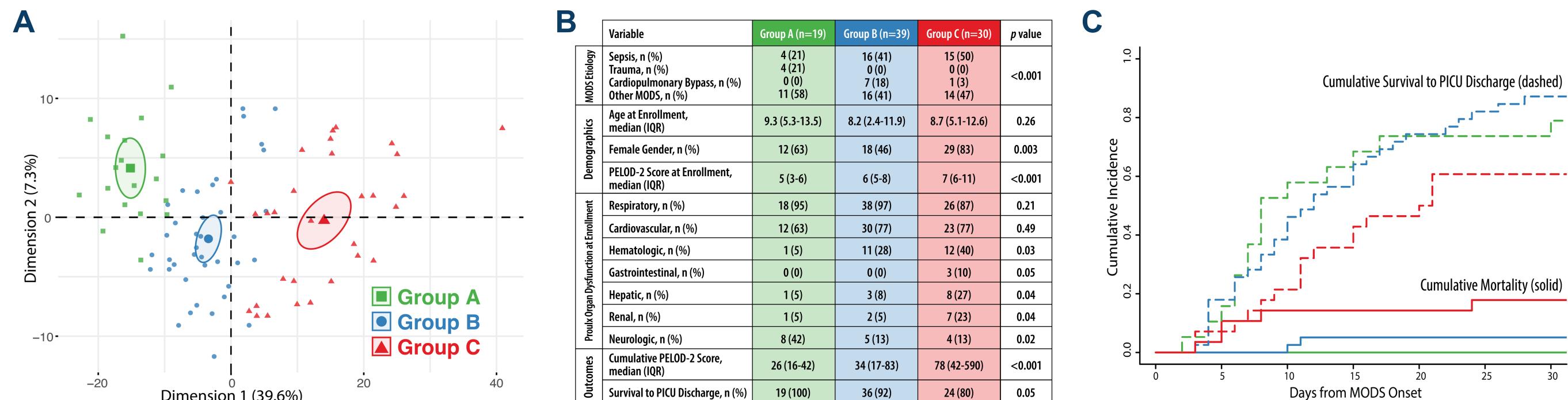


Fig. 1. Identification of three MODS subphenotypes based on protein expression at MODS onset. (A) Three MODS subphenotypes defined by consensus clustering of 214 severity-associated plasma proteins. (B) Differences in etiology, cohort demographics, and outcomes by MODS subphenotype. (C) Cumulative incidence of survival to PICU discharge and PICU mortality by MODS day demonstrates poor Group C outcomes.

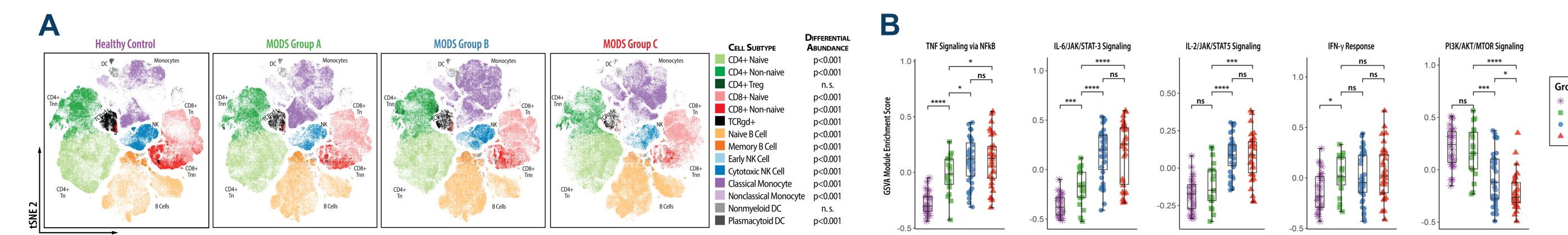


Fig. 2. PBMC frequency and mechanisms of immune activation vary by subphenotype. (A) tSNE projections highlighting PBMC immune profiles which vary across subphenotypes. (B) MSigDB Hallmark inflammatory pathway enrichment across subphenotypes at MODS onset.

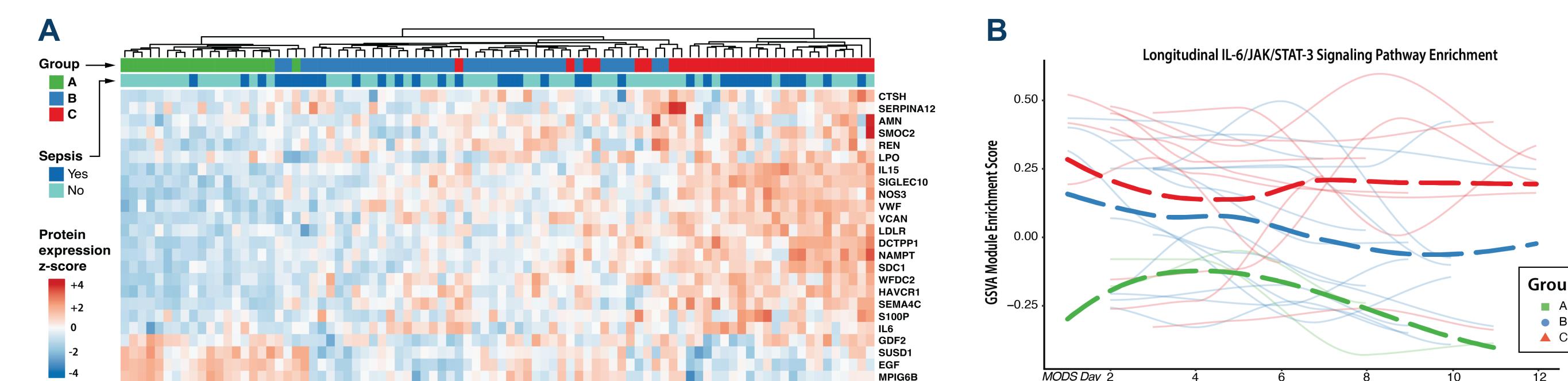


Fig. 3. PBMC frequency and mechanisms of immune activation vary by subphenotype. (A) Parsimonious 24 protein signature to resolve MODS subphenotypes identified via ordinal elastic net regression. (B) Longitudinal IL-6/JAK/STAT3 enrichment varies by MODS subphenotype.

CONCLUSIONS

- We identified a parsimonious 24 protein signature present at MODS onset which:
 - is present in patients with/without sepsis,
 - reflects common MODS pathobiology across diagnoses, and
 - reliably identifies MODS subphenotypes corresponding to defined mechanisms of immune dysregulation.
- Patients in **Group C** are defined by:
 - high severity of illness and poor prognosis,
 - pathologic JAK/STAT3 hyperactivation, and
 - persistent immune dysregulation which continues for up to two weeks.
- These findings advance our understanding of **MODS immunobiology** and highlight potential opportunities for a precision medicine approach to the treatment of **STAT3-mediated hyperinflammation** in critically ill children.

WHAT COMES NEXT?

- Validation of our prognostic protein signature in a 100-patient replication cohort (Olink + Ella).
- Comparison of predictive validity with SRSq and PERSEVERE stratification scores.
- Impact of ex vivo selective and non-selective JAK inhibition on PBMC immune phenotype.

Our MODS subphenotype preprint, data, and code are available on [Lindell Lab Github](#).

