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Individual-specific principal component analysis of circulating inflammatory mediators predicts early organ dysfunction in trauma patients

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ABSTRACT

Purpose: We hypothesized that early inflammation can drive, or impact, later multiple organ dysfunction syndrome (MODS), that patient-specific principal component analysis (PCA) of circulating inflammatory mediators could reveal conserved dynamic responses which would not be apparent from the unprocessed data, and that this computational approach could segregate trauma patients with regard to subsequent MODS.
Methods: From a cohort of 472 blunt trauma survivors, 2 separate subcohorts of moderately/severely injured patients were studied. Multiple inflammatory mediators were assessed in serial blood samples in the first 24 hours postinjury. PCA of these time course data was used to derive patient-specific "inflammation barcodes," followed by hierarchical clustering to define patient subgroups. To define the generalizability of this approach, 2 different but overlapping Luminex kits were used.
Results: PCA/hierarchical clustering of 24-hour Luminex data segregated the patients into 2 groups that differed significantly in their Marshall multiple organ dysfunction score on subsequent days, independently of the specific set of inflammatory mediators analyzed. Multiple inflammatory mediators and their dynamic networks were significantly different in the 2 groups in both patient cohorts, demonstrating that the groups were defined based on "core" early responses exhibit truly different dynamic inflammatory trajectories.
Conclusion: Identification of patient-specific "core responses" can lead to early segregation of diverse trauma patients with regard to later MODS. Hence, we suggest that a focus on dynamic inflammatory networks rather than individual biomarkers is warranted.

1. Introduction

Traumatic injury, often accompanied by hemorrhage, represents the most common cause of death for young people, as well as a significant source of morbidity and mortality for all ages [1,2]. Initial survivors of acute trauma are particularly susceptible to multiple organ dysfunction syndrome (MODS), a poorly understood syndrome of sequential impairment of organ function [3]. The early emergence of trauma-induced MODS appears to correlate with a complicated clinical course, accounting for substantial morbidity and mortality [4-6] postinjury. In addition, MODS is thought to be due, in part, to excessive or sustained activation of specific maladaptive inflammatory pathways [7]. Importantly, the posttraumatic inflammatory response is not in and of itself detrimental: an adequately robust early inflammatory response appears to be crucial for the survival of both human trauma patients and experimental animal models subjected to experimental trauma/hemorrhage [8]. Thus, focusing on the circulating levels of individual inflammatory mediators may be insufficient for stratifying injured patients with regard to their propensity to develop MODS. Indeed, single inflammatory mediators have been associated with adverse outcomes in studies of large trauma patient cohorts because of the large variability observed in the inflammatory response observed in trauma patients [9-11] but not on a patient-specific level.

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Further complicating attempts to stratify trauma patient outcomes is the fact that the outcomes landscape in trauma/hemorrhage has expanded beyond mortality (now ~5%-10%) to include not only MODS but also other complications (eg, nosocomial infection), extended hospital and intensive care unit (ICU) length of stay, and long-term morbidity following discharge [12,13]. However, the clinical trajectory of most blunt trauma patients is difficult to predict upon admission. Complicating this analysis is the multidimensional, complex, and apparently patient-specific interplay between inflammation and organ (dys) function that appears to drive outcomes in trauma [9-11,14,15]. Numerous prior studies have documented dynamic changes in circulating inflammatory mediators in trauma patients, which have in some settings correlated with detrimental outcomes such as MODS [9-11,15] or nosocomial infection [13].

Typical statistical analyses are geared toward identifying the average behavior of a population. In contrast, computational techniques such as principal components analysis (PCA) are aimed at determining key variables within a dynamic, complex response by examining the variance in a given time-varying data set [16]. We have previously shown the utility of PCA to distinguish circulating inflammatory mediator profiles in mice subjected to either minor or severe injury [17], for highlighting inflammatory recompartmentalization and reprogramming in experimental gram-negative sepsis [18], and for suggesting patient subgroups in the setting of pediatric acute liver failure [19]. However, the use of PCA on a patient-specific level as a predictive tool in trauma has not been tested yet. We therefore hypothesized that although the inflammatory responses of individual patients might be variable, these individual responses are characterized by a core set of mediators that could be discerned in these individuals via PCA. Our findings suggest that PCA based on circulating inflammatory mediators assessed within the first 24 hours postinjury is capable of segregating moderately/severely injured patients into distinct subgroups, which are associated with differential degree of MODS that persists up to 5 days postinjury. Importantly, the unprocessed inflammatory mediator data were incapable of similar outcome segregation. These results suggest that it is not any one individual inflammatory mediator that distinguishes patients; rather, it is the PCA-based "inflammation barcode," which denotes core, dynamic inflammatory responses that actually distinguishes patients.

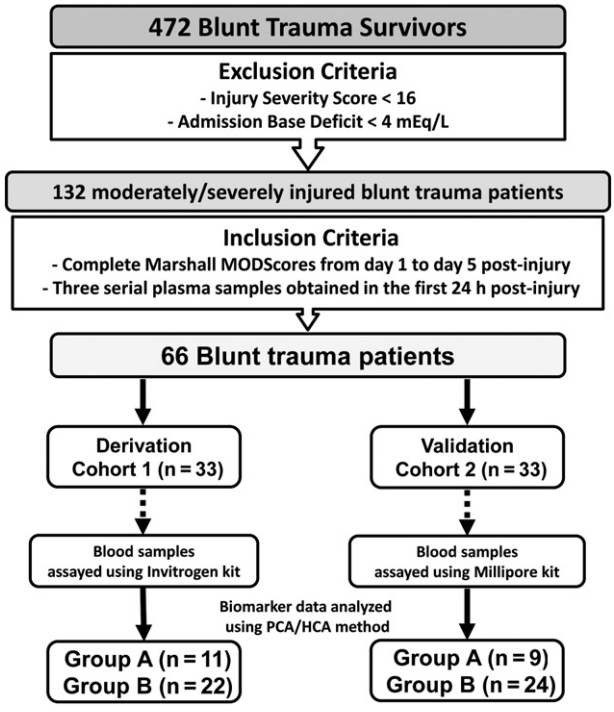

Fig. 1. Flowchart of recruitment and study participation. From a large cohort of 472 blunt trauma survivors and after exclusion of patients with ISS less than 16 and admission BD less than 4 mEq/L, we identified 132 moderately/severely injured patients. From this cohort, we derived two separate subcohorts with at least three blood samples within the first 24 hours of injury and with complete Marshall MODScores from time of injury up to day 5: derivation cohort 1 (n = 33) and validation cohort 2 (n = 33).

2. Materials and methods

2.1. Human trauma patients and analyses

2.1.1. Patient recruitment, sampling, and data elements

All human sampling was done following approval by the University of Pittsburgh Institutional Review Board, and informed consent was obtained from each patient or next of kin as per Institutional Review Board regulations. Patients eligible for enrollment in the study were at least 18 years of age; admitted to the ICU after being resuscitated; and, per treating physician, were expected to live more than 24 hours. Reasons for ineligibility were isolated head injury, pregnancy, and penetrating trauma.

From a cohort of 472 blunt trauma survivors detailed recently [13], we identified 132 patients with injury severity score (ISS) greater than 16 and admission base deficit (BD) greater than 4 mEq/L (Fig. 1). This large cohort reflected moderately/severely injured patients from which we derived 2 separate subcohorts with at least three blood samples within the first 24 hours of injury and complete Marshall multiple organ dysfunction scores (MODScores) from time of injury up to day 5 (Fig. 1): derivation cohort 1 (33 patients [19 men, 14 women; age: 44 ± 3 {mean ± SEM}; ISS: 24 ± 3]) and validation cohort 2: (33 patients [19 men, 14 women; age: 46 ± 1; ISS: 22 ± 1]). The overall demographics, mechanism of injury, and clinical outcomes for both subcohorts are shown in Table 1. Clinical data, including ISS, ICU length of stay (LOS), hospital LOS, days on mechanical ventilation, admission BD, and shock index (which identifies the degree of shock in trauma patients, calculated based upon the ratio of heart rate to the systolic blood pressure, where an index >1 signifies hypovolemic shock), were collected from the hospital inpatient electronic database. Laboratory results and other basic demographic data were recorded in the database via direct interface with electronic medical record. Three plasma samples, starting with the initial blood draw upon arrival, were assayed within the first 24 hours following trauma and then from days 1 to 5 postinjury. The blood samples were centrifuged, and plasma aliquots were stored in cryopreservation tubes at −80°C for subsequent analysis of inflammatory mediators.

Table 1
Cohorts 1 and 2 trauma patients' demographic data, clinical characteristics, and outcome

	Derivation cohort 1 n = 33	Validation cohort 2 n = 33	*P* value
Demographics			
Age, y	44.3 ± 3.15	44.3 ± 1.3	1
Sex, male/female	M = 19 F = 14	M = 19 F = 14	1
ISS	24 ± 2.50	23.3 ± 1	0.65
Mechanism of injury			
MVA, n (%)	28 (85%)	27 (82%)	1
Fall, n (%)	5 (15%)	5 (15%)	1
Others, n (%)	0	1 (3%)	N/A
Comorbid conditions			
Psychiatric conditions, n (%)	4 (12%)	4 (12%)	1
Hypertension, n (%)	9 (27%)	8 (24%)	0.7
Diabetes mellitus, n (%)	5 (15%)	4 (12%)	0.7
Bronchial asthma, n (%)	3 (9%)	3 (9%)	1
Chronic anemia, n (%)	1 (3%)	0	N/A
Alcohol use	4 (12%)	4 (12%)	1
Chronic liver diseases, n (%)	1 (3%)	1 (3%)	1
None, n (%)	10 (30%)	14 (42%)	1
Outcomes			
ICU LOS, d	7.2 ± 1.36	8 ± 1.4	0.6
Mechanical ventilator, d	3.6 ± 0.9	4.3 ± 1.2	0.86
Hospital LOS, d	14.3 ± 2	14.7 ± 2	0.77

Values are mean ± SEM. Statistical significance set at $P < 0.05$ by either Mann-Whitney *U* test or χ^2 as appropriate. MVA indicates motor vehicle accidents.