Mapping Cellular Composition Shifts in Multicomplicated vs. Uncomplicated Trauma Using Cellular Deconvolution Analysis

Tracey Z. He, BA[1]; Ninh Vu, MS[1,2]; Eric A. Elster, MD[1,3]; Seth A. Schobel, PhD[1]

[1]Uniformed Services University (USU) Surgical Critical Care Initiative (SC2i), Bethesda, MD; [2]The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, MD;
[3]Walter Reed National Military Medical Center, Bethesda, MD

INTRODUCTION

Severe traumatic injury triggers an immediate and systemic storm of immune cells. While this acute phase is necessary for survival and tissue repair, its intensity and duration must be carefully regulated to prevent secondary damage. A subset of patients fails to resolve this initial inflammation, instead developing a state of prolonged immune dysfunction characterized by multiple clinical complications.

- **The gap**: While bulk transcriptomic signatures are known to predict trauma outcomes, the specific cellular proportions contributing to these signatures, and how they shift during the recovery process, remain poorly characterized.
- **Objective**: Employ cellular deconvolution to explore the relationship between circulating immune cell proportions and clinical outcomes, identifying potential biological windows that may distinguish pathological recovery patterns.

METHODS

- **Cohort:** 472 whole blood samples from 249 adult trauma patients treated at Walter Reed National Military Medical Center, Emory University Hospital, and Duke University Medical Center from 2015 to 2022.
- **Temporal sampling:** Serial samples were collected from admission (day 0) through the acute (days 1–7) and subacute stages (day > 7) of recovery.
- **Cellular deconvolution:** Bulk RNA-seq data were processed through the absolute blood immune system (ABIS) signature matrix to estimate absolute proportions of circulating immune cell subsets. ABIS is an established transcriptomic reference panel optimized for whole-blood deconvolution, which translates bulk gene expression data into 22 cell type proportions.
- **Groups:** Uncomplicated (N=92) vs. Multicomplicated (N=157). Uncomplicated is defined as 0 complications at discharge. Multicomplicated is defined as ≥1 complication (*e.g.,* sepsis, pneumonia, surgical site infection) at discharge.
- **Statistical analysis:** Longitudinal group differences were assessed via Wilcoxon rank-sum tests, and functional enrichment was performed using gene ontology.

RESULTS

Table 1. Patient Demographics

Characteristic	Uncomplicated	Multicomplicated	P-value
Number of patients, N	92	157	-
Number of samples, N	109	363	-
Age (years), median [IQR]	34 [29 - 43.2]	38 [26 - 55]	0.144
Male sex, N (%)	80 (87%)	122 (77.7%)	0.0929
Injury Severity Score (ISS), median [IQR]	16 [9 - 19.8]	27 [18-38.8]	NS
Hospital length of stay (days), median [IQR]	8 [4.8 - 19.2]	27.5 [16 - 49.5]	<0.001
ICU length of stay (days), median [IQR]	0 [0 - 3]	10 [2.7 - 25]	<0.001
Ventilator treatment duration (days), median [IQR]	0 [0 - 0]	4 [0 - 15.5]	<0.001

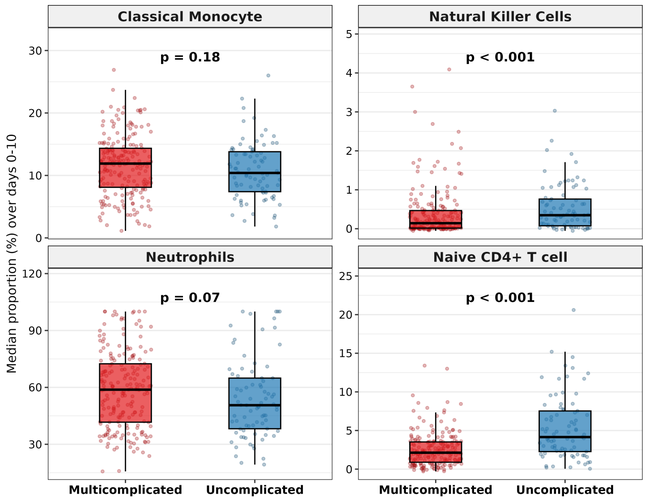

Figure 1. Aggregated 10-day distribution of key circulating immune cell subsets post-trauma. Boxplots show the overall median cell proportions across all patients and serial samples (days 0–10) for multicomplicated (red) vs. uncomplicated (blue) patient groups. Individual samples are represented by jittered dots.

- Uncomplicated recoveries exhibited significantly higher aggregated proportions of immune cells that bridge the innate and adaptive immune systems (naive CD4+ T cells, 5.3% vs. 2.6%; natural killer (NK) cells, 0.5% vs. 0.4%) (**Fig. 1**). In contrast, multicomplicated patients had an expanded innate inflammatory compartment especially driven by neutrophils (59.0% vs. 54.5%) and classical monocytes (11.6% vs. 10.8%).

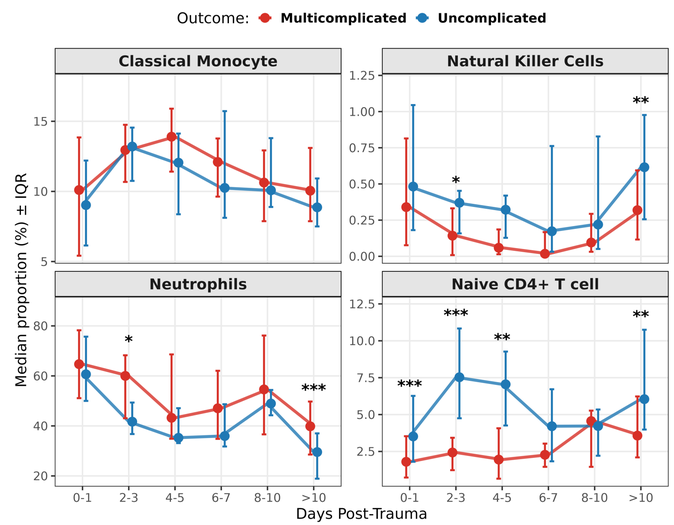

Figure 2. Longitudinal trajectories of key circulating immune cell subsets post-trauma. Temporal immune cell trajectories were modeled using absolute proportions estimated via ABIS deconvolution of whole-blood transcriptomes. Data points represent the median proportion for each time bin (days 0–1 to >10). Asterisks indicate significant differences within specific time windows (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

- In multicomplicated patients, classical monocytes peaked on days 4–5, and neutrophils tracked significantly higher during days 2–3 and day >10 (**Fig. 2**). This coincided with a concurrent suppression of cytotoxic NK cells, which failed to recover by day >10 ($p < 0.01$), and a continuous depletion of Naive CD4+ T cells.

CONCLUSION

- **Suppressed circulating lymphocytes:** Multicomplicated patients exhibit a significant overall reduction of circulating naive CD4+ T cells and NK cells ($p < 0.001$) across the aggregate 10-day recovery window.
- **Temporal immune alterations:** Longitudinal tracking reveals distinct, time-specific differences in cellular proportions, featuring elevated neutrophils and depressed lymphocyte subsets at both early post-injury intervals and late (>10 days) timepoints.
- **Clinical target:** Characterizing these longitudinal immune trajectories highlights potential windows for future research into targeted immunomodulatory strategies aimed at supporting adaptive recovery before prolonged systemic dysfunction becomes established.

*SC2i is a consortium of Uniformed Services University of the Health Sciences, Walter Reed National Military Medical Center, Duke Health, Emory University School of Medicine, and Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.