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Diagnosis-Dependent Relationships between Cytokine Levels and Survival in Patients Admitted for Surgical Critical Care

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Abstract

Background—Death following trauma, infection, or other critical illness has been attributed to unbalanced inflammation, where dysregulation of cytokines leads to multiple organ dysfunction and death. We hypothesized that admission cytokine profiles associated with death would differ based on admitting diagnosis.

Study Design—This five-year study included patients admitted for trauma or surgical intensive care for more than 48 hours at two academic, tertiary care hospitals between 10/01 and 05/06. Cytokine analysis for IL-1, 2, 4, 6, 8, 10, 12, IFN-gamma, and TNF alpha was performed using ELISA on specimens drawn within 72 hours of admission. Mann-Whitney U test was used to compare median admission cytokines levels between alive and deceased patients. Relative risks and odds of death associated with admission cytokines were generated using univariate analysis and multivariate logistic regression models, respectively.

Results—1655 patients had complete cytokine data: 290 infected, non-trauma, 343 non-infected, non-trauma, and 1022 trauma. Among infected patients, non-survivors had higher median admission levels of IL-2, -8, -10 and GMCSF; non-infected, non-trauma patients IL-6, -8 and IL-10; and non-surviving trauma patients had higher IL-4, -6, -8 and TNF-α. Interleukin-4 was the most significant predictor of death and carried the highest relative risk of dying in trauma patients, and IL-8 in non-trauma, non-infected patients. In infected patients, no cytokine independently predicted death.

Conclusions—Cytokine profiles of certain disease states may identify persons at risk of dying and allow for selective targeting of multiple cytokines to prevent organ dysfunction and death.

Cytokine release is a normal, highly complex and tightly modulated response to traumatic insult or infection, capable of producing different effects depending on the body's regional composition.[1] Infection or trauma induce an immediate, system-wide pro-inflammatory

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release, unleashing cytokines that help to recruit neutrophils, B cells and T cells, platelets and coagulation factors to the site of damage.[1-3] This leads to destruction of the already wounded tissue, healthy tissue growth promotion and an attempt at eradication of pathogenic microorganisms or foreign antigens.[1-3] Compensatory anti-inflammatory responses soon follow and are believed to exist to attenuate the pro-inflammatory state by decreasing expression of monocytic major histocompatibility complex (MHC) class II, imparing antigen presenting activity and reducing cells' ability to produce pro-inflammatory cytokines.[4-9]

Disequilibrium between pro- and anti-inflammatory cytokines is now believed to initiate a physiologic state that can ultimately lead to patient demise. The disequilibrium may cause the Systemic Inflammatory Response Syndrome (SIRS) – a generalized, cytokine response in organs distant from the original site of injury or infection.[1] SIRS is characterized by progressive microvascular permeability,[10-14] organ ischemia due to microcirculation plugging,[15] activation of the coagulation system,[16] and vasodilation with fluid transudation and global tissue hypoxia.[17-19] SIRS can in turn progress to a multiple organ dysfunction syndrome (MODS), which may cause death in up to 30% of critically ill patients unless cytokine homeostasis is restored.[20]

Although great clinical advances have been made regarding mortality among injured or septic patients through early goal-directed therapy and resuscitation, the frequency of organ dysfunction and its ensuing death have remained largely unchanged.[21,25] There is an increased recognition of the role of cytokines in inflammatory dysregulation, with recent evidence suggesting that elevated cytokine levels correlate with poor patient outcomes.[23,25] Furthermore, the highest cytokine concentrations have been obtained early in the posttraumatic and infectious periods.[39] Nonetheless, specific cytokine patterns, truly predictive of outcomes, are yet to be established; with further uncertainty stemming from the fact that the release of systemic cytokines can occur in a variety of diseases without leading to organ dysfunction.[1,22] For the purpose of this study, we hypothesized that admission cytokine levels and patterns would predict mortality in patients admitted for intensive care and would differ based on admission diagnosis.

Methods

Study design/Data origin

Patients, 18 years of age or older, admitted to the surgical or trauma intensive care units (ICU) of two institutions - Vanderbilt University Medical Center and the University of Virginia Medical Center – were enrolled in this prospective, multicenter cohort study from October 2001 to May 2006. The study was approved by the local Institutional Review Board at each medical center, with the University of Virginia having approval for waiver of consent, while Vanderbilt required an assent from a surrogate prior to data collection and informed consent from the patient in case of resolution of the critical illness.

Critically injured or infected patients with a minimum of 48-hour ICU stay were eligible for enrollment in this study. This time point was created to ensure that patients with overwhelming events (*e.g.*, non-survivable hemorrhage, traumatic brain injury, etc.) and those with less severe illnesses or at lower risk for mortality would be excluded from enrollment. Individuals primarily admitted for burn injuries and/or without complete cytokine data were not included in this report. Subjects were divided into three separate groups based on the reason for ICU admission: (1) trauma patients, (2) non-trauma patients admitted for the treatment of infection and (3) non-infected, non-trauma patients.

Data collection/Variables

Full-time research nurses collected clinical data at each facility by interviewing patients, their families and healthcare providers, or reviewing electronic and paper medical records. Baseline demographics as well as date of hospital/ICU admission and discharge, in-hospital death, co-morbidities (diabetes mellitus, hypertension, cardiovascular disease, malignancy etc), and in-hospital complications were entered into a secure, password-protected computer database. Data including Acute Physiology and Chronic Health Evaluation (APACHE) II score,[26] the Marshall or Multiple Organ Dysfunction score (MODS),[27] and the McCabe (underlying disease) score[28] were calculated for *all* patients at the time of ICU admission. The Injury Severity Score (ISS)[29] and the Trauma-Score Injury Severity Score (TRISS),[30] evaluating the probability of survival in injured patients, were calculated for trauma patients at the time of admission. Glasgow Coma Scale (GCS) score was calculated for all patients. For patients who were iatrogenically sedated, the GCS score was estimated as if the patient was not sedated, and that value was recorded and used in the calculation of APACHE II score and MODS. Mortality included deaths from any cause occurring prior to hospital discharge.

Infections—Definitions for infections with the exception of catheter related infections followed the United States Centers for Disease Control and Prevention guidelines.[31] Diagnosis of *pneumonia* was based on systemic evidence of infection, production of sputum, isolation of a predominant organism, development of a new or changing infiltrate or effusion on chest radiograph or growth of >100,000 colony-forming units (CFU) on quantitative culture via endotracheal aspiration or >10,000 CFU via broncheoalveolar lavage. *Bloodstream infections* were diagnosed by isolating organisms from any single blood culture using aseptic technique, except for coagulase-negative *Staphylococcus* (i.e. *Staphylococcus Epidermidis)*. Diagnosis of coagulase-negative *Staphylococcus* blood stream infections required growth from two separate positive blood cultures. *Urinary tract infections* required growth of either >100,000 organisms/ml of urine or >10,000 organisms/ml with symptoms. *Catheter-related infections* were defined as isolation of >15 colonies with the semi-quantitative roll plate technique in the setting of clinical infection with possible but not necessary positive blood culture with the same organism. Catheter tips were cultured only when removed from patients with a temperature of >38.5°C or a persistently rising or elevated white blood cell count.[32] For infections of the *skin, soft tissue, wound and peritoneal infections*, culture-positive evidence was helpful, but not required, since most of these infections were diagnosed clinically.

Cytokine assay—At the time of study entry (within 72 hours of admission), a 10-ml blood sample was collected from each patient for assessment of cytokine levels including pro-inflammatory cytokines (IL-1, -2,-6, -12, interferon –γ (IFN), tumor necrosis factor-α (TNFα), granulocyte-macrophage colony-stimulating factor (GM-CSF)), anti-inflammatory cytokines (IL-4 and -10), the chemokine IL-8 and the miscellaneous cytokine IL-5. The blood sample was centrifuged and plasma separated and stored at -70°C prior to evaluation. To determine cytokine concentrations, plasma was assayed with an ELISA-based technology, the Luminex^{100} system® (Miraibio, Inc., Alameda, CA), and all data recorded into our database. Minimal level of cytokine detectability was defined as 2.7 pg/mL.

Statistical analysis

Univariate analysis—Descriptive analyses comparing demographic data between survivors and non-survivors for the three patient groups (trauma, infected non-trauma, and non-infected, non-trauma) were performed using univariate analysis with a statistical significance set at <0.05. Continuous variables are presented as a mean ± 95% confidence interval (CI) and compared using a two-sample t test for independent samples. Categorical

variables were analyzed using a Chi-square or Fisher's exact test. Cytokine levels had a marked rightward skew and are also presented as a median and interquartile range (IQR) with p-value generated through a group comparison using the Wilcoxon rank sum test. Cytokine concentrations were subsequently divided into quartiles with all further comparisons carried out between the highest cytokine concentrations (top quartile) and all other quartiles combined. Relative risk (RR) of death imposed by or associated with each cytokine, found on univariate analysis to be significant, was then calculated. To describe the relationship between the cytokines that were found to be statistically significant on univariate analysis and the severity of illness (TRISS in trauma patients and APACHE II score in non-trauma patients), Spearman correlation coefficient was calculated.

Multivariate analysis—Cytokines that were statistically significantly different by univariate analysis were used to build three multivariable logistic regression models for trauma, infected non-trauma, and non-infected non-trauma patients. In order to predict the odds of death with respect to cytokine levels, admission cytokine concentrations were divided into quartiles and entered into the models as categorical variables; the patients with the highest quartile of cytokine expression were compared to those in the lowest three quartiles, ultimately generating odds ratios for death. For each model, maximum adjusted R^2 value and c statistics were calculated to ensure that the models performed well and were able to adequately discriminate between survivors and non-survivors, respectively. To confirm the results generated by the logistic regression analysis, our model was internally validated via bootstrapping method (80:20).

Additional variables found in previous publications to be important predictors of mortality in critically ill patients were included in the logistic regression model as follows. The trauma model utilized age, gender, temperature,[32] serum creatinine,[32] GCS, TRISS, MODS and ISS score in addition to significant cytokines. Only patients with ISS ≥ 16 were included in the model in order to ensure severe injuries requiring surgical critical care.[25] In addition to significant cytokines, the model predicting survival in infected patients included age, gender, GCS score, APACHE II score, MODS, McCabe admit score and the model for non-injured non-infected patients included age, gender, GCS, APACHE II score, MODS, McCabe admit score.

In previous publications,[33] cytokine concentrations have been log-transformed with models created using a natural log scale. However, our model performance was unaltered using log-transformed cytokine concentrations and thus, results using only the original form of data are included in this paper. Additionally, no imputation techniques were required in our study, since only patients with 100% of cytokine data were included. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC).

Results

Baseline demographics

A total of 2291 patients were enrolled in this study, with 1655 (72.2%) having complete admission cytokine data. One-thousand-twenty-two (61.8%) patients were included in the trauma group and 633 (38.2%) in the non-trauma group. The non-trauma patients were further subdivided into infected (290) and non-infected (343) patients. One-hundred-nine (10.7%) injured patients, 87 (30%) infected, non-trauma patients, and 54 (15.7%) non-infected, non-trauma patients died during the study period.

Population factors associated with survival

Univariate analysis of individual variables within each study group revealed several differences between alive and deceased patients. For all cohorts, patients who survived were younger and had lower APACHE II scores. Alive *trauma* patients tended to be white, have longer hospital and ICU length of stay, higher GCS score, lower MODS score and increased TRISS score and comorbidities including cardiovascular, cerebrovascular and renal disease (table 1). *Infected, non-trauma* patients who survived also had longer hospital stay, higher McCabe scores, and a greater incidence of malignancy (table 2). *Non-infected, non-trauma* patients who lived had higher GCS score and incidence of McCabe score of 3, but lower white blood cell (WBC) count (table 3).

Mean and median cytokine levels of the three respective study groups were listed in table 4 with medians compared using the Mann-Whitney U test due to a non-Gaussian distribution of values. Significant differences were noted between the following patient categories in terms of admission cytokine levels: IL-1, IFN, GMCSF, TNFα, IL-10, IL-8 and IL-5.

Cytokine differences between survivors and non-survivors

Analysis of the entire study population revealed that median cytokine differences between survivors and non-survivors were most significant for IL-4, -6, -8, -10, and TNFα. In trauma patients, IL-4, -6, -8, and TNFα were found to be significantly higher in non-survivors. Median levels of IL-2, -8, -10 and GMCSF in infected, non-trauma patients and IL-6, -8, and -10 in non-infected, non-trauma patients were higher in patients who eventually died (table 5 and 6). A considerable number of patients had cytokine levels that were below the minimal level of detectability for the assay used, ranging from 3.1% of IL-10 to 67.0% of IL-1 assays. The most likely detected cytokines/chemokines were IL-6,-8, and IL-10, while the least likely detected cytokines were IL-1,-5 and IL-12.

Relative risk associated with elevated cytokine concentrations

To further assess the importance of elevated admission cytokine concentrations, the relative risk of death was estimated by comparing patients with the highest cytokine concentrations (top quartile) to the other three quartiles within their respective study groups. Severely injured patients were found to have the highest relative risk of dying with the highest concentrations of IL-4 (relative risk = 2.18, $p<0.01$). Interleukin-6, -8 and TNFα, individually also carried an increased risk of death in trauma patients as follows: 60%, 73% and 48%, respectively. IL-8 was associated with a 56% increased risk of death in infected, non-trauma patients. An increased risk of death in non-infected, non-trauma patients was associated with the highest levels of IL-8 with a relative risk of 2.22 ($p<0.01$). These results are shown in table 7.

Correlation between cytokines and severity of illness

In *trauma* patients, IL-4 and IL-8 significantly and inversely correlated with TRISS (σ_{IL-4}= -0.12, $p<0.01$; σ_{IL-8}= -0.09, $p=0.02$). APACHE II score correlated significantly with IL-8 and IL-10 in *infected* (σ_{IL-8}= 0.19, $p<0.01$; σ_{IL-10}= 0.20, $p<0.01$), and *non-infected non-trauma* (σ_{IL-8}= 0.13, $p=0.02$; σ_{IL-10}= 0.17, $p<0.01$), patients.

Multivariate models

A multivariable logistic regression model was estimated to predict patient death as a function of cytokine concentrations identified by univariate analysis to differ significantly between survivors and non-survivors. All cytokine data were adjusted for the previously established risk factors (see methods section). Results of the multivariate logistic regression

model for cytokines only are shown in table 8, while table 9 displays the most statistically significant independent predictors of mortality.

In *trauma* patients, cytokine results were adjusted for presenting temperature, GCS, TRISS, age, creatinine, MODS, ISS, and gender. Only patients with ISS≥16 were included, a total of 811 patients. IL-4 was shown to be an independent predictor of mortality with a 2.5 times adjusted increased odds of death (95%CI 1.2 – 5.4). The logistic regression model was an accurate predictor of outcome in trauma patients with a c-statistic of 0.88, demonstrating an adequate discrimination between survivors and decedents, and had a maximum adjusted R^2 value of 0.40, designating the model as a good performer. The most predictive information for the model was provided by the GCS score, age and creatinine, followed closely by IL-4 and ISS. Predicting death in *infected*, non-trauma patients was more difficult with a c-statistic of 0.74 and maximum adjusted R^2 value of 0.20. No cytokines were found to be independent predictors of death, but age, McCabe score and APACHE II score provided the most predictive information. Admission IL-8 concentration was independently associated with a 2.5 fold (95%CI 1.0 – 6.2) increased risk of death when adjusted for GCS score, APACHE II score, age, McCabe score, MODS, gender and cytokines in *non-infected, non-trauma patients*. The model's c-statistic was 0.81 and maximum adjusted R^2 0.26. The most predictive information in the model was provided by the APACHE II score, age, McCabe score, GCS score and IL-8.

Discussion

Although the term Systemic Inflammatory Response Syndrome (SIRS) generically refers to a common pathologic event that ensues as a result of an injury or an infectious process, the body's response is a highly complex and heterogeneous sequence of events.[36] It is dependent on a number of factors, including the nature of the inciting event, patient's genetic background, clinical interventions, etc.[36] Patient management to date has been limited to antimicrobial administration, surgical or radiologic interventions and a multitude of supportive therapies including fluids, vasoactive drugs and other ICU interventions with the intent of preventing progression of SIRS to MODS and death.[20,36] Animal and human experiments have suggested the possibility of modifying the pathophysiologic processes that lead to SIRS by modulating the host inflammatory response. Clinical trials directed at altering the activity of these modulators, however, have been almost uniformly unsuccessful. Perhaps the most important difficulty has been in differentiating actual mediators of inflammation from inactive markers of inflammation. Marshall et al[36] described mediators as ‘rational targets for therapeutic intervention,’ while markers merely represent the sequelae of the inflammatory processes. We believe, however, that as patterns of cytokines emerge and allow us to discriminate consistently between survivors and non-survivors (in combination with more sophisticated models), that beneficial mediator immunomodulation may yet be achieved.

In this study, we have analyzed prospectively collected admission cytokine data in patients who were admitted to the intensive care units of two medical centers. Demographic data suggested that the patients had a considerable severity of illness, whether based on scoring systems (mean ISS of 29 for trauma patients and mean APACHE II of 19 for non-trauma patients), or overall mortality (11 to 30% based on the group). The cohort was further used to create models using both clinical and cytokine data that could predict patient death after a severe illness. To our knowledge, this is the largest dataset examining the relationship between admission serum cytokine levels and outcomes among surgical patients. By solely analyzing admission concentrations, our initial hypothesis that the early cytokine expression and the relationship between cytokine expression and death are dependent on the nature of the critical illness leading to ICU admission appears valid. Compared to the other groups,

trauma was associated with high levels of GMCSF and IFNγ, and lower levels of TNF- α, IL-8 and IL-10. Infected patients had the highest levels of IL-10. Death following trauma was associated with increased levels of IL-4, IL-6, IL-8, and TNF-α; death following an admission for infection was associated with increased concentrations of IL-2, IL-8, IL-10, and GM-CSF; while death following admissions without trauma or infection were associated with increased expression of IL-6, IL-8, and IL-10.

Although some animal models suggest a relatively stereotypic proinflammatory response to most forms of acute stress, the populations described here demonstrated significant intergroup differences and we are left to speculate on the causes of these findings. Obviously, the nature of the inciting event is different between traumatized patients and patients with other forms of critical illness. For example, traumatically injured patients are exhibiting a host response to pain, injury, and potentially hemorrhage and reperfusion, while infected patients are displaying an immune response to live pathogens. Also, the timing of cytokine assay related to the beginning of the patient's illness is undoubtedly different between trauma and non-trauma patients. The exact time of a traumatic event is generally easy to ascertain and treatment is ideally rapid, while patients with other diseases may only seek treatment after many hours and days of illness.

Finally, the cytokine levels measured even at admission must reflect to some degree differences in early therapies between groups, such as pre-hospital resuscitation for trauma patients or early antibiotics for infected patients. Whatever the reasons for these observations, it is clear that different subgroups of critically ill surgical patients cannot be considered similarly under a generic category of “hyperinflamed.”

Examining the individual cytokines, it appears that the association between elevated IL-6 and IL-8 levels and increasing risk of mortality is fairly uniform across patients. On the other hand, among counter inflammatory mediators, IL-4 seems to be most closely associated with death among trauma patients while IL-10 is expressed more among non-trauma patients who die. Although IL-4 inhibits cytokine production to some degree, it more profoundly acts to polarize lymphocyte toward a less inflammatory Th2 phenotype, more closely associated with B cell activity, immunoglobulin production, and a more chronic response to infection. IL-10, on the other hand, significantly and rapidly downregulates the production and secretion of multiple pro-inflammatory mediators. These differences might imply that traumatized patients expressing IL-4 would be deficient in Th1 response and at risk for death from cell-mediated subacute infections, while non-traumatized patients may be less able to mount an appropriate innate immune response and be more likely to die from acute infections, though data to support this theory will be hard to obtain.

Given previous data generated in animals and smaller human studies, the finding that death was not associated with either a clear predominance of either pro-inflammatory or anti-inflammatory mediators, even after analyzing different etiologies of disease, was somewhat surprising. These results, however, corroborate the work of Kellum et al[34] who studied 1886 patients admitted for the treatment of community-acquired pneumonia. They found that the risk of death was highest among patients expressing high levels of both IL-6 and IL-10, and the best survival was among patients with low levels of both cytokines. Discerning which patients would be the best candidates for mediator targeted therapy, therefore, will be more difficult than detecting patients with merely an overly pro- or anti-inflammatory response.

Several weaknesses in our study ought to be highlighted. First, due to the study design we analyzed cytokine levels drawn within 72 hours of admission, and ideally we would have considered values only at the actual time of admission. Although some changes undoubtedly occurred over the first three days of illness, around 40% of the values analyzed actually

were from the first day and no notable differences could be discerned between cytokines from day one and those drawn on days two or three after admission (data not shown). Second, although the increased expression of several cytokines were associated with mortality by univariate analysis, only IL-4 for trauma patients and IL-8 for non-infected, non-trauma patients were independent predictors of death in our final models. Part of the explanation for this, however, might lie in the close relationship between severity of illness and cytokine expression. It is possible that the inclusion of severity of illness scores in our predictive models nullified the effects of cytokine levels. Finally, even though the object of the current study was to analyze the effects of cytokine expression on different patient subgroups, many more factors must be important determinants of mediator release. Among the infected patients, for example, there may be a different relationship between cytokines and survival conditioned on whether the infection is Gram negative, Gram positive, fungal, or even viral in origin. Thus, it is clear that even among the subgroups studied that a varied response to mediators will occur.

In conclusion, among surgical patients admitted for critical care, there are significant differences in cytokine levels conditioned on the admitting diagnosis. In addition, for the subgroups studied, the relationship between the different cytokines and survival are also dependent on the admitting diagnosis. These data can be used as an early step to designing trials intended to improve outcomes through the modulation of these important mediators.

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Table 1

Frequency and Percentage Distribution of Trauma Population Characteristics, by Discharge Status

	Discharged alive		Discharged deceased		p Value
	n	%*	n	%*	
n	913	89.3	109	10.7	-
Age, y†	41.9 ± 0.6	-	51.5 ± 1.9	-	<0.01
Hospital length of stay†	23.4 ± 1.0	-	13.6 ± 1.4	-	<0.01
ICU length of stay†	12.0 ± 0.3	-	10.8 ± 1.2	-	<0.01
White blood cell count†	16.1 ± 0.3	-	16.3 ± 0.8	-	0.37
Race/Ethnicity					
White	743	81.4	98	89.9	0.03
African American	119	13.0	8	7.3	0.09
Hispanic	41	4.5	3	2.8	0.40
Native American	2	0.2	0	0	0.62
Other	8	0.9	0	0	0.44
Comorbidities					
Coronary artery disease	98	10.7	30	27.5	<0.01
Cerebrovascular disease	21	2.3	8	7.3	<0.01
Chronic renal disease	5	0.5	4	3.7	<0.01
Corticosteroids	8	0.9	3	2.8	0.07
Liver disease	23	2.5	9	8.3	0.62
Malignancy	17	1.9	4	3.7	0.21
Peripheral vascular disease	16	1.8	2	1.8	0.95
Pulmonary disease	83	9.1	15	13.8	0.12
Autoimmune disorders	10	1.1	3	2.8	0.15
Diabetes mellitus	64	7.0	10	9.2	0.41
Other	7	0.8	3	2.8	0.08
Interventions					
Mechanical ventilation	845	92.6	103	94.5	0.48

	Discharged alive		Discharged deceased		p Value
	n	%*	n	%*	
Total days intubated†	9.0 ± 0.3	-	8.6 ± 0.6	-	0.75
Tracheostomy	90	9.9	9	8.3	0.56
Transfusions	638	69.9	79	72.5	0.72
Scoring†					
ISS	28.6 ± 0.4	-	29.8 ± 1.4	-	0.48
TRISS	0.70 ± 0.01	-	0.54 ± 0.04	-	<0.01
GCS	12.9 ± 0.1	-	10.1 ± 0.4	-	<0.01
APACHE II	15.4 ± 0.2	-	21.8 ± 0.6	-	<0.01
MODS	7.2 ± 0.1	-	8.8 ± 0.3	-	<0.01

*Percent based on total trauma population.

†Expressed as mean ± Standard error of the mean.

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Table 2

Frequency and Percentage Distribution of Infected Non-Trauma Population Characteristics, by Discharge Status

	Discharged alive		Discharged deceased		p Value
	n	%*	n	%*	
n	203	70	87	30	-
Age, y†	54.8 ± 1.0	-	63.0 ± 1.6	-	<0.01
Hospital length of stay†	41.2 ± 2.4	-	31.2 ± 3.0	-	<0.01
ICU length of stay†	20.1 ± 1.0	-	21.3 ± 2.2	-	0.90
White blood cell count†	15.9 ± 0.9	-	16.2 ± 1.3	-	0.73
Race/Ethnicity					
White	176	86.7	75	86.2	0.91
African American	22	10.8	7	8.0	0.47
Hispanic	1	0.5	2	2.3	0.16
Other	4	2.0	3	3.4	0.03
No. of infections treated during ICU admission					
1	124	61.1	48	55.2	0.35
2	51	25.1	15	17.2	0.14
3 or more	16	7.9	13	14.5	<0.01
Total infections during ICU admission	310	-	150	-	-
Comorbidities					
Coronary artery disease	66	32.5	33	37.9	0.39
Cerebrovascular disease	17	8.4	10	11.5	0.41
Chronic renal disease	21	10.3	7	8.0	0.54
Corticosteroids	20	9.9	14	16.1	0.13
Liver disease	29	14.3	18	20.7	0.18
Malignancy	48	23.6	35	40.2	<0.01
Peripheral vascular disease	20	9.9	8	9.2	0.85
Pulmonary disease	50	24.6	20	23.0	0.75
Autoimmune disorders	6	3.0	3	3.4	0.83

	Discharged alive		Discharged deceased		p Value
	n	%*	n	%*	
Diabetes mellitus	68	33.5	20	23.0	0.07
Other	42	20.7	17	19.5	0.82
Interventions					
Mechanical ventilation	175	86.2	74	85.1	0.80
Total days intubated†	14.9 ± 0.8	-	15.9 ± 1.0	-	0.35
Tracheostomy	15	7.4	5	5.7	0.60
Transfusions	142	70.0	68	78.2	0.07
Scoring†					
GCS	14.2 ± 0.2	-	13.8 ± 0.2	-	0.08
APACHE II	18.5 ± 0.5	-	22.2 ± 0.7	-	<0.01
MODS	8 ± 0.3	-	8.3 ± 0.5	-	0.60
McCabe score					
0	37	18.2	13	14.9	0.50
1	133	65.5	45	51.7	0.03
2	29	14.3	24	27.6	<0.01
3	3	1.5	5	5.7	0.04

*Percent based on total infected non-trauma population.

†Expressed as mean ± Standard error of the mean.

Table 3

Frequency and Percentage Distribution of Non-Infected Non-Trauma Population Characteristics, by Discharge Status and Overall

	Discharged alive		Discharged deceased		p Value
	n	%*	n		n
n	289	84.3	54	15.7	-
Age, y†	59.2 ± 0.9	-	65.6 ± 2.22	-	<0.01
Hospital length of stay, d†	22.7 ± 1.1	-	40.1 ±14.4	-	0.84
ICU length of stay, d†	8.9 ± 0.4	-	22.9 ± 13.5	-	0.49
White blood cell count†	13.0 ± 0.6	-	17.4 ± 2.0	-	<0.01
Race/Ethnicity					
White	249	86.2	45	83.3	0.59
African American	35	12.1	9	16.7	0.36
Other	5	1.7	0	0	0.33
Comorbidities					
Coronary artery disease	93	32.2	24	44.4	0.08
Cerebrovascular disease	28	9.7	5	9.3	0.92
Chronic renal disease	34	11.8	8	14.8	0.53
Corticosteroids	18	6.2	5	9.3	0.41
Crohn's/Ulcerative colitis	17	5.9	0	0	0.07
Hemodialysis	13	4.5	3	5.6	0.74
Liver disease	55	19.0	11	20.4	0.82
Malignancy	64	22.1	17	31.5	0.14
Peripheral vascular disease	32	11.1	4	7.4	0.42
Pulmonary disease	79	27.3	11	20.4	0.29
Inflammatory disorders	8	2.8	1	1.9	0.70
Diabetes mellitus	78	27.0	12	22.2	0.46
Transplant	45	15.6	6	11.1	0.40
Interventions					
Mechanical ventilation	246	85.1	51	94.4	0.07

	Discharged alive		Discharged deceased		p Value
	n	%*	n		n
Total days intubated	7.1 ± 0.5	-	8.2 ± 1.2	-	0.26
Tracheostomy	17	5.9	4	7.4	0.59
Transfusions	200	69.2	40	74.1	0.24
Scoring†					
GCS	14.2 ±0.1	-	13.4 ± 0.3	-	<0.01
APACHE II	17.6 ± 0.4	-	22.2 ± 0.9	-	<0.01
MODS	7.6 ± ± 0.3	-	7.1 ± 0.8	-	0.47
McCabe score					
0	60	20.8	9	16.7	0.49
1	163	56.4	29	53.7	0.71
2	52	18.0	8	14.8	0.57
3	14	4.8	7	13.0	0.02

*Percent based on total non-infected non-trauma population.

†Expressed as mean ± Standard error of the mean.

Table 4

Mean and Median Levels of Pro-Inflammatory, Anti-Inflammatory and Miscellaneous Cytokines and Chemokines, within 48 h of ICU Admission

				p Values			
	Trauma	**Infected, non-trauma**	**Non-infected, non-trauma**	**All groups**	**Infected versus non-infected**	**Infected versus trauma**	**Non-infected versus trauma**
Pro-inflammatory cytokines							
IL-1	8.8 ± 1.2 2.7 (2.7, 5.2)	7.3 ± 0.7 2.7 (2.7, 4.4)	8.5 ± 1.2 2.7 (2.7,2.9)	0.0314	0.3977	0.1361	0.0111
IL-2	14.3 ± 1.8 3.2 (2.7, 12.7)	21.7 ± 6.8 3.7 (2.7, 14.5)	13.3 ± 2.5 2.7 (2.7, 10.9)	0.1642			
IL-6	363.2 ± 36.5 144.1 (57.3, 320.6)	529.0 ± 63.1 170.9 (45.4, 497.3)	408.2 ± 46.5 120.0 (43.0, 393.7)	0.2041			
IL-12	16.5 ± 3.0 2.7 (2.7, 9.8)	45.2 ± 17.2 2.7 (2.7, 12.8)	58.0 ± 26.1 2.7 (2.7, 9.1)	0.102			
IFN	15.0 ± 1.7 3.2 (2.7, 10.7)	17.8 ± 6.4 2.7 (2.7, 8.3)	43.9 ± 19.2 2.7 (2.7, 8.4)	0.0063	0.4728	0.0314	0.0035
GMCSF	11.0 ± 1.7 4.4 (2.7, 9.6)	8.8 ± 1.2 2.9 (2.7,7.9)	13.4 ± 2.6 2.8 (2.7, 7.3)	0.0011	0.8837	0.0041	0.0014
TNFα	19.6 ± 11.1 4.9 (2.7, 9.2)	15.7 ± 1.9 9.2 (2.7, 17.6)	16.9 ± 2.3 8.8 (3.5, 16.2)	<0.0001	0.7887	<0.0001	<0.0001
Anti-inflammatory cytokines							
IL-4	243.9 ± 23.8 31.6 (6.1, 236.4)	221.6 ± 27.2 36.9 (7.1, 223.4)	215.8 ± 27.6 31.9 (4.4, 174.5)	0.6352			
IL-10	187.8 ± 25.3	352.6 ± 53.1 104.9 (37.8, 275.0)	339.6 ± 54.0 60.5 (24.5, 225.3)	<0.0001	0.0005	<0.0001	0.0067

				p Values			
	Trauma	**Infected, non-trauma**	**Non-infected, non-trauma**	**All groups**	**Infected versus non-infected**	**Infected versus trauma**	**Non-infected versus trauma**
	49.9 (20.4, 123.0)						
Chemokines							
IL-8	87.7 ± 16.3 28.0 (12.6, 60.4)	102.9 ± 10.7 52.1 (14.8, 121.8)	140.1 ± 29.4 46.6 (16.3, 100.1)	<0.0001	0.6378	<0.0001	<0.0001
Miscellaneous							
IL-5	6.9 ± 0.5 2.7 (2.7, 4.7)	5.7 ± 0.5 2.7 (2.7, 5.3)	6.8 ± 0.8 2.7 (2.7,4.0)	0.088			

Levels of cytokines are expressed as mean ± SE, median (interquartile range).

Divided according to their respective groups: trauma; infected, non-trauma; and non-infected non-trauma. Because of the non-Gaussian distribution of the data, medians were compared using the Mann-Whitney U test.

Table 5

Mean and Median Levels of the Highest Concentration of Cytokines (Top Quartile), Compared between the Living and Deceased Patients Using Mann-Whitney U Test

	All pts.			Trauma pts.			Non-trauma patients, infected at ICU admission			Non-trauma patients, not infected at ICU admission		
Pro-inflammatory cytokines	**Lived (1,405)**	**Died (250)**	**p Value**	**Lived (913)**	**Died (109)**	**p Value**	**Lived (203)**	**Died (87)**	**p Value**	**Lived (289)**	**Died (54)**	**p Value**
IL-1	8.4±0.4 2.7 (2.7,5.0)	10.9±2.4 2.7 (2.7,2.6)	0.82	8.5±0.5 2.7 (2.7,5.5)	14.9±5.3 2.7 (2.7,6.6)	0.55	7.1±0.8 2.7 (2.7,3.8)	7.9±1.3 2.7 (2.7,5.2)	0.48	8.7±1.4 2.7 (2.7,2.9)	7.8±1.9 2.7 (2.7,2.7)	0.78
IL-2	16.4±1.8 3.1 (2.7,12.5)	19.6±4.5 3.3 (2.7,13.3)	0.67	15.7±1.6 3.2 (2.7,13.4)	25.4±9.8 3.1 (2.7,10.2)	0.56	24.5±9.6 2.7 (2.7,13.8)	15.4±2.3 5.9 (2.7,18.7)	0.04	13.1±2.9 2.8 (2.7,10.9)	14.6±4.7 2.7 (2.7,8.4)	0.25
IL-6	374.3±21.5 137.4 (49.7,359.6)	702.3±83.8 218 (71.2,629.5)	<0.01	355.1±25.3 144.4 (54.9,349.8)	769.5±139.5 192.7 (99.4,668.4)	<0.01	522.1±78.6 154.6 (40.1,424.4)	545.1±104 215.1 (65.2,602.0)	0.10	331.3±37.8 113.3 (43.0,301.4)	820.3±207.4 261.9 (46.3,670.8)	0.02
IL-12	32.2±7.4 2.7 (2.7,10.3)	13.9±1.9 2.7 (2.7,10.7)	0.53	15.8±2.0 2.7 (2.7,9.9)	12.6±2.8 2.7 (2.7,18.7)	0.98	56.9±24.5 2.7 (2.7,13.1)	17.8±4 3.4 (2.7,12.8)	0.37	66.8±31.0 2.7 (2.7,9.2)	10.5±2.25 2.7 (2.7,7.5)	0.71
IFN	19.2±2.6 2.7 (2.7,10.1)	53.1±25.3 2.7 (2.7,12.0)	0.70	19.5±2.8 3.4 (2.7,11.0)	20.9±5.5 2.7 (2.7,13.2)	0.90	11.5±3.8 2.7 (2.7,7.3)	32.4±19.2 2.8 (2.7,9.5)	0.15	23.9±9.0 2.7 (2.7,8.1)	151.4±112.1 2.7 (2.7,11.5)	0.54
TNFα	15.2±4.2 5.8 (2.7,11.6)	18.1±3.1 8.8 (3.0,16.2)	<0.01	15.8±6.5 4.9 (2.7,9.5)	10.1±0.9 6.1 (3.0,13.3)	0.01	13.4±1.4 8.7 (2.7,16.6)	21.0±5.3 11.5 (2.8,21.8)	0.12	14.6±1.7 8.7 (3.5,16.1)	29.4±11.4 10.3 (4.2,23.1)	0.31
GMCSF	11.1±1.0 3.3 (2.7,8.6)	14.8±2.8 4.2 (2.7,9.8)	0.20	12.0±1.3 4.2 (2.7,9.6)	10.8±1.9 4.9 (2.7,11.7)	0.34	7.5±1.2 2.7 (2.7,7.1)	11.9±3 4.4 (2.7,9.5)	0.01	10.8±2.2 2.8 (2.7,7.3)	27.6±11.1 2.7 (2.7,7.6)	0.85

Table 6

Mean and Median Levels of the Highest Concentration of Anti-Inflammatory Cytokines, Chemokines, and Miscellaneous (Top Quartile), Compared between the Living and Deceased Patients Using Mann-Whitney U Test

	Anti-inflammatory cytokines		Chemokines	Miscellaneous
	IL-4	**IL-10**	**IL-8**	**IL-5**
All patients				
Lived (1405)	215.8±14.0 30.9 (5.8,175.8)	240.7±19.9 54.4 (22.7,146.8)	83.0±7.7 34.3 (13.6,73.0)	7.1±0.5 2.7 (2.7,4.6)
Died (250)	324.0±38.3 86.7 (9.8,355.2)	279.2±44.6 102.4 (36.7,240.0)	187.0±37.6 61 (15.0,143.2)	6.5±0.7 2.7 (2.7,5.3)
p Value	<0.01	<0.01	<0.01	0.38
Trauma patients				
Lived (913)	228.7±18.7 31.1 (5.9,177.1)	183.3±18.3 51.9 (21.3,126.6)	77.9±10.0 30.0 (12.8,64.0)	7.6±0.7 2.7 (2.7,4.7)
Died (109)	340.4±55.1 108.1 (17.3,424.0)	200.5±59.3 65.3 (24.9,143.3)	132.1±30.2 42.5 (16.1,102.9)	6.4±0.9 2.7 (2.7,5.9)
p Value	<0.01	=0.24	<0.01	0.35
Non-trauma patients, infected at ICU admission				
Lived (203)	193.6±29.6 30.5 (6.7,194.2)	35.7±68.6 75.2 (30.0,264.6)	85.7±9.1 44.0 (14.4,99.9)	5.4±0.5 2.7 (2.7,4.7)
Died (87)	287.0±58.7 64.2 (8.8,249.9)	341.1±76.4 167.8 (64.2,343.1)	143.0±28.2 72.9 (14.8,169.8)	6.8±0.8 2.7 (2.7,5.9)
p Value	0.20	<0.01	0.04	0.31
Non-trauma patients, not infected at ICU admission				
Lived (289)	190.6±26.5 29.1 (4.6,155.7)	339.0±60.5 55.4 (22.3,201.8)	97.3±18.7 43.8 (16.6,93.3)	6.8±0.8 2.7 (2.7,4.0)
Died (54)	350.0±102 67.9 (4.2,281.6)	338.0±114.3 148.2 (31.7,320.6)	368.8±155.2 84.0 (11.4,207.3)	7.2±2.5 2.7 (2.7,2.7)
p Value	0.16	0.03	0.02	0.45

Table 7

Relative Risk of Death Estimated by Comparing the Highest Concentration of Cytokines (Top Quartile) to All Other Quartiles Combined

Patients	**Cytokines**			
Trauma patients	**IL4**	**IL6**	**IL8**	**TNF**
Relative risk	2.18	1.60	1.73	1.48
95% CI	(1.535, 3.109)	(1.109, 2.313)	(1.207, 2.494)	(1.016, 2.143)
p Value	<0.01	0.01	<0.01	0.04
Infected, non-trauma patients	IL2	IL8	IL10	GMCSF
Relative risk	1.20	1.56	1.27	1.34
95% CI	(0.819, 1.755)	(1.098, 2.228)	(0.871, 1.843)	(0.925, 1.934)
p Value	0.36	0.02	0.23	0.13
Non-infected, non-trauma patients	IL6	IL8	IL10	
Relative risk	1.62	2.22	1.49	
95% CI	(0.982, 2.681)	(1.371, 3.587)	(0.897, 2.489)	
p Value	0.06	<0.01	0.13	

Table 8

Adjusted Odds of Death with their Respective 95% Confidence Intervals for Patients with Admission Cytokine Levels in the Top Quartile as Generated by the Logistic Regression Model

Cytokines	Odds ratio	95% CI
Trauma		
IL4	2.538	1.204 - 5.351
IL6	2.333	0.898 - 6.059
IL8	0.989	0.348 - 2.809
TNF	0.943	0.391 - 2.274
Infected non-trauma		
IL2	1.313	0.652 - 2.646
IL8	1.594	0.783 - 3.242
IL10	1.238	0.615 - 2.494
GMCSF	1.704	0.867 - 3.349
Non-infected non-trauma		
IL6	1.197	0.503 - 2.853
IL8	2.543	1.049 - 6.165
IL10	0.836	0.352 - 1.990

Table 9

Statistically Significant Independent Predictors of Mortality Arranged by their Wald Chi-Square Values

Effects	Odds ratio	95% CI	Wald Chi-square	p Value
Trauma				
GCS score	0.642	0.569 - 0.725	51.6	<0.0001
Age	1.032	1.010 - 1.054	8.10	0.0044
Creatinine	2.483	1.233 - 4.999	6.49	0.0108
IL4	2.538	1.204 - 5.351	5.99	0.0144
ISS	2.643	1.126 - 2.643	4.99	0.0256
Infected non-trauma				
Age	1.035	1.012 - 1.059	9.18	0.0025
McCabe (1 versus 0)	2.430	1.230 - 4.801	6.54	0.0106
APACHE II score	1.098	1.004 - 1.117	4.45	0.0350
Non-infected non-trauma				
APACHE II score	1.098	1.029 - 1.171	7.93	0.0049
Age	1.035	1.008 - 1.064	6.24	0.0125
McCabe score (3 vs 0)	5.380	1.133 - 25.554	6.20	0.0128
GCS	0.843	0.717 - 0.991	4.28	0.0385
IL8	2.543	1.049 - 6.165	4.27	0.0389

Cytokine values are calculated based on the comparison of the highest quartile concentration of admission cytokines to all other quartiles combined. Also shown, adjusted odds ratios for each independent mortality predictor with their respective 95% confidence intervals (95% CI) as generated by the multivariate logistic regression analysis.