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Inhalation injury severity and systemic immune perturbations in burned adults

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Abstract

Objective—We aimed to determine if the severity of inhalation injury evokes an immune response measurable at the systemic level and to further characterize the balance of systemic pro- and anti-inflammation early after burn and inhalation injury.

Summary Background Data—Previously we reported that the pulmonary inflammatory response is enhanced with worse grades of inhalation injury, and that those who die from their injuries have a blunted pulmonary immune profile compared to survivors.

Methods—From August 2007 to June 2011, bronchoscopy was performed on 80 patients admitted to the burn intensive care unit when smoke inhalation was suspected. Of these, inhalation injury was graded into one of five categories (0, 1, 2, 3, and 4), with Grade 0 being the absence of visible injury and Grade 4 corresponding to massive injury. Plasma was collected at the time of bronchoscopy and analyzed for 28 immunomodulating proteins via multiplex bead array or ELISA.

Results—The concentrations of several plasma immune mediators were increased with worse inhalation injury severity, even after adjusting for age and % TBSA. These included interleukin (IL)-1RA ($p=0.002$), IL-6 ($p=0.002$), IL-8 ($p=0.026$), granulocyte colony stimulating factor ($p=0.002$), and monocyte chemotactic protein (MCP)-1 ($p=0.007$). Differences in plasma immune mediator concentrations in surviving and deceased patients were also identified. Briefly, plasma concentrations of IL-1RA, IL-6, IL-8, IL-15, Eotaxin, and MCP-1 were higher in deceased patients compared to survivors ($p<0.05$ for all), while IL-4 and IL-7 were lower ($p<0.05$). After adjusting for the effects of age, % TBSA, and inhalation injury grade, plasma IL-1RA remained significantly associated with mortality (OR 3.12, 95% CI 1.03–9.44). Plasma IL-1RA also correlated with % TBSA, inhalation injury grade, fluid resuscitation, Baux score, revised Baux score, Denver score, and the Sequential Organ Failure Assessment score.

Conclusion—The severity of smoke inhalation injury has systemically reaching effects, which argues in favor of treating inhalation injury in a graded manner. Additionally, several plasma immune mediators measured early after injury were associated with mortality. Of these, IL-1RA

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appeared to have the strongest correlation with injury severity and outcomes measures, which may explain the blunted pulmonary immune response we previously found in non-survivors.

Keywords

Burn; Inhalation injury; Cytokines; Chemokines; Growth Factors; Interleukin-1 receptor antagonist; Mortality

Introduction

Early excision of the burn wound, improved understanding of the hypermetabolic response to injury, and modern advancements in critical care with appreciation for acute lung injury have all dramatically improved our ability to support the severely burn-injured patient.¹ Despite these advancements, however, inhalation injury remains a significant contributor to mortality, increasing its likelihood by as much as 25%.² Inhalation injury is also relatively common among patients with burns, yet there remains no standard for its diagnosis, scoring, and subsequent treatment. Further, as surgeons and critical care specialists, our understanding of the local and systemic inflammatory response to injury and sepsis continues to evolve, particularly in light of failed clinical trials designed to modulate the immune response to these conditions. Recent studies are also challenging the paradigm of a systemic inflammatory response syndrome that shifts over time to a compensatory anti-inflammatory response syndrome, in that the pro- and anti-inflammatory responses to injury and sepsis appear as processes with considerable overlap.³ Understanding the interplay between these mediators in the face of critical illness remains at the forefront of clinical and laboratory research efforts.

Concurrent to the evolving understanding of local and systemic inflammatory responses to injury and sepsis, we have found in burn patients with smoke inhalation that the pulmonary inflammatory response is enhanced with worse grades of inhalation injury, and that those who die from their injuries have a blunted pulmonary immune responsiveness compared to survivors.^{4,5} Based on the conclusions of these prior studies, we sought to answer two important questions: 1) Does the severity of inhalation injury evoke an immune response measurable at the systemic level, and 2) Does the systemic immune response to burn and smoke inhalation explain the pulmonary immune hyporesponsiveness that we have seen in non-survivors? Therefore, the present report investigated the plasma immune response early after burn and smoke inhalation, aiming to describe the balance of circulating pro- and anti-inflammatory mediators, and to correlate the systemic immune profile with both the severity of inhalation injury and outcomes.

Methods

Patients and Parameters

From August 2007 to June 2011, bronchoscopy was performed on 80 consecutive patients admitted to the burn intensive care unit (ICU) when smoke inhalation was suspected by history, physical, and/or laboratory findings. Specifically, the criteria for bronchoscopy included evidence of carbonaceous sputum, soot at the nares, burn of the head and neck, injury within a confined space, prolonged extrication, and/or elevated % plasma carboxyhemoglobin (% COHb). Participants were excluded for the following: under age 18, use of immunosuppressive medications, the presence of malignancy, autoimmune condition, chronic inflammatory disease, or declining study participation. Plasma was collected at the time of bronchoscopy, which was within 15 hours of injury in all cases. The plasma of 17 non-smoking healthy adult volunteers, free of known pulmonary, cardiac, infectious, allergic, autoimmune, or cancerous disease, was also assessed for comparison.

Clinical variables and outcomes of interest were recorded, including: age, gender, race/ethnicity, % total body surface area burn (% TBSA), Baux score (Age + % TBSA), revised Baux score [Age + % TBSA + 17*Inhalation injury (0=No, 1=Yes)],⁶ Denver score, Sequential Organ Failure Assessment (SOFA) score, 24- and 72-hour fluid resuscitation (cc/kg), grade of inhalation injury, % plasma COHb, initial 48-hour and full hospitalization nadir of the ratio of plasma oxygen content to fraction of inspired oxygen (P:F ratio), initial 48-hour and full hospitalization peak of plasma creatinine and bilirubin, frequency of pneumonia, sepsis, and tracheostomy, ventilator days, ventilator free days, ICU length of stay (LOS), hospital LOS, and mortality. Pneumonia and sepsis were defined according to American Burn Association Consensus Conference criteria.⁷ Mortality was defined as any death from the time of injury to discharge from our tertiary burn center. This study was conducted under institutional review board approval.

Grading of Inhalation Injury and Sample Processing

During bronchoscopy, inhalation injury was graded into one of five categories (0, 1, 2, 3, and 4) based on Abbreviated Injury Score criteria, with Grade 0 being the absence of visible injury and Grade 4 corresponding to massive injury.⁸ Plasma was analyzed in duplicate for 28 immunomodulating proteins via multiplex immunoassay (Bio-Rad Laboratories, Hercules, CA) or ELISA (R&D Systems, Minneapolis, MN) as previously described, and according to manufacturer instructions.⁹ These results were compared between those with different grades of inhalation injury and outcomes.

Statistical analysis

All data were assessed for normality and parametric or non-parametric tests applied where appropriate. Dichotomous variables are reported as a percent and number, non-parametric variables are reported as median with the interquartile range, and continuous variables of parametric tests are reported as mean with standard deviation. Multivariable regression was performed based on log-transformed data in order to adjust for relevant confounders. Statistical analyses were calculated with SAS Version 9.1 (SAS Institute Inc., Cary, NC).

Results

Demographics, Clinical Characteristics, and Outcomes

Bronchoscopy was performed on 80 patients suspected of inhalation injury; of these, 72 had no exclusion criteria and were enrolled in these investigations. The median (interquartile range) time from injury to BALF and plasma collection was 6 (5–10) hours. Patients had a median age of 49 years, were 40% female, and had the following distribution of inhalation injury grades: Grade 0 (n=13); Grade 1, (n=16); Grade 2, (n=18); Grade 3, (n=20); Grade 4, (n=5). The mean ($\pm$ SD) % TBSA burn of the entire cohort was 20.2 ($\pm$ 23.2) %, and the median (interquartile range) % TBSA burn was 12.5 (1.0 to 31.3) %. No patient died during the initial 72 hours of resuscitation, and the subsequent primary causes of mortality were the following: multiple organ failure (n=8), cardiogenic shock (n=4), septic shock (n=1), acute respiratory distress syndrome (n=1), CO poisoning (n=1), and massive cerebrovascular accident (n=1). Of the 16 mortalities, 11 involved withdrawal of care when further heroic efforts became futile.

Table 1 demonstrates data corresponding to survival status, with select comparisons represented in Figure 1. Compared to survivors (n=56), those who succumbed to their injuries (n=16) were older (median 64 vs 46 years; $p=0.005$), had fewer ventilator-free days (median 0 vs 6; $p<0.001$), and had a greater % TBSA burn (median 38 vs 8; $p<0.001$), Baux score (median 96.0 vs 61.0; $p<0.0001$), Revised Baux score (median 113.0 vs 76.0; $p<0.0001$), Denver score (median 6 vs 2, $p<0.0001$), SOFA score (median 10 vs 4;

$p < 0.0001$), 24-hour fluid resuscitation (median 185 cc/kg vs 74 cc/kg; $p < 0.001$), and 72-hour fluid resuscitation (median 351 cc/kg vs 187 cc/kg; $p < 0.001$). Indeed, 25% of deceased patients compared to only 5% of survivors exceeded a 24-hour fluid resuscitation of 250 cc/kg ($p = 0.039$), re-affirming this potentially important cutoff.¹⁰ Likewise, deceased patients also had a lower initial 48-hour P:F ratio nadir (median 142.5 vs 207.5; $p = 0.003$), and had a greater peak of plasma creatinine and bilirubin levels during their hospitalization [median 2.50 vs 1.03 ($p < 0.001$) and median 1.3 vs 0.8 ($p < 0.001$), respectively]. Finally, deceased patients had a greater frequency of sepsis (38% vs 8%) and pneumonia (69% vs 45%), though these clinically relevant comparisons fell short of statistical significance ($p < 0.10$ for both).

Plasma immune mediator concentrations according to smoke inhalation severity and burn size

The primary focus of this study was to determine whether or not the severity of smoke inhalation induced systemic immune mediator changes. Of the 72 patients enrolled in the study, 64 had plasma collected at the time of bronchoscopic diagnosis of their inhalation injury. We found that the concentrations of several plasma immune mediators were increased with worse inhalation injury severity, even after adjusting for age and % TBSA (Table 2). These included interleukin (IL)-1RA ($p = 0.002$), IL-6 ($p = 0.002$), IL-8 ($p = 0.026$), granulocyte colony-stimulating factor (G-CSF) ($p = 0.002$), and monocyte chemotactic protein (MCP)-1 ($p = 0.007$). Likewise, the following plasma mediators were also increased with worse inhalation injury, though failed to reach statistical significance: IL-1 β ($p = 0.078$), IL-10 ($p = 0.075$), IL-15 ($p = 0.060$), and tumor necrosis factor (TNF)- α ($p = 0.099$).

Plasma cytokine, chemokine, and growth factors as related to mortality

Differences in plasma immune mediator concentrations in surviving and deceased patients were identified (Table 3). Those most researched in burns, trauma, and sepsis, and/or which we found at physiologically relevant levels, are demonstrated in Figure 2. Plasma concentrations of IL-1RA, IL-6, IL-8, IL-15, Eotaxin, and MCP-1 were higher in deceased patients compared with survivors ($p < 0.05$ for all), while IL-4 and IL-7 were lower ($p < 0.05$). After adjusting for the effects of age, % TBSA, and inhalation injury grade, plasma IL-1RA remained significantly associated with mortality (OR 3.12, 95% CI 1.03–9.44). Likewise, deceased patients had a much lower IL-1 β to IL-1RA ratio than did survivors ($p = 0.0001$) (Figure 2). Of note is that the timing of plasma sample collection did not differ between survivors and non-survivors ($p = 0.479$).

Correlations of plasma immune mediators with injury severity and outcomes

Of all the immune mediators measured in the BALF and the plasma, only the plasma concentration of macrophage inhibitory protein (MIP)-1 β correlated with the time of sample collection ($r = -0.35$; $p = 0.005$). In addition to being associated with burn patient mortality, numerous plasma immune mediator concentrations correlated significantly with injury severity and outcomes. Those mediators most studied in burn care and with the strongest correlations to % TBSA, inhalation injury grade, 24-hour fluid resuscitation, revised Baux score, Denver score, SOFA score, initial 48-hour P:F nadir, hospital LOS, and mortality are demonstrated in Table 4. Again, high levels of plasma IL-1RA were the most associated with injury severity and numerous outcomes measures, though plasma IL-6, IL-8, and MCP-1 had similarly significant correlations. Finally, the ratio of plasma IL-1 β to IL-1RA was negatively correlated with Baux score ($r = -0.380$, $p = 0.002$), revised Baux score ($r = -0.372$, $p = 0.003$), Denver score ($r = -0.250$, $p = 0.046$), 72h fluid resuscitation ($r = -0.278$, $p = 0.030$), and mortality ($r = -0.487$, $p < 0.0001$).

Discussion

The results of our study are threefold. First, numerous routine clinical parameters and indicators of outcome were associated with mortality, which substantiates the generalizability of our data.^{1,2,8,11–16} Second, the severity of smoke inhalation injury appeared to induce systemically measureable effects, in that plasma concentrations of IL-1RA, IL-6, IL-8, G-CSF, and MCP-1 were increased with worse grades of inhalation injury. And third, several plasma immune mediators measured early after injury were associated with mortality, including IL-1RA, IL-4, IL-6, IL-7, IL-8, IL-15, Eotaxin, and MCP-1. Of these, increased plasma concentrations of anti-inflammatory IL-1RA (and therefore a reduced ratio of IL-1 β to IL-1RA) had the strongest correlations with injury severity, outcomes measures, and mortality, which may have contributed to the blunted pulmonary immune response we previously found in non-survivors.⁵

Abundant animal and human studies have investigated the immune response to burns, trauma, and sepsis, implicating both the pro- and anti-inflammatory response as potential determinants of outcome and survival. To date, however, no single mediator, be it pro- or anti-inflammatory, has been identified as a successful candidate for immunomodulation, despite attempts in phase I, phase II, and even phase III clinical trials.^{17–39} These findings suggest either that our understanding of the immune response to burns, trauma, and sepsis is incomplete, or that our approach to immunomodulation of inherently heterogeneous patients with a single mediator is inappropriate. Indeed, our study affirms the recent one of Xiao et al, which indicated a simultaneous induction of pro- and anti-inflammatory processes after injury.³ These data suggests that an appreciation for the balance of inflammatory signaling may be most crucial to efforts at modulating the immune profile after burn injury.

The current study is important as it is only the second of which we are aware as having identified inhalation injury as inducing systemic immune mediator changes. Previously, Rodriguez et al reported that the addition of inhalation injury magnified the amount of circulating IL-8 detected.⁴⁰ In our study, the systemic effects of inhalation injury are evidenced by numerous plasma immune mediator concentrations being elevated in response to more severe grades of inhalation injury, even after adjusting for relevant variables such as age and % TBSA. These findings are in contrast to those of Finnerty et al, who also tested the hypothesis that inhalation injury augments the systemic inflammatory response.⁴¹ In a study of 72 children, they failed to demonstrate that the presence of inhalation injury altered the systemic immune profile as determined by changes in plasma immune mediator concentrations. However, as compared to our study of adults with a mean % TBSA burn of 20%, the sample population in the study of Finnerty et al consisted of children with and without inhalation injury, who had a mean % TBSA burn of approximately 60% or greater. Not only then was the size of burn injury considerably different in our study, so was the population age, which is known to influence the immune response to injury and is a factor actively investigated at our own institution. Therefore, comparisons between our study and theirs may be difficult, especially as the study of Finnerty et al did not take into account the severity of inhalation injury, which, as we have observed, is an important determinant of the systemic immune response to burns combined with smoke inhalation. Further yet, plasma and BALF samples were collected in our study in a well-defined post-injury window of approximately 5–10 hours, thus minimizing the effect of time since injury on immune mediator concentrations.

Having previously found that the pulmonary immune response is blunted in non-survivors of burn and smoke inhalation injury,⁵ we also sought to identify a circulating mediator of anti-inflammation potentially responsible for this phenomenon. Of all 28 plasma immunomodulating proteins that we examined within 15 hours of injury, an elevated plasma

concentration of IL-1RA was most predictive of mortality, independent of age, % TBSA, and inhalation injury grade. This finding provides a plausible explanation for the pulmonary immune anergy that we previously identified in non-survivors of burn and inhalation injury.⁵ Moreover, IL-1RA, and the imbalance of IL-1 α / β to IL-1RA signaling, could serve as a legitimate target for future research.⁴² For instance, in a study of 31 burn-injured patients, Cannon et al found that low circulating IL-1 β was associated with mortality.⁴³ As other studies had noted a similar role of IL-1 α / β in human and animal survival from sepsis,^{44–49} Cannon et al concluded that IL-1 β is an essential component of the host defense to injury. Indeed, Kupper et al found that defective antigen presentation after burn injury could be restored with IL-1 β ,⁵⁰ and Mancilla et al found that high doses of IL-1RA decreased survival in an animal model of *Klebsiella* infection.⁴⁷ Finally, more recent studies in burns, trauma, and sepsis validate the hypothesis that insufficient IL-1 α / β or excessive IL-1RA results in systemic immune dysfunction that may be detrimental to survival.^{51–53} As phase III trials investigating IL-1RA therapy in severe sepsis have been disappointing,¹⁹ one may surmise then that some degree of IL-1 signaling could be important for various facets of the immune response to injury and sepsis, such as B- and T-cell proliferation, activation of neutrophils and macrophages, and release of hematopoietic factors.^{54–66} Yet, data are conflicting regarding the role of IL-1 after burn injury, particularly as mice deficient for IL-1 receptor associated kinase-1 have been shown to have less cardiac contractile dysfunction after burns than their wild-type counterparts.⁶⁷ Additionally, IL-1RA synthesis may be differentially regulated amongst individuals, which could explain why some have an enhanced production of this anti-inflammatory cytokine, independent from even age, % TBSA, and inhalation injury grade.⁶⁸ Future studies are warranted to examine the role of IL-1RA as a mediator of subsequent burn patient outcome by understanding its mechanistic role in immune signaling, which could very well involve IL-6 and IL-8 through mitogen-activated protein kinase and NF- κ B pathways, in addition to steric inhibition of IL-1 α / β binding to their membrane-bound receptors.⁶⁹ Alternatively, early measurement of IL-1RA may serve as an ideal candidate for predicting burn patient outcomes.

Several other cytokines and chemokines which our study identified as correlating with morbidity and mortality have been frequently implicated as important mediators of injury response and outcome, most notably IL-6 and IL-8. For instance, we found that plasma concentrations of IL-6 were elevated early after injury in non-survivors, and that higher levels of IL-6 correlated with inhalation injury grade, fluid resuscitation, pulmonary dysfunction, and subsequent multiple organ failure and death. Similar findings to ours have been routinely published in other studies of burns, trauma, and sepsis, whereby IL-6 is elevated in those at greatest risk for poor outcomes.^{70–78} As with many mediators of the immune response to injury, the precise role of IL-6 (which has demonstrated both pro- and anti-inflammatory effects) other than as a marker of disease severity remains unclear.^{79–84} Along these lines, knock-out (KO) studies in mice have demonstrated IL-6 to be important for the stimulation of hepatic glutamine transport after burn injury, and in mediating myocardial dysfunction after burn injury in the setting of sepsis.^{67,85,86} Moreover, animal models of burn injury using IL-6 deficient mice and wild-type mice given neutralizing concentrations of anti-IL-6 antibody have suggested beneficial effects to cell-mediated immunity, cytokine production, and organ function with reduced or absent IL-6.^{87–89}

Our study also appears to confirm IL-8 as an important determinant and/or marker of burn patient outcome. As a chemokine, IL-8 primarily serves to recruit neutrophils to the site of injury and to activate their expression of surface adhesion molecules, degranulation, and oxidative-burst capacity. Likewise, IL-8 is frequently identified as a correlate to morbidity and mortality in animals as well as patients with burns, trauma, and sepsis.^{34,35,40,76,90–92} As with IL-1RA, IL-6, and the balance of pro- and anti-inflammation, further studies are required to better elucidate the role for locally produced and circulating IL-8 as an effector

of burn patient outcomes. Such investigations are ongoing at our burn center and research laboratories, with the aim through translational studies to further refine our understanding of the immune response to injury, especially among specific groups who vary in terms of gender, age, and alcohol intoxication. These investigations will continue to involve injury-response modification through antibody suppression, transgenic animal models, and elucidation of intracellular signaling pathways.

We acknowledge important limitations to our study. First, though a sample size of 72 patients is relatively robust, the specificity of our results is hindered by the heterogeneity of the study population, particularly along the lines of age and % TBSA. However, our regression approach accounted for the most important effectors of outcome. Second, our study has an inherent selection bias, in that only those with a suspected inhalation injury were candidates for enrollment, thereby excluding many with skin burns alone. Nonetheless, many widely accepted correlates with outcomes were applicable to our study population, such as age, % TBSA, and measures of organ dysfunction, rendering our results interpretable and generalizable to the majority of burn-injured patients. Third, the data are limited to the acute phase of injury response, in that the concentrations of plasma immune mediators were assessed within 15 hours of injury. Therefore, our study neither examines the immune response to injury during the full resuscitation phase nor over the course of hospitalization. Lastly, our study does not provide mechanistic data that may hold additional clues as to how seemingly important mediators of injury, such as IL-1 β , IL-1RA, IL-6, and IL-8, may induce their effects. We hope that continued patient enrollment, collaboration with other centers, and additional bench-side studies will advance our understanding of the immune response to burn injury, trauma, and sepsis.

We conclude that the early anti-inflammatory response to burn and smoke inhalation injury may play a significant role in subsequent outcome, and that it could still serve as a potential target for therapeutic intervention. We also conclude that the severity of smoke inhalation injury evokes systemically-reaching effects that alter the immune response to injury, arguing in favor of treating inhalation injury in a graded manner.

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Figure 1.

Comparison of clinical parameters and outcomes measures between surviving and deceased patients of combined burn and smoke inhalation injury. Age (A), % TBSA (B), Baux score (C), Revised Baux score (D), Denver score (E), SOFA Score (F), Initial 24 hour resuscitation (G), Initial 72 hour resuscitation (H), P:F nadir within the first 48 hours of injury. * $p < 0.05$ vs Survivor, Kruskal-Wallis test.

Figure 2.

Select immune mediators in the plasma of patients within 15 hours of burn and smoke inhalation injury, comparing survivors and deceased. IL-1RA (B), IL-6 (D), IL-8 (E), and MCP-1 (H) were increased in deceased patients while the ratio of IL-1 β to IL-1RA was markedly decreased (* p <0.05). The concentrations of IL-1 β (A), G-CSF (F), GM-CSF (G), and TNF- α (I) were statistically no different between groups. After adjusting for the effects of Age, % TBSA, and inhalation injury grade, the concentration of IL-1RA remained significantly associated with mortality († OR 3.12; 95% CI 1.03–9.44).

Table 1

Demographics, clinical characteristics, outcomes, and mortality

	Survivors n=56	Deceased n=16	<i>p</i> Value
Age (years)	46.0 (29.0–59.5)	64.0 (42.5–80.0)	0.005
Gender			0.897
Male	34 (61)	10 (63)	
Female	22 (39)	6 (38)	
Race/Ethnicity			0.096
Caucasian	34 (61)	9 (56)	
African American	17 (30)	2 (13)	
Hispanic	3 (5)	3 (19)	
Asian	2 (4)	2 (13)	
TBSA (%)	8.0 (1.0–21.8)	38.0 (16.3–68.8)	<0.001
Baux score	61.0 (48.3–74.5)	96.0 (87.5–118.5)	<0.0001
Revised Baux score	76.0 (60.3–88.5)	113.0 (104.5–135.5)	<0.0001
Denver Score	2 (1–4)	6 (5–8)	<0.0001
SOFA Score	4 (4–8)	10 (7–13)	<0.0001
24 hr fluid resuscitation (cc/kg)	73.9 (39.0–132.1)	184.8 (143.9–244.1)	<0.001
72 hr fluid resuscitation (cc/kg)	186.9 (113.6–256.2)	351.3 (292.0–439.3)	<0.001
Inhalation injury	44 (79)	15 (94)	0.272
Inhalation injury grade	2 (1–3)	2 (1–3)	0.436
COHb (%)	7.5 (3.7–12.2)	4.1 (1.1–18.1)	0.162
Lowest P:F			
(Initial 48 hours)	207.5 (136.0–282.5)	142.5 (82.5–172.5)	0.003
(Full hospitalization)	143.0 (97.1–227.5)	89.4 (65.3–135.2)	0.001
Peak Creatinine			
(Initial 48 hours)	1.01 (0.80–1.20)	1.17 (0.98–1.53)	0.092
(Full hospitalization)	1.03 (0.82–1.63)	2.50 (1.33–3.37)	<0.001
Peak Bilirubin			
(Full hospitalization)	0.8 (0.6–1.0)	1.3 (0.9–1.9)	<0.001
Pneumonia	25 (45)	11 (69)	0.089
Sepsis	10 (18)	6 (38)	0.096
Tracheostomy	19 (34)	7 (44)	0.471
Ventilator days	9.5 (3.0–25.0)	25.0 (6.3–37.5)	0.061
Ventilator free days	6.0 (1.5–16.0)	0.0 (0.0–0.0)	<0.001
ICU Days	17.5 (9.0–33.8)	24.0 (7.0–43.3)	0.750
Hospital LOS	23.0 (9.3–36.3)	25.5 (6.3–44.0)	0.973

Data represented as n (%) or median (interquartile range)

Baux score = Age + % TBSA

Revised Baux score = Age + % TBSA + 17*Inhalation injury (0=No, 1=Yes)

COHb, carboxyhemoglobin; ICU, intensive care unit; LOS, length of stay; SOFA, sequential organ failure assessment; TBSA, total body surface area burn

Table 2

Plasma immune mediator concentrations according to smoke inhalation severity and burn size

Mediator (pg/ml)	Control	Burn Size (% TBSA)	None (Grade 0)	Low (Grade 1/2)	High (Grade 3/4)	p-value	Adjusted p-value*
C5a	1494	10 % >10 %	2795 516.9	1640 648.8	1738 527.6	0.529 0.829	0.921
IL-1 β	1.3	10 % >10 %	1.8 4.0	3.2 3.9	3.3 4.7	0.312 0.196	0.078
IL-1RA	123.2	10 % >10 %	167.8 484.4	218.2 781.9	409.4 1656	0.191 0.045	0.002
IL-2	0.0	10 % >10 %	3.5 8.5	7.6 5.5	8.0 9.3	0.926 0.618	0.940
IL-4	9.0	10 % >10 %	1.3 7.7	4.0 2.1	3.9 3.5	0.350 0.116	0.650
IL-5	3.7	10 % >10 %	2.6 3.0	2.2 1.6	2.9 1.7	0.937 0.229	0.319
IL-6	11.5	10 % >10 %	33.8 116.5	54.2 140.7	234.6 274.4	0.010 0.211	0.002
IL-7	19.8	10 % >10 %	20.0 31.3	22.3 6.2	9.3 7.1	0.717 0.157	0.198
IL-8	18.9	10 % >10 %	16.5 26.8	11.4 28.5	59.3 44.1	0.014 0.344	0.026
IL-9	0.0	10 % >10 %	2.6 56.7	45.1 44.0	36.5 29.8	0.404 0.894	0.259
IL-10	0.0	10 % >10 %	4.1 17.6	5.5 15.0	12.1 19.2	0.085 0.354	0.075
IL-12	4.8	10 % >10 %	4.5 25.3	12.7 12.3	10.4 13.2	0.313 0.229	0.714
IL-13	3.9	10 % >10 %	1.2 6.1	5.7 5.0	5.4 4.9	0.123 0.938	0.313
IL-15	0.0	10 % >10 %	10.4 7.4	7.7 10.8	10.7 14.5	0.401 0.103	0.060
IL-17	0.0	10 % >10 %	0.3 31.6	18.3 11.5	25.0 31.5	0.178 0.138	0.291
Eotaxin	0.0	10 % >10 %	154.5 247.8	166.4 182.1	147.3 185.9	0.945 0.209	0.470
FGF-basic	0.0	10 % >10 %	0.0 20.1	10.0 30.4	26.1 20.7	0.087 0.890	0.392

Mediator (pg/ml)	Control	Burn Size (% TBSA)	None (Grade 0)	Low (Grade 1/2)	High (Grade 3/4)	p-value	Adjusted p-value *
G-CSF	24.3	10 % >10 %	27.5 58.9	37.9 56.8	145.3 93.9	0.003 0.191	0.002
GM-CSF	0.0	10 % >10 %	30.1 52.3	28.3 18.6	35.4 35.0	0.658 0.110	0.604
IFN- γ	118.4	10 % >10 %	106.1 259.9	212.3 163.6	219.6 230.3	0.436 0.601	0.993
IP-10	1152	10 % >10 %	1914 656.4	883.7 810.9	680.6 1283	0.587 0.164	0.736
MCP-1	13.6	10 % >10 %	33.4 94.5	98.2 372.6	174.3 234.9	0.018 0.117	0.007
MIP-1 α	0.0	10 % >10 %	0.0 3.7	1.8 0.1	1.8 8.3	0.439 0.230	0.281
MIP-1 β	37.4	10 % >10 %	60.8 29.2	46.0 46.2	23.6 78.6	0.532 0.637	0.612
PDGF	6575	10 % >10 %	446.0 2316	792.6 1484	1301 3679	0.633 0.334	0.902
TNF- α	0.0	10 % >10 %	32.9 55.5	71.0 69.5	105.1 133.2	0.061 0.324	0.099
VEGF	1.2	10 % >10 %	8.3 80.7	26.8 41.4	47.5 33.4	0.221 0.358	0.988

* Adjusted for Age and % TBSA; all values in pg/ml plasma

Table 3

Plasma cytokine, chemokine, and growth factors as related to mortality

Immune Mediator	Survivors n=51	Deceased n=13	p Value
C5a	516.9 (303.5–1996)	1453 (628.2–2295)	0.154
IL-1 β	3.3 (2.4–4.8)	5.0 (1.0–5.7)	0.634
IL-1RA	280.1 (191.6–584.0)	1562 (781.9–7670)	<0.001 *
IL-2	7.4 (3.1–13.1)	9.8 (3.2–17.0)	0.531
IL-4	4.6 (2.0–10.2)	1.9 (1.2–4.5)	0.045
IL-5	2.3 (1.2–4.0)	1.4 (0.9–4.3)	0.381
IL-6	114.2 (44.0–250.2)	491.0 (136.8–1552)	0.005
IL-7	11.4 (5.5–35.9)	5.2 (3.4–11.5)	0.044
IL-8	26.8 (14.2–61.2)	65.1 (26.2–132.6)	0.028
IL-9	43.3 (20.1–61.8)	34.2 (22.9–69.0)	0.778
IL-10	11.5 (6.0–19.2)	16.0 (11.2–42.1)	0.142
IL-12	14.6 (7.9–25.3)	10.8 (6.4–16.8)	0.390
IL-13	5.0 (3.8–7.3)	5.8 (4.0–8.6)	0.515
IL-15	10.4 (5.3–14.8)	13.6 (10.5–32.1)	0.038
IL-17	18.0 (0–76.5)	16.2 (12.2–43.7)	0.724
Eotaxin	173.0 (111.4–238.1)	233.4 (181.3–342.8)	0.024
FGF-basic	15.7 (0–36.7)	18.9 (0–41.8)	0.679
G-CSF	50.9 (33.6–119.9)	131.3 (38.3–380.5)	0.072
GM-CSF	34.0 (17.5–58.5)	34.8 (21.7–71.0)	0.433
IFN- γ	218.2 (118.0–319.4)	246.8 (99.3–376.0)	1.000
IP-10	818.2 (534.3–1341)	1221 (479.0–2429)	0.489
MCP-1	129.3 (61.1–285.8)	531.5 (158.8–1348)	0.006
MIP-1 α	2.3 (0–10.9)	1.0 (0–10.6)	0.663
MIP-1 β	43.8 (21.0–72.4)	70.5 (10.7–123.7)	0.548
PDGF	1641 (493.5–5842)	869.4 (514.5–5773)	0.606
TNF- α	71.0 (37.9–138.9)	123.3 (29.7–232.3)	0.537
VEGF	41.3 (21.0–83.4)	41.4 (15.1–75.8)	0.701

Data represented as median (interquartile range); all values are pg/ml;

* Statistically significant after adjusting for Age, % TBSA, and Inhalation injury grade (OR 3.12; 95% CI 1.03–9.44)

Table 4

Spearman correlation of select plasma immune mediators with injury severity and outcomes

	% TBSA	Inhalation Injury Grade	Initial 24 hr Fluid	Revised Baux	Denver Score	SOFA Score	Initial 48hr P:F Nadir	Hospital LOS	Mortality
IL-1 β	0.274	0.146	0.398	0.197	0.185	0.232	-0.037	0.128	0.061
<i>p</i>	0.028	0.249	0.001	0.119	0.143	0.065	0.774	0.312	0.632
IL-1RA	0.411	0.282	0.512	0.495	0.424	0.449	-0.171	0.130	0.453
<i>p</i>	<0.001	0.024	<0.0001	<0.0001	<0.0001	<0.001	0.182	0.307	<0.001
IL-6	0.233	0.438	0.444	0.429	0.463	0.438	-0.267	0.269	0.364
<i>p</i>	0.068	<0.001	<0.001	<0.001	<0.001	<0.001	0.038	0.035	0.004
IL-8	0.225	0.365	0.358	0.340	0.354	0.344	-0.183	0.282	0.279
<i>p</i>	0.074	0.003	0.004	0.006	0.004	0.005	0.150	0.024	0.026
IL-10	0.330	0.200	0.389	0.233	0.320	0.305	-0.172	0.217	0.186
<i>p</i>	0.008	0.113	0.002	0.064	0.010	0.014	0.177	0.085	0.141
IL-15	0.193	0.195	0.280	0.309	0.238	0.195	-0.093	0.110	0.263
<i>p</i>	0.126	0.123	0.025	0.013	0.058	0.123	0.466	0.389	0.036
G-CSF	0.195	0.418	0.302	0.310	0.376	0.370	-0.243	0.307	0.228
<i>p</i>	0.123	<0.001	0.015	0.013	0.002	0.003	0.055	0.014	0.070
GM-CSF	0.189	0.056	0.082	0.123	0.069	0.125	-0.083	0.211	0.114
<i>p</i>	0.189	0.697	0.571	0.394	0.633	0.386	0.568	0.141	0.432
IFN- γ	0.123	0.010	0.008	0.029	0.163	0.180	-0.141	0.209	0.001
<i>p</i>	0.334	0.936	0.949	0.818	0.200	0.154	0.269	0.098	0.993
MCP-1	0.302	0.368	0.499	0.444	0.420	0.417	-0.274	0.219	0.348
<i>p</i>	0.015	0.003	<0.0001	<0.001	<0.001	<0.001	0.030	0.082	0.005
MIP-1 β	0.267	0.044	0.264	0.175	0.097	0.118	-0.082	0.026	0.077
<i>p</i>	0.033	0.731	0.035	0.168	0.447	0.353	0.521	0.840	0.547
PDGF	0.205	-0.058	0.377	-0.002	-0.137	-0.005	0.276	0.186	-0.074
<i>p</i>	0.145	0.683	0.006	0.989	0.333	0.973	0.050	0.188	0.603
TNF- α	0.145	0.239	0.283	0.266	0.234	0.167	-0.135	0.121	0.079
<i>p</i>	0.252	0.057	0.024	0.034	0.063	0.187	0.292	0.340	0.536
VEGF	0.169	-0.020	0.097	0.013	0.050	0.135	-0.104	0.111	-0.049
<i>p</i>	0.181	0.876	0.447	0.917	0.697	0.288	0.416	0.383	0.698

Each cell represents Spearman's rank correlation coefficient (top) and p-value (bottom)

Revised Baux score = Age + % TBSA + 17*Inhalation injury (0=No, 1=Yes)

LOS, length of stay; SOFA, sequential organ failure assessment; TBSA, total body surface area burn.