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EARLY ELEVATION IN RANDOM PLASMA IL-6 FOLLOWING SEVERE INJURY IS ASSOCIATED WITH DEVELOPMENT OF ORGAN FAILURE*

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Abstract

Background—Excessive pro-inflammatory activation following trauma plays a role in late morbidity and mortality including the development of multiple organ dysfunction syndrome (MODS). To date, identification of patients at risk has been challenging. Results from animal and human studies suggest that circulating IL-6, may serve as a biomarker for excessive inflammation. The purpose of this analysis was to determine the association of IL-6 to outcome in a multi-center developmental cohort and in a single-center validation cohort.

Methods—Severely injured patients with shock due to hemorrhage were evaluated within a multi-center developmental cohort (n=79). All had blood drawn within 12 hours of injury. Plasma IL-6 was determined by multiplex proteomic analysis. Clinical and outcome data were prospectively obtained. Within this developmental cohort, a plasma IL-6 level was determined for the subsequent development of MODS by developing a receiver operating curve (ROC) and

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defining the optimal IL-6 level using the Youden index. This IL-6 level was then evaluated within a separate validation cohort (n=56).

Results—A receiver operating curve was generated for IL-6 and MODS development with an IL-6 level of 350 pg/ml having the highest sensitivity and specificity within the developmental cohort. IL-6 was associated with MODS after adjusting for APACHE II, ISS, male gender and blood transfusions with an odds ratio of 3.9 [95% CI: 1.33–11.19]. An IL-6 level greater than 350 pg/ml within the validation cohort was associated with an increase in MODS score, MODS development, ventilator days, ICU length of stay (LOS), and hospital LOS. However, this IL-6 level was not associated with either the development of nosocomial infection or mortality.

Conclusion—Elevation in plasma IL-6 appears to correlate with a poor prognosis. This measurement may be useful as a biomarker for prognosis and serve to identify patients at higher risk of adverse outcome that would benefit from novel therapeutic interventions.

INTRODUCTION

An exaggerated immune response, with overproduction of inflammatory mediators, is pivotal to diffuse tissue injury resulting in multiple organ dysfunction syndrome (MODS) following severe trauma(1). Despite an increased understanding of these various mediators and their mechanisms of action, poor outcome following trauma remains common(2). It is important to understand the role of these mediators and accurately estimate an injured patient's risk for organ dysfunction. Reliable characterization of risk may help in determining therapeutic intervention, and could therefore impact outcome.

Of the multitude of mediators released following injury, IL-6 has been consistently demonstrated to be released early and thus may serve a prognostic role(3). Interleukin 6 (IL-6) is a multifunctional cytokine that is released rapidly by various cells following injury(4). Several clinical studies, primarily involving patients with systemic infection, have demonstrated that the circulating plasma level of IL-6 is associated with outcome(5–11). Patients with higher circulating concentrations of IL-6 are more likely to die. Although strongly correlated with the severity of injury, the predictive utility of circulating IL-6 for adverse outcomes after injury is unknown (10, 12, 13).

Recent investigations have demonstrated rapid changes in IL-6 levels during elective surgery(14, 15). In fact, IL-6 levels are detected as early as 90 minutes following initial skin incision. Similar changes in IL-6 have been characterized following traumatic injury. In a cohort prospective observational trial, Gebhard and colleagues demonstrated that IL-6 levels obtained soon after hospital admission were closely associated with the degree of injury(10). In fact, this relationship was maintained for up to 12 hours following hospital admission. Despite this relationship, IL-6 has only been shown to correlate well with subsequent morbidity in only one single center study(12).

The purpose of this study was to determine whether early plasma concentration of IL-6 randomly obtained within 12 hours of injury was associated with poor outcomes in a cohort of severely injured trauma patients. We then sought to determine whether a threshold concentration of IL-6 could identify patients at high risk for organ failure, infection and death after traumatic injury. We hypothesized that patients with significant early elevation in IL-6, despite similar severity of injury, would be at a greater risk for poor clinical outcome.

METHODS

Study Design

This study is a primary analysis of data collected in the context of an ongoing large multicenter prospective cohort study whose primary objective is to evaluate the relationship between the inflammatory response to injury and posttraumatic MODS, and a single center prospective trial whose primary objective is to evaluate the protein lipid changes in response to injury associated with the development of posttraumatic MODS(16). In this analysis, the exposure represented the plasma IL-6 level within 12 hours following injury and the primary outcome was development of MODS defined by a Marshall MODS score greater than or equal to 6.

Patients

The development cohort was made up of patients from the *Inflammation and the Host Response to Injury Large Scale Collaborative Program*. This program is supported by the National Institute of General Medical Sciences and is designed to characterize the genomic and proteomic response in injured patients at high risk for posttraumatic multiple organ failure. This report focuses on patients admitted to any one of seven participating institutions during the interval April 2004 and March 2007. Criteria for enrollment were age ≥ 16 years, blunt trauma, arrival to hospital within 6 hours of injury, either hypotension (SBP < 90 mmHg) or an elevated base deficit (≥ 6), blood transfusion within 12 hours of injury, and body region exclusive of brain with an Abbreviated Injury Scale score (AIS) ≥ 2 , and intact cervical spinal cord to exclude those with isolated severe head injuries or spinal cord injuries respectively. As the primary objective of this analysis was to determine the association of IL-6 and organ dysfunction following severe injury, we further limited inclusion to subjects undergoing random plasma IL-6 analysis within 12 hours of injury that survived at least 48 hours. Standard operating procedures (SOPs) were developed and implemented across all institutional centers to minimize variation in post-injury care, including: early goal directed resuscitation, strict glycemic control, venous thrombo-embolism prophylaxis, appropriate tidal volume ventilation, ventilator associated pneumonia management, use of sedation and analgesic, antimicrobial therapy, and restrictive transfusion guidelines(16–25). The institutional review board of each participating center approved the cohort study.

The validation cohort was made up of an identical cohort of patients using similar inclusion and exclusion criteria from an ongoing prospective observation trial during the period of June 2008 to July 2009 supported by National Institute of Graduate Medical Sciences at Harborview Medical Center in Seattle, Washington.

Data Collection

Clinical data were obtained by trained nurse abstractors and entered into TrialDb, a Web-based data collection platform(26). Injuries were coded by body region using the AIS, with an AIS ≥ 3 considered a severe injury(27). The Injury Severity Score (ISS) was used as a global measure of injury severity(28). Data integrity was evaluated centrally through an assessment of missing values, range checks, evaluation for implausible values and internal consistency. Additionally, data were validated through an external review of a random sample of charts by a physician and independent chart abstractor.

MODS

Multiple organ dysfunction syndrome was diagnosed following ICU admission. Individual organ failure scores for renal, hepatic, cardiovascular, metabolic, hematological, respiratory and neurological systems were determined daily(29). The diagnosis of MODS required a maximum Marshall multiple organ dysfunction score greater than or equal to 6.

Outcome variables

All other outcome variables in addition to MODS were defined as previously described by *Inflammation and the Host Response to Injury Large Scale Collaborative Program*(30). In particular, all nosocomial infections were monitored for and recorded (infection type, culture specimen source, and bacteriology). Diagnosis of a ventilator associated pneumonia required a quantitative culture threshold of $\geq 10^4$ CFU/ml for bronchoalveolar lavage specimens. Diagnosis of catheter-related blood stream infections required positive peripheral cultures with the identical organism obtained from either a positive semi-quantitative culture (>15 CFU/segment), or positive quantitative culture ($>10^3$ CFU/segment) from a catheter segment specimen. Urinary tract infections required $> 10^5$ organisms/ml of urine.

Cytokine Analysis

All patients were admitted to one of seven institutions. Of the patients evaluated, only 167 underwent plasma cytokine concentration measurements within the first 12 hours. To obtain cytokine concentration measurements whole blood obtained from patients was spun down at 4°C. Plasma was then separated from the cellular component, frozen at -80°C , and then stored for analysis. Cytokine concentrations from thawed plasma from individual samples were assayed with the LINCoplex kit for 21 analytes (Millipore, Billerica, MA) using the LUMINEX (Millipore) technology. Cytokines measured included IL-6, which was the primary interest of this analysis.

Statistical Analysis

The IL-6 expression over the first 12 hours was log transformed for normality assumptions and repeated measures analysis of variance (ANOVA). Additionally, plasma IL-6 level was correlated with subsequent development of MODS by developing a receiver operating curve (ROC) and defining the optimal IL-6 level using the Youden index. Once calculated, the relationship between plasma IL-6 level and several patient and/or injury characteristics were determined by chi-square for categorical variables and the t test for continuous variables. All variables with a <0.1 on univariate analysis were entered into a forward stepwise regression model to identify risk factors for MODS development. Model parameters for entry and exit into the model were $\alpha=0.1$ and $\alpha=0.05$, respectively. All analysis was performed using Stata Version 9 (College Station, Tex).

RESULTS

Development Cohort

There were 862 patients enrolled during the interval of the study within the *Inflammation and the Host Response to Injury Large Scale Collaborative Program*. Of this cohort, only 152 patients that survived greater than 48 hours underwent plasma analysis for IL-6 within 12 hours of injury and thus made up the development cohort, given that the primary outcome was organ dysfunction. Of the patients within this cohort, plasma IL-6 varied from 33.3 to 11293.7pg/ml. Overall the study cohort was young, male predominant, and seriously injured. Mortality was low occurring in only 4 (5.1%) of patients. However, the rate of organ dysfunction defined as a Marshall MODS score of 6 or greater occurred in 29 (36.7%) of patients.

Within 12 hours of injury (9 ± 3 hours), there was a significant difference in the mean IL-6 plasma concentration between patients that developed MODS and those that did not develop MODS (Figure 1). Area under the ROC was predictive of MODS development (AUC 0.749, 95% CI 0.643–0.855). Using the Youden index (sensitivity + specificity-1) an IL-6 plasma level of 350 pg/ml was determined to be the optimal cut-off point for MODS development (Figure 2).

To determine if this random early level of IL-6 was an independent factors associated with the development of MODS, we performed a forward stepwise logistic regression model assessing the contributions of several factors determined by an initial univariate analysis (data not shown). Factors that were kept in the model included age, sex, ISS, blood transfusion > 6 units, crystalloid infusion in the first 12 hours, institutional site and initial plasma IL-6 level > 350 pg/ml. A plasma IL-6 within 12 hours of injury following this analysis remained associated with an increased odds of MODS development (Table 1). Thus, this IL-6 concentration cutoff of 350 pg/ml was used in all subsequent analyses, without *post hoc* calibrations.

Validation Cohort

We next sought to test the ability of a plasma IL-6 concentration greater than 350 pg/ml to predict the development of MODS in an independent cohort of severely injured blunt trauma patients at Harborview Medical Center with similar inclusion and exclusion criteria. Fifty-six patients that same inclusion and exclusion criteria to the *Inflammation and the Host Response to Injury Large Scale Collaborative Program* had random plasma IL-6 levels drawn within 12 hours of injury and survived greater than 48 hours. Tables 2 and 3 demonstrates that both the patient demographics and injury characteristics between the development cohort and validation cohort were similar.

The IL-6 cutoff of 350 pg/ml established within the development cohort was used to determine the ability to predict MODS in the validation cohort (Figure 3). A plasma IL-6 concentration greater than 350 pg/ml had 79% sensitivity, 76% specificity, and 63% positive predictive value. In contrast, a plasma IL-6 level of 400 pg/ml or less had a negative predictive value for MODS of 88%. In other words, a plasma IL-6 concentration of 350 pg/ml or less predicted that MODS would not develop with 88% accuracy in the validation cohort.

Using the plasma IL-6 cut-off value of 350 pg/ml, patients were separated into two groups within the validation cohort and patient outcome was evaluated. An elevated plasma IL-6 level within 12 hours was associated with an increased rate of organ dysfunction, and an associated increase in ventilator days, ICU days and hospital length of stay (Table 4). Despite this increase in resource utilization, no difference was found in the rate of nosocomial infection or mortality between study groups.

DISCUSSION

Previous work has demonstrated that early elevation in plasma IL-6 correlates well with the underlying injury severity(10). This early correlation with underlying injury severity is consistent with other investigational work demonstrating that IL-6 levels similarly reflect the degree of tissue injury found during elective surgery(14, 15, 31). This, however, is problematic when attempting to differentiate the inflammatory state of similarly injured patients. Thus, the purpose of this study was to determine if patients with similar severe injury could be differentiated on an early but randomly obtained plasma IL-6 level within 12 hours of injury.

Although circulating levels of IL-6 have been examined following trauma, only two studies to date has attempted to prognosticate subsequent morbidity and mortality(11, 12). The remainder of the studies have been descriptive showing a strong correlation with various scoring systems such as ISS and APACHE II. Since this pleiotropic cytokine that is intimately involved in the acute phase response and is produced from a variety of cells types following hypoxia or ischemia, the release of this cytokine should correlate well with the severity of ischemia and shock following blunt injury(32–34).

The results from this current analysis provide evidence that early elevation in IL-6 to a level greater than 350 pg/ml following severe injury correlates well with subsequent morbidity. Overall the cohort was male predominate, severely injured with an ISS of 31 ± 13 , and with half requiring massive transfusions defined as 6 units of blood within the first 12 hours. Plasma IL-6 levels varied early on with a range from 33.3 to 11293.7 pg/ml. Despite this wide range, it appeared that a level of 350 pg/ml was an appropriate cut-off to differentiate patient morbidity. Patients with an initial plasma IL-6 level greater than 350 pg/ml were more likely to receive massive transfusions. Given that blood transfusion remains highly correlated with subsequent morbidity following severe injury, a step wise logistic regression was performed demonstrating IL-6 elevation as an independent risk factor for MODS development with nearly a four-fold increase in risk(35).

The results of this analysis is consistent with previous work by Woiciechowsky and colleagues demonstrating correlation of IL-6 obtained within the first day following acute cerebral hemorrhage or brain injury and outcome(11). In their analysis, they determined that a plasma IL-6 level of 100 pg/ml was predictive of short term prognosis following brain injury and subsequent development of pneumonia within the first week. Additionally, these results are consistent with the previous study by Jastrow and colleagues demonstrating a correlation of IL-6 within the first 4–8 hours following injury to be associated with outcome(12). In their analysis, unlike our study, an IL-6 value of 4110 pg/ml was predictive of MODS development. In the only other study evaluating IL-6 and the development of MODS, Lausovic and colleagues found that IL-6 at 24 hours was on average below 200 pg/ml for patients that did not go on to develop MODS more consistent with our findings(13). Unfortunately, both these studies evaluated several other cytokines, demonstrated significant variability between values, were obtained at a relatively narrow time period, and were not subsequently validated. Our study, unlike the previous studies, did not demonstrate a difference in the rate of nosocomial infection. Additionally, our study did not examine patients with severe traumatic head injury, similar to Jastrow and colleagues. It is currently uncertain, what role, cerebral injury plays in the regulation of immunity and subsequent cytokine generation following injury.

Despite this concern, this early elevation and utility as a biomarker is consistent with the plethora of literature examining the role of IL-6 in sepsis(36, 37). Initial work using a mouse model demonstrated that a plasma IL-6 level greater than 2000 pg/ml within 6 hours following cecal ligation and puncture predicated mortality three days later(38). Similar findings have been demonstrated in septic patients(37, 39, 40). However, within this study cohort IL-6 level was not predictive of mortality given an overall mortality rate of only 4%, but early elevation in IL-6 obtained on average at 9 ± 3 hours within our study cohort was associated with dysregulated inflammation as noted by the increased development of organ dysfunction. This increase in MODS development although not associated with a significant increase in mortality was clearly associated with increased resource utilization as demonstrated by increased length of ventilator days, ICU length of stay, and hospital length of stay.

This correlation of plasma IL-6 with MODS has not been previously demonstrated following injury. In fact, previous studies have questioned the utility of this biomarker as a prognosticator for inflammation and subsequent morbidity (13, 41). Although no previous study has demonstrated this correlation, an explanation for our findings may be due to underlying severity of injury found within our cohort compared to previous studies. Our study, unlike previous studies only examined severely injured patients with an ISS of at least 15 with the presence of shock. These patients, based on previous observations, are the patients currently believed to be at the greatest risk for MODS and thus serve as an optimal cohort for investigation of this process(42).

This analysis has several additional limitations and concerns. First this study is a secondary analysis of a prospective cohort study looking at the genomic and proteomic response following severe injury and hemorrhagic shock, and the lipid and membrane changes induced by severe injury. As a result, this data collected was not recorded to answer the hypothesis of this analysis. Additionally, it represents a subset of the patients enrolled in two large independent cohort studies. However, the patients that underwent plasma cytokine analysis are similar due to similar treatments based on various SOP's to minimize variations in care. These studied patients, however, represents a significantly ill population with a mean ISS of 31, and thus may not be generalizable to less severely injured patients. Additionally, samples obtained were limited to patients over the age of 18 and under the age of 55, thus extremes of age are not represented within the study cohort. More importantly, unlike some other studies that specifically drew plasma samples six hours following injury, the samples drawn in these patients were obtained within 12 hours of injury but varied between 3 and 10 hours. Thus, peak levels that are expected to occur at about 6 hours following injury may have been missed (38, 43). However, this range in obtaining samples would be more consistent with normal clinical care. Finally, the method of plasma cytokine analysis was performed in both the developmental and validation cohort by LUMINEX, and as a result may not be translated similarly using other techniques. Despite these limitations, this paper does demonstrate that elevated plasma IL-6 early after injury is associated with an independent risk for the development of MODS and poor outcome.

In conclusion, the results of this analysis suggest that early elevation in plasma IL-6 to a level of 350 pg/ml or greater is associated with increased inflammatory sequelae. Although no casual relationship was established, this level appears to be a useful biomarker for determining the subsequent development of MODS. Although further research is warranted, it does provide some short-term prognostication that may be useful in the implementation of prophylactic/therapeutic strategies to improve the outcome following severe blunt trauma.

REFERENCES

1. Tsukamoto T, Savanh Chanthaphavong R, Pape HC. Current theories on the pathophysiology of multiple organ failure after trauma. *Injury*. 2009
2. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. *Injury*. 2009; 40:912–918. [PubMed: 19541301]
3. Pasquale MD, Cipolle MD, Monaco J, Simon N. Early inflammatory response correlates with the severity of injury. *Crit Care Med*. 1996; 24:1238–1242. [PubMed: 8674342]
4. Biffl WL, Moore EE, Moore FA, Peterson VM. Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? *Ann Surg*. 1996; 224:647–664. [PubMed: 8916880]
5. Leonidou L, Mouzaki A, Michalaki M, Delastic AL, Kyriazopoulou V, Bassaris HP, Gogos CA. Cytokine production and hospital mortality in patients with sepsis-induced stress hyperglycemia. *J Infect*. 2007
6. Tateishi Y, Oda S, Nakamura M, Watanabe K, Kuwaki T, Moriguchi T, Hirasawa H. Depressed Heart Rate Variability Is Associated with High IL-6 Blood Level and Decline in the Blood Pressure in Septic Patients. *Shock*. 2007
7. Skrablin S, Lovric H, Banovic V, Kralik S, Djakovic A, Kalafatic D. Maternal plasma interleukin-6, interleukin-1beta and C-reactive protein as indicators of tocolysis failure and neonatal outcome after preterm delivery. *J Matern Fetal Neonatal Med*. 2007; 20:335–341. [PubMed: 17437242]
8. Ghani RA, Zainudin S, Ctkong N, Rahman AF, Wafa SR, Mohamad M, Manaf MR, Ismail R. Serum IL-6 and IL-1-ra with sequential organ failure assessment scores in septic patients receiving high-volume haemofiltration and continuous venovenous haemofiltration. *Nephrology (Carlton)*. 2006; 11:386–393. [PubMed: 17014550]

9. S C, Mahadevan C, Thomas N, Vasantaha Kumar KC, Shivanand NV, Yeragani VK. Do baseline IL-6 levels predict post-operative morbidity after surgery (CABG) in cardiac patients? *J Card Surg.* 2006; 21:521–522. [PubMed: 16948777]
10. Gebhard F, Pfetsch H, Steinbach G, Strecker W, Kinzl L, Bruckner UB. Is interleukin 6 an early marker of injury severity following major trauma in humans? *Arch Surg.* 2000; 135:291–295. [PubMed: 10722030]
11. Woiciechowsky C, Schoning B, Cobanov J, Lanksch WR, Volk HD, Docke WD. Early IL-6 plasma concentrations correlate with severity of brain injury and pneumonia in brain-injured patients. *J Trauma.* 2002; 52:339–345. [PubMed: 11834998]
12. Jastrow KM 3rd, Gonzalez EA, McGuire MF, Suliburk JW, Kozar RA, Iyengar S, Motschall DA, McKinley BA, Moore FA, Mercer DW. Early cytokine production risk stratifies trauma patients for multiple organ failure. *J Am Coll Surg.* 2009; 209:320–331. [PubMed: 19717036]
13. Lausevic Z, Lausevic M, Trbojevic-Stankovic J, Krstic S, Stojimirovic B. Predicting multiple organ failure in patients with severe trauma. *Can J Surg.* 2008; 51:97–102. [PubMed: 18377749]
14. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg.* 1992; 79:757–760. [PubMed: 1393463]
15. Ueo H, Inoue H, Honda M, Uchida I, Nishimura M, Arinaga S, Nakashima H, Akiyoshi T. Production of interleukin-6 at operative wound sites in surgical patients. *J Am Coll Surg.* 1994; 179:326–332. [PubMed: 8069430]
16. Maier RV, Bankey PBM, Nathens AB, Moore EE. Inflammation and the host response to injury, a large-scale collaborative project: patient oriented research core standard operating porcedures for clinical care: foreword. *J Trauma.* 2005; 59:762–763.
17. Cuschieri J, Freeman B, O'Keefe G, Harbrecht BG, Bankey P, Johnson JL, Minei JP, Sperry J, West M, Nathens A, Moore EE, Maier RV. I., and the Host Response to Injury Collaborative Research, P. Inflammation and the host response to injury a large-scale collaborative project: patient-oriented research core standard operating procedure for clinical care X. Guidelines for venous thromboembolism prophylaxis in the trauma patient. *J Trauma.* 2008; 65:944–950. [PubMed: 18849816]
18. Harbrecht BG, Minei JP, Shapiro MB, Nathens AB, Moore EE, West MA, Bankey PE, Cuschieri J, Johnson JL, Maier RV. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core-standard operating procedures for clinical care: VI. Blood glucose control in the critically ill trauma patient. *J Trauma.* 2007; 63:703–708. [PubMed: 18073622]
19. Minei JP, Nathens AB, West M, Harbrecht BG, Moore EE, Shapiro MB, Bankey PE, Johnson JL, Freeman B, McKinley BA, Moore FA, Maier RV. Inflammation and the Host Response to Injury, a Large-Scale Collaborative Project: patient-oriented research core--standard operating procedures for clinical care. II. Guidelines for prevention, diagnosis and treatment of ventilator-associated pneumonia (VAP) in the trauma patient. *J Trauma.* 2006; 60:1106–1113. discussion 1113. [PubMed: 16688078]
20. Moore FA, McKinley BA, Moore EE, Nathens AB, West M, Shapiro MB, Bankey P, Freeman B, Harbrecht BG, Johnson JL, Minei JP, Maier RV. I., and the Host Response to Injury Collaborative Research, P. Inflammation and the Host Response to Injury, a large-scale collaborative project: patient-oriented research core--standard operating procedures for clinical care. III. Guidelines for shock resuscitation. *J Trauma.* 2006; 61:82–89. [PubMed: 16832253]
21. Nathens AB, Johnson JL, Minei JP, Moore EE, Shapiro M, Bankey P, Freeman B, Harbrecht BG, Lowry SF, McKinley B, Moore F, West M, Maier RV. Inflammation and the Host Response to Injury, a large-scale collaborative project: Patient-Oriented Research Core--standard operating procedures for clinical care. I. Guidelines for mechanical ventilation of the trauma patient. *J Trauma.* 2005; 59:764–769. [PubMed: 16361929]
22. O'Keefe GE, Shelton M, Cuschieri J, Moore EE, Lowry SF, Harbrecht BG, Maier RV. I., and the Host Response to Injury Collaborative Research, P. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core--standard operating procedures for clinical care VIII--Nutritional support of the trauma patient. *J Trauma.* 2008; 65:1520–1528. [PubMed: 19077652]

23. Shapiro MB, West MA, Nathens AB, Harbrecht BG, Moore FA, Bankey PE, Freeman B, Johnson JL, McKinley BA, Minei JP, Moore EE, Maier RVV. Guidelines for sedation and analgesia during mechanical ventilation general overview. *J Trauma*. 2007; 63:945–950. [PubMed: 18090028]
24. West MA, Moore EE, Shapiro MB, Nathens AB, Cuschieri J, Johnson JL, Harbrecht BG, Minei JP, Bankey PE, Maier RV. Inflammation and the host response to injury, a large-scale collaborative project: patient-oriented research core--standard operating procedures for clinical care VII--Guidelines for antibiotic administration in severely injured patients. *J Trauma*. 2008; 65:1511–1519. [PubMed: 19077651]
25. West MA, Shapiro MB, Nathens AB, Johnson JL, Moore EE, Minei JP, Bankey PE, Freeman B, Harbrecht BG, McKinley BA, Moore FA, Maier RV. I., and the Host Response to Injury Collaborative Research, P. Inflammation and the host response to injury, a large-scale collaborative project: Patient-oriented research core-standard operating procedures for clinical care. IV. Guidelines for transfusion in the trauma patient. *J Trauma*. 2006; 61:436–439. [PubMed: 16917462]
26. Brandt, CA.; Deshpande, AM.; Lu, C.; Ananth, G.; Sun, K.; Gadagkar, R.; Morse, R.; Rodriguez, C.; Miller, PL.; Nadkarni, PM. TrialDB: A web-based Clinical Study Data Management System. *AMIA Annu Symp Proc*; 2003. p. 794
27. The Abbreviated Injury Scale, 1990 revision. Des Plaines, IL: 1990. Association for the Advancement of Automotive Medicine.
28. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974; 14:187–196. [PubMed: 4814394]
29. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med*. 1995; 23:1638–1652. [PubMed: 7587228]
30. Evans HL, Cuschieri J, Moore EE, Shapiro MB, Nathens AB, Johnson JL, Harbrecht BG, Minei JP, Bankey PE, Maier RV, West MA. Inflammation and the host response to injury, a Large-Scale Collaborative Project: patient-oriented research core standard operating procedures for clinical care IX. Definitions for complications of clinical care of critically injured patients. *J Trauma*. 2009; 67:384–388. [PubMed: 19667895]
31. Glaser F, Sannwald GA, Buhr HJ, Kuntz C, Mayer H, Klee F, Herfarth C. General stress response to conventional and laparoscopic cholecystectomy. *Ann Surg*. 1995; 221:372–380. [PubMed: 7726672]
32. Jeong HJ, Hong SH, Park RK, Shin T, An NH, Kim HM. Hypoxia-induced IL-6 production is associated with activation of MAP kinase, HIF-1, and NF-kappaB on HEI-OC1 cells. *Hear Res*. 2005; 207:59–67. [PubMed: 15913932]
33. Feng J, Chen BY, Guo MN, Cao J, Zhao HY, Liang DC, Zuo AJ. Interleukin-6 and tumor necrosis factor-alpha levels of endothelial cells in different hypoxia modes: in vitro experiment. *Zhonghua Yi Xue Za Zhi*. 2007; 87:774–777. [PubMed: 17565849]
34. Moreau C, Devos D, Brunaud-Danel V, Defebvre L, Perez T, Destee A, Tonnel AB, Lassalle P, Just N. Elevated IL-6 and TNF-alpha levels in patients with ALS: inflammation or hypoxia? *Neurology*. 2005; 65:1958–1960. [PubMed: 16380619]
35. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. *Arch Surg*. 1994; 129:39–45. [PubMed: 8279939]
36. Remick DG, Bolgos G, Copeland S, Siddiqui J. Role of interleukin-6 in mortality from and physiologic response to sepsis. *Infect Immun*. 2005; 73:2751–2757. [PubMed: 15845478]
37. Friedland JS, Porter JC, Daryanani S, Bland JM, Screatton NJ, Vesely MJ, Griffin GE, Bennett ED, Remick DG. Plasma proinflammatory cytokine concentrations, Acute Physiology and Chronic Health Evaluation (APACHE) III scores and survival in patients in an intensive care unit. *Crit Care Med*. 1996; 24:1775–1781. [PubMed: 8917024]
38. Remick DG, Bolgos GR, Siddiqui J, Shin J, Nemzek JA. Six at six: interleukin-6 measured 6 h after the initiation of sepsis predicts mortality over 3 days. *Shock*. 2002; 17:463–467. [PubMed: 12069181]

39. Sturk A, Hack CE, Aarden LA, Brouwer M, Koster RR, Sanders GT. Interleukin-6 release and the acute-phase reaction in patients with acute myocardial infarction: a pilot study. *J Lab Clin Med.* 1992; 11:574–579. [PubMed: 1583414]
40. Hack CE, De Groot ER, Felt-Bersma RJ, Nuijens JH, Strack Van Schijndel RJ, Eerenberg-Belmer AJ, Thijs LG, Aarden LA. Increased plasma levels of interleukin-6 in sepsis. *Blood.* 1989; 74:1704–1710. [PubMed: 2790194]
41. Giannoudis PV, Harwood PJ, Loughenbury P, Van Griensven M, Krettek C, Pape HC. Correlation between IL-6 levels and the systemic inflammatory response score: can an IL-6 cutoff predict a SIRS state? *J Trauma.* 2008; 65:646–652. [PubMed: 18784579]
42. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. *Arch Surg.* 1997; 132:620–624. discussion 624–625. [PubMed: 9197854]
43. Moore EE. Blood substitutes: the future is now. *J Am Coll Surg.* 2003; 196:1–17. [PubMed: 12517544]

Figure 1. Early plasma IL-6 level in patients that did and did not develop MODS. Asterisk (*) represents statistical significance with a $p=0.006$

Figure 2.
ROC curve for plasma IL-6 relative to MODS development following injury.

	No MODS	MODS	
IL-6 > 350 pg/ml	9	15	PPV 62.5 (CI 42.7 to 78.8) LR 3.25 (CI 1.76 to 6)
IL-6 ≤ 350 pg/ml	28	4	NPV 87.5 (CI 71.9 to 95.0) LR 0.28 (CI 0.11 to 0.68)
	Sensitivity 79% (CI 0.57 to 0.91)	Specificity 76% (CI 0.60 to 0.87)	

Figure 3.

Contingency table depicting sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), for MODS development, of IL-6 cutoff (350 pg/ml) when applied to validation cohort (n=56). Also shown are the MODS likelihood ratios (LR) for a positive test (IL-6 > 350 pg/ml) and a negative test (IL-6 ≤ 350 pg/ml), respectively.

Table 1

Independent Predictors for the Development of MODS with development cohort

Clinical Parameter	Odds Ratio for Development of MODS* (95% CI)
Sex, male	9.19 (2.07–40.85)
ISS	1.02 (1.01–1.05)
Blood transfusion > 6 u/12 h	1.68 (1.10–3.26)
IL-6 $\geq$ 350 pg/ml	3.87 (1.13–11.19)

* Compared to patients without that characteristic.

Table 2

Comparison of Baseline Patient Characteristics between the Development and Validation Cohorts.

	Development Cohort (n=79)	Validation Cohort (n=56)
Median age, yr*	33 (25–41)	35 (23–45)
Sex, no. male/female	45/34	32/24
Ethnic origin: n (%)		
White	59 (75)	43 (77)
African descent	8 (10)	4 (7)
Asian	2 (3)	3 (5)
Hispanic	9 (11)	5 (9)
Other (mixed racial)	1 (1)	1 (1)
Body-Mass Index*	27 (24–31)	29 (21–36)
Comorbid disease: n (%)		
None	65 (82)	45 (80)
Cardiac	8 (10)	4 (7)
Pulmonary	8 (10)	5 (9)
Hepatic	2 (3)	1 (1)
Renal	2 (3)	1 (1)
Mechanism of injury: n (%)		
Motor vehicle crash	63 (80)	41 (73)
Pedestrian-MVC	6 (8)	5 (9)
Fall	6 (8)	8 (14)
Other blunt mechanism	4 (5)	2 (4)

Differences are not significant unless otherwise specified.

* Median (25th–75th Percentile).

Table 3

Comparison of Injury Characteristics between the Development and Validation Cohorts.

	Development Cohort (n=79)	Validation Cohort (n=56)
Injury Severity Score *	29 (21–40)	32 (24–39)
Maximum AIS *	4 (3–5)	4 (3–5)
Apache II score *	27 (24–32)	25 (22–32)
ER Lowest BP, mmHg *	87 (76–103)	86 (68–101)
Worst base excess in first 12 h *	8 (6–10)	9 (7–12)
Crystalloids in first 12h, L *	10.9 (7.6–16.9)	11.6 (6.9–18.4)
Blood transfusion > 6 units/12 h, n (%)	42 (53)	35 (63)
Blood transfusion in first 12 h (units) *	7 (3–10)	8 (2–11)
Plasma IL-6 Level *	276 (103–443)	322 (156–524)

Differences are not significant unless otherwise specified.

* Median (25th–75th Percentile).

Table 4

Outcome Variables Associated with Elevated Plasma IL-6 Levels within Validation Cohort*

	Group 1 (IL-6≤350 pg/ml) n=32	Group 2 (IL-6>350 pg/ml) n=24	p – value
Mechanical Ventilation (days)	5.72 ± 0.83	13.41 ± 1.86	0.001
ICU length of stay	6.85 ± 0.89	11.7 ± 1.99	0.017
Hospital length of stay (days)	16.79 ± 1.99	28.66 ± 4.06	0.012
Maximum MODS score	5.88 ± 1.53	7.54 ± 1.96	0.001
MODS development, n (%)	4 (12.5)	15 (62.5)	0.001
Infections			
Ventilator-associated pneumonia, n (%)	9 (28.1)	8 (33.3)	0.313
Bloodstream infection, n (%)	2 (6.3)	2 (8.3)	0.764
Urinary tract infection, n (%)	6 (18.8)	8 (33.3)	0.212
Other, n (%)	1 (3.1)	3 (12.5)	0.177
Mortality, n (%)	2 (6.3)	3 (12.5)	0.416

*
Data expressed as mean ± standard deviation