Differential Roles of Inflammatory Mediators in Organ Dysfunction After Osseous vs. Non-Osseous Injury

Sambodh Sinha[1,2], Hamed Moheimani[2], Greg Gaski[3], Katherine Frey[4], Simon Tallowin[5], Upendra Kar[2], Timothy Billiar[2], Todd McKinley[6], METRC
[1]Vanderbilt University, Nashville, TN, [2]Department of Surgery, University of Pittsburgh, Pittsburgh, PA, [3]Department of Orthopedic Surgery, Inova Fairfax Medical Campus, Fairfax, VA, [4]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [5]Surgical Critical Care Initiative, Uniformed Services University of the Health Sciences, Bethesda, MD, [6]Department of Orthopedic Surgery, Indiana University, Indianapolis, IN
Email of Presenting Author: sambodh.sinha@vanderbilt.edu

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INTRODUCTION: Polytrauma involves multiple injuries to varied tissue types as well as anatomical regions. However, the mechanisms by which damage to different tissues lead to impaired immune response and subsequent organ dysfunction are unexplored. Here, we investigated the circulating immune response to injury and assessed whether it mediates the association between osseous vs. non-osseous tissue damage and organ dysfunction.

METHODS: We analyzed data from 317 patients enrolled in PRECISE, an IRB-approved prospective observational cohort enrolling polytrauma patients aged 18–55 years with destabilizing orthopedic injuries. Tissue damage volumes (mL) were determined by whole-body computed tomography. Organ dysfunction was estimated by the average Marshall Organ Dysfunction Score from days 2 to 5 ($aMODS_{D2\text{-}D5}$). Circulating levels of 33 immune mediators were measured at 24 h post-injury. Sparse partial least-squares discriminant analysis (sPLS-DA) was performed to identify an immune signature predictive of high (≥ 3) vs. low $aMODS_{D2–D5}$. Causal mediation analysis quantified the proportion of the effect of tissue damage volume on $aMODS_{D2–D5}$ that was mediated through the sPLS-DA-defined immune component.

RESULTS SECTION: sPLS-DA showed that a single component composed of five inflammatory mediators (CCL-2, IL-6, CXCL-8, IL-10, and CXCL-9) measured at 24 h post-injury can effectively distinguish between high and low $aMODS_{D2\text{-}D5}$ groups (AUC = 0.82). Mediation analysis, adjusted for age, gender, head abbreviated injury score, and shock index, revealed that this inflammatory component significantly mediated 67% of the total association between volume of non-osseous injury with organ dysfunction (total effect: 0.27, indirect effect: 0.18, both $p<0.05$). Conversely, the association of damaged osseous tissue with organ dysfunction was not significantly mediated by the immune component.

DISCUSSION: We found that a small subset of inflammatory mediators measured at 24 h post-injury mediates two-thirds of the association between tissue damage and organ dysfunction, selectively for injured non-osseous tissues.

SIGNIFICANCE/CLINICAL RELEVANCE: Circulating inflammatory response post-injury partially mediates the relationship between non-osseous tissue injury and subsequent organ dysfunction. The findings highlight the potential for immune-modulating therapies that are tailored to each patient's specific injury pattern.

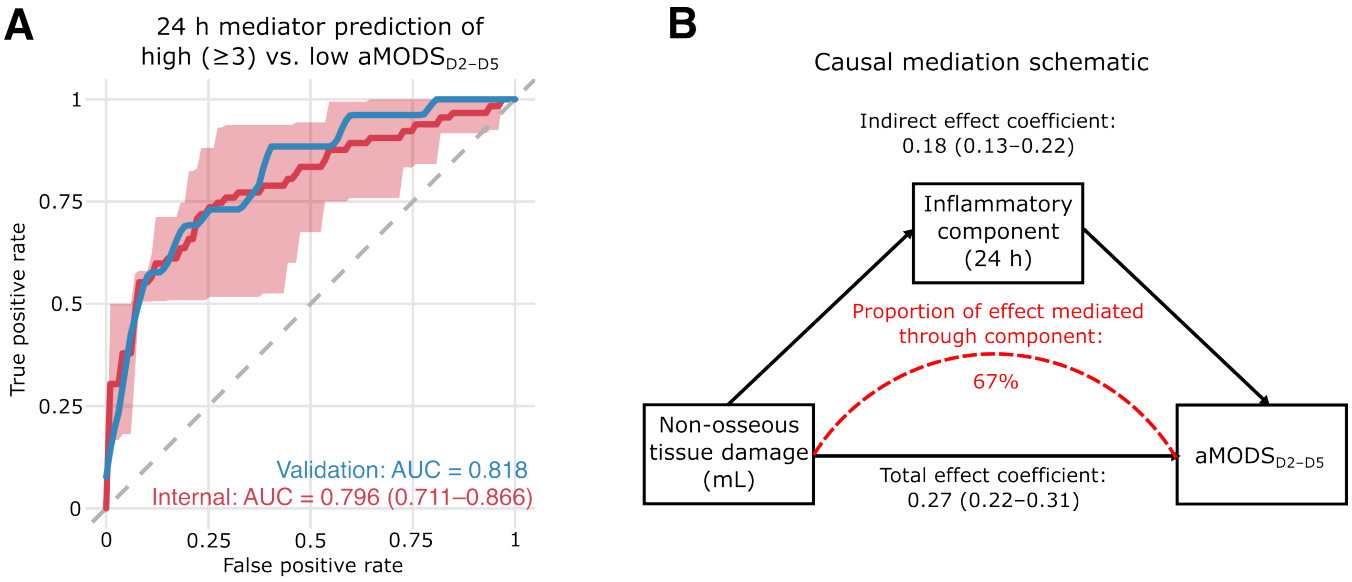

Figure 1. a Levels of an inflammatory subset of immune mediators at 24 hours post-injury predicts subsequent organ dysfunction. **b** The relationship of non-bone injury with organ dysfunction is signficantly mediated through the inflammatory subset.