Serum Lipopolysaccharide-Binding Protein Concentrations in Trauma Victims

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ABSTRACT

Background: In low concentrations, lipopolysaccharide-binding protein (LBP), an acute-phase protein recognizing lipopolysaccharide (LPS), catalyzes its transfer to the cellular receptor consisting of CD14 and Toll-like receptor-4. Previous studies have documented increased serum LBP concentrations in patients with sepsis, systemic inflammatory response syndrome (SIRS), or acute pancreatitis and after cardiopulmonary bypass. No prior studies have examined LBP expression in trauma victims. We hypothesized that admission LBP plasma concentrations are predictive of outcome (mortality) in trauma. This study assessed time-dependent changes in serum LBP concentrations in trauma patients soon after injury.

Methods: A prospective, single-institution, observational cohort study of 121 adult trauma patients (age ≥17 years) with moderate to severe injury who required hospitalization. The trauma patients were male in 79.6% of the cases and had a mean age of 43.0 ± 20.6 years. The mean injury severity score (ISS) was 23 ± 12, and the crystalloid resuscitation volume given in the first 24 h averaged 6,640 ± 3,729 mL. Informed consent was obtained on admission, and blood samples were drawn on admission and at 24 h postadmission. Prospective data were collected for daily SIRS score, multiple organ dysfunction score (MODS), and sequential organ failure assessment (SOFA) score, complications, and outcomes. Plasma concentrations of LBP were measured by enzyme-linked immunosorbent assay.

Results: Sixty patients (48.8% of the study cohort) required emergency surgical intervention and sustained a substantial intraoperative blood loss (mean 1,404 ± 2,757 mL). The hospital mortality rate was 16.3% (20 patients). The mean intensive care unit stay was 8.9 ± 16.4 days, and the hospital stay was 14.8 ± 19.6 days. The patients had a significantly higher serum concentrations of LBP on admission (mean 28.0 ± 25.3 mg/L; range 2–100 mg/L) than did control subjects (mean 6.2 ± 2.1 mg/L; range 1.3–12.8 mg/L; $p < 0.01$), similar to the plasma concentrations previously reported in septic patients. A significant increase in LBP concentration was noted at 24 h (mean 72.3 ± 45.7 mg/L; range 8–210 mg/L; $p < 0.05$). The admission LBP concentration was significantly greater in nonsurvivors than in survivors. However, after controlling for age and ISS, the admission LBP concentration did not predict death.

Conclusions: **In this prospective study of trauma patients, LBP concentrations were significantly increased early post-injury (on admission), and higher concentrations were associated with a higher mortality rate. However, the independent prognostic value of admission LBP was not incremental to clinical outcome predictors (age and ISS) in logistic regression analysis. Additional studies are necessary to determine the peak and nadir LBP concentrations. The serum concentration of LBP in trauma victims soon after injury may have prognostic importance, and further studies are warranted.**

INTRODUCTION

TRAUMA ACCOUNTS for hospital admission of 1.8 million persons annually in the United States [1]. Infection is a major cause of morbidity in the trauma patient population, with 40% to 50% of severely injured patients developing serious infections [2,3]. Systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction are important clinical complications of trauma for which no satisfactory therapy is available [4]. Multiple organ dysfunction remains the most common cause of late death in critically ill trauma patients.

Biologic mediators play a key role in the development of SIRS and multiple organ dysfunction. The release of mediators depends primarily on the severity of tissue trauma and shock and secondarily on the activation of various cascades that culminate in the expression of polymorphonuclear neutrophil-derived substances, cytokines, and adhesion molecules. Similarly, a number of specific biomarkers—a measure that identifies a biologic state or that predicts the presence or severity of a pathologic process or disease—have been identified in sepsis and are prognostic markers for patients at higher risk of death [5]. Delineation of time-dependent alterations in specific mediators after trauma, and determination of accurate predictors of SIRS and multiple organ dysfunction, will provide critical information for the development of appropriate therapeutic modalities for this disease and its complications.

Lipopolysaccharide-binding protein (LBP) is an acute-phase protein that catalyzes the transfer of lipopolysaccharide (LPS) to a cellular receptor [6,7] consisting of CD14 and a member of the Toll-like receptor family. In low concentrations, LBP enhances the cell's response to tumor necrosis factor (TNF) [8,9], but in high concentrations, LBP inhibits LPS effects and protects mice from an otherwise-lethal infection [10]. A single LBP molecule may transport hundreds of LPS molecules to CD14 [11] but also transports LPS to other acceptors, including high-density lipoprotein [12–14], which neutralizes the potency of LPS. These data document a dual role for LBP in both enabling and inhibiting host responses to LPS.

Lipopolysaccharide-binding protein also has been recognized as a marker of overall inflammation in SIRS. Previous studies have documented higher serum LBP concentrations in patients with sepsis [15], SIRS [16], or acute pancreatitis [17] and after cardiopulmonary bypass [18]. Because LBP initially was appreciated as an acute-phase response protein whose expression was triggered by infection—first gram-negative [19] and later gram-positive, fungal, and mycobacterial [20–22] infections—several recent studies have investigated the ability of the serum LBP concentration to distinguish between infective and non-infective causes of early SIRS, with various results in different populations. In a study of neutropenic cancer patients, the LBP concentration at the onset of febrile neutropenia was significantly higher in patients with gram-negative bacteremia that in those with fever of unknown origin [23]. In contrast, Prucha et al. concluded that LBP is a nonspecific marker of the acute-phase response in non-neutropenic adults and cannot be used to differentiate infective from non-infective SIRS [24].

Several studies have evaluated the effect on LBP of burns in animals [25,26], but to our knowledge, no studies have examined LBP expression in human victims of trauma. We hypothesized that the admission LBP plasma concentration is predictive of outcome (mortality) in trauma. This study assessed time-dependent changes in serum LBP concentrations in trauma patients soon after injury.

PATIENTS AND METHODS

Setting and study design

This prospective observational cohort study was conducted at the R. Adams Cowley Shock Trauma Center of the University of Maryland, the statewide adult trauma center. Over a 12-month period (October 1999 to October 2000), 121 trauma patients with moderate to severe injury were enrolled at the time of hospital admission. Written informed consent was obtained from all patients or surrogates. The inclusion criteria were age ≥17 years, major intra-abdominal injury, pelvic fracture, fracture of two or more long bones, hypovolemia, shock, or any admission to the intensive care unit (ICU). Exclusion criteria were transfers, death within 24 hours, pregnancy, known acquired immunodeficiency syndrome, chemotherapy, and transplanted organ or other chronic immune disorders. Blood samples were drawn at admission and 24 h after admission. Prospective data were collected for daily SIRS [27], multiple organ dysfunction score (MODS), and sequential organ failure assessment (SOFA) score [28], complications, outcome, and injury severity score (ISS) [29]. This study was approved by the Human Institutional Review Board of the Office of Research Subjects of the University of Maryland School of Medicine.

LBP assay

Blood was collected in sterile endotoxin-free tubes containing ethylenediaminotetraacetic acid or citrate and cooled to 4°C. After centrifugation, the plasma was removed and immediately frozen at −80°C. The LBP concentration in the plasma samples was measured in duplicate using the Human LBP solid-phase enzyme-linked immunosorbent assay (Cell Sciences, Norwood, MA). The functional limit of detection of this assay is 1 ng/mL. This assay has a large measurable concentration range, from 1–100 ng/mL, with high sensitivity, specificity, and reproducibility. All patients had LBP measured on admission, and 96 patients had repeat measurement at 24 h. Twenty healthy adults were used as control subjects (mean age 35 years; 80% male).

Statistics

The mean values and standard deviations were calculated for each parameter. Categorical variables were compared using Pearson chi-square and contingency table analysis. Significance was accepted where p was <0.05. Analysis of variance (ANOVA) and multiple logistic regression analysis were used for binary outcomes, including two main covariates (age and ISS). Continuous variables were compared using ANOVA and multiple linear regression analysis. Statistical analyses were performed using the Stata 7.0 Special Edition software package (Stata Corporation, College Station, TX).

RESULTS

Clinical characteristics

The characteristics of the study population are presented in Table 1. The patients were predominantly male (79.3%), and 35% were of non-Caucasian race. All had sustained moderate to severe injuries with a mean ISS of 23. Emergency surgery was required by 48% of the

TABLE 1. CLINICAL CHARACTERISTICS OF 121 PATIENTS IN STUDY COHORT

Mean age (years) (SD)	43.0	(20.7)
Male (%)	96	(79.3)
Non-Caucasian race (%)	42	(34.7)
Mean Injury Severity Score (SD)	23	(12)
Glasgow Coma Score on admission (SD)	11	(5)
Systolic blood pressure on admission (mm Hg)(SD)	132	(32)
Emergency operation (n, %)	60	(48.8)
Intraoperative blood loss (mL)(SD)	1,407	(2,757)
Crystalloid resuscitation in first 24 h (mL)(SD)	6,640	(3,729)
ICU admission (n, %)	72	(64.3)
ICU length of stay (days)(SD)	15.2	(19.2)
Hospital length of stay (days)(SD)	13.8	(17.5)
Hospital mortality (n, %)	22	(18.2)
SIRS score on admission (SD)	2.55	(1.02)
SOFA score on admission (SD)	3.50	(3.01)
Multiple organ dysfunction on admission (n, %)	87	(71.9)
MODS on admission (SD)	3.9	(3.4)

Abbreviations: SIRS = systemic inflammatory response score; SOFA = sequential organ failure assessment; MODS = multiple organ dysfunction score.

TABLE 2. PATIENT CHARACTERISTICS BY MULTIPLE ORGAN
DYSFUNCTION SCORE (MODS)

	MODS = 0		MODS > 0	
N (%)	22	(20.2)	87	(79.8)
Mean age (years)(SD)	42.1	(19.3)	43.2	(21.4)
Non-Caucasian race (n, %)	8	(22.2)	28	(77.8)
Injury Severity Score (SD)	17	(9)	25	(12)[a]
Systolic blood pressure on admission (mm Hg)(SD)	145.8	(23.4)	128.6	(33.6)[a]
ICU admission (n, %)	8	(38.1)	57	(69.5)[a]
ICU length of stay (days) (SD)	5.17	(2.8)	15.84	(19.9)
Hospital length of stay (days)(SD)	7.43	(6.9)	14.67	(18.9)[b]
MODS score on admission (SD)		0	4.84	(3.1)[a]
Mortality (n, %)		0	19	(16.5)
Admission LBP (mg/L) (SD)	30.4	(24.0)	27.3	(26.9)
24-hour LBP (mg/L)(SD)	69.5	(44.3)	72.2	(45.1)

[a]P <0.05.
[b]P <0.10.
Abbreviation: LBP = lipopolysaccharide-binding protein; LOS = length of stay.

patients with a mean intraoperative blood loss of 1,407 ± 2,757 mL and a mean 24-h crystalloid fluid resuscitation volume of 6,640 mL. Admission to the ICU was required by 64% of the patients with a mean length of stay (LOS) of 15 days. The mean hospital LOS was 14 days. The hospital mortality rate was 18%. No significant differences in clinical characteristics were observed between the patients who had complete LBP data available and those who did not.

The majority of the study population had evidence of SIRS and organ dysfunction on admission, as measured by the SOFA and MODS. Patients with multiple organ dysfunction on admission had a significantly higher ISS, lower systolic blood pressure, and higher ICU admission rate. Patients with multiple organ dysfunction also tended to have a longer ICU LOS and to be of non-Caucasian race; however, the differences were not statistically significant (Table 2).

LBP concentrations at admission and at 24 h

The patients had significantly higher LBP plasma concentrations on admission (mean 28.0 ± 25.3 mg/L; range 2–100 mg/L) than did the control subjects (mean 6.2 ± 2.1 mg/L; range 1.3–12.8 mg/L; p < 0.01; Fig. 1). The plasma LBP concentrations at 24 h were significantly higher than the admission values (mean 72.3 ± 45.7 mg/L; range 8–210 mg/L; p < 0.05; Fig. 1). Figure 2 shows the distribution of the plasma LBP concentrations on admission and 24 h after injury. All LBP data displayed are for the 96 patients who had measurements both at admission and at 24 h.

Patients were categorized into either a low-LBP group (<20 mg/L on admission) or a high-LBP group (≥20 mg/L on admission) on the basis of the observation that a serum LBP concentration of 20 mg/L is two standard deviations above the mean for normal subjects [16].
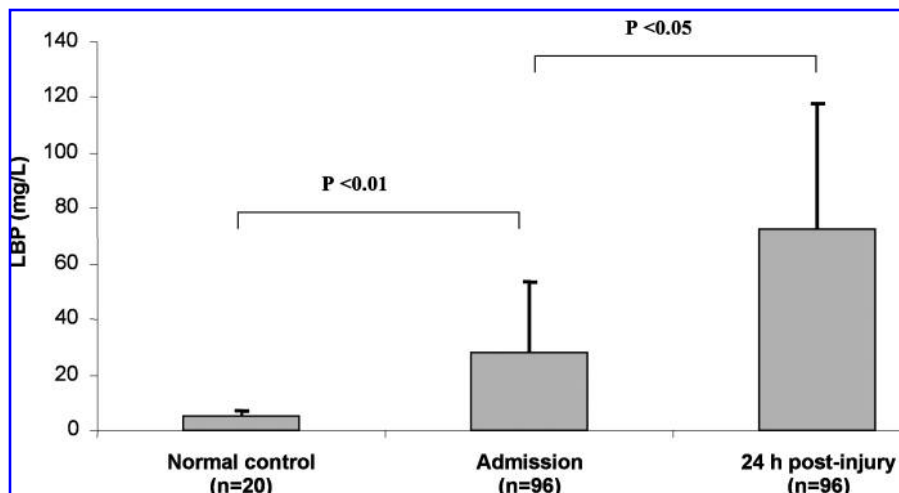

FIG. 1. Lipopolysaccharide-binding protein concentration in control subjects and in trauma patients on admission and 24 h post-injury. Values are mean ± standard deviation.
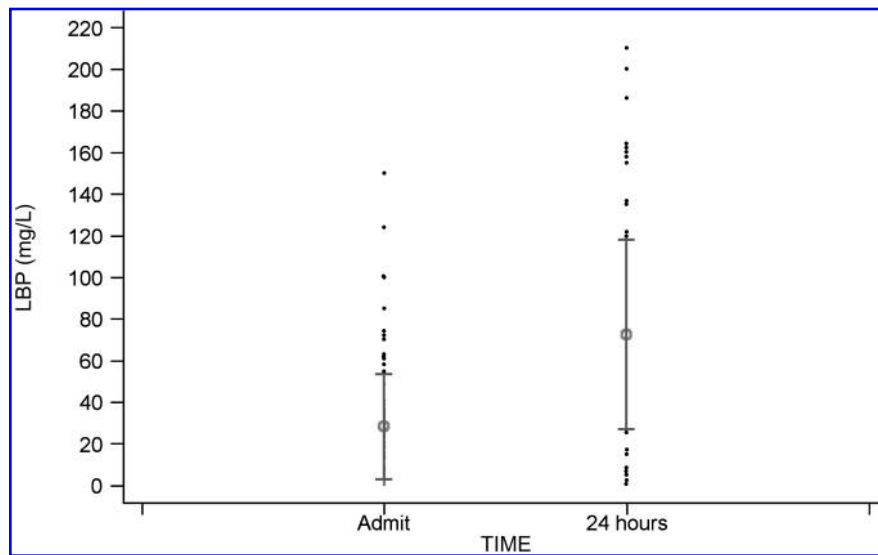
FIG. 2. Lipopolysaccharide-binding protein (LBP) distribution at trauma admission and 24 h (n = 96). Bars represent mean ± 1 SD.

The mean LBP concentration in the low-LBP group (n = 44) was 11.04 ± 5.48 mg/L vs. 42.66 ± 26.56 mg/L in the high-LBP group (n = 52; p < 0.05). Interestingly, by 24 h, the LBP concentrations in patients in the low-LBP group had increased to approximately the same mean value as in patients in the high-LBP group (65.43 ± 47.34 mg/L vs. 78.17 ± 43.80 mg/L).

Correlation of LBP with age, sex, and ISS

The characteristics of the high-LBP and low-LBP groups are shown in Table 3. Patients in the high-LBP group were significantly older (mean age 38.1 vs. 46.8 years). When stratified by age (Fig. 3) patients older than 65 years had significantly greater plasma LBP concentrations than patients younger than 46 years

TABLE 3.   PATIENT CHARACTERISTICS BY LIPOPOLYSACCHARIDE-BINDING PROTEIN
CONCENTRATION ON ADMISSION

	LBP ≤ 20 mg/L		LBP > 20 mg/L	
N (%)	44		52	
Mean age (years)(SD)	38.1	(18.0)	46.8	(21.5)[a]
Non-Caucasian race (n, %)	14	(31.8)	18	(34.6)
Injury Severity Score	24	(12)	20	(10)
Glasgow Coma Score on admission (SD)	11	(5)	12	(4)
Systolic blood pressure on admission (mm Hg)(SD)	128.7	(36.1)	138.0	(27.7)
ICU admission (n, %)	28	(66.7)	30	(65.2)
ICU length of stay (days)(SD)	15.0	(17.9)	10.4	(11.8)
Hospital length of stay (SD)	15.1	(19.2)	12.2	(11.6)
Mortality (n, %)	3	(6.8)	7	(13.5)
SIRS score on admission (SD)	2.5	(0.9)	2.7	(1.0)
MODS score on admission (SD)	4.00	(3.7)	2.95	(2.9)
SOFA score on admission (SD)	3.66	(3.2)	2.68	(2.6)

[a]P <0.05.
   Abbreviations: SIRS = systemic inflammatory response syndrome score; MODS = multiple organ dysfunction syndrome score; SOFA = sequential organ failure assessment.
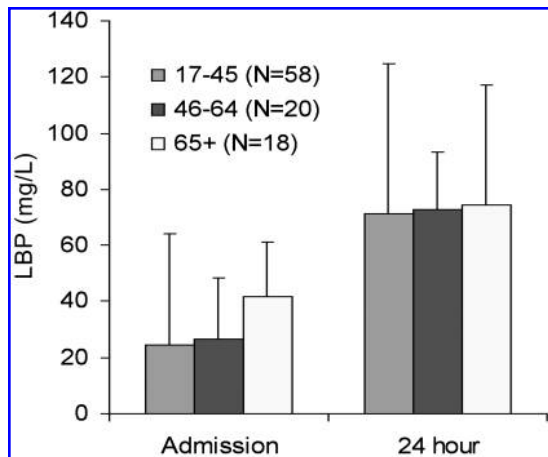
FIG. 3. Lipopolysaccharide binding protein (LBP) concentrations at admission and 24 h by age group (mean ± SD; n = 96). Greater age (age >65 years) was associated with higher LBP concentration on admission (p = 0.023).

(41.7 ± 39.6 mg/L vs. 26.56 ± 21.57 mg/L; p = 0.023).

Male and female patients had similar concentrations of LBP on admission and at 24 h (Fig. 4). Likewise, no differences in plasma LBP concentrations were identified on the basis of injury severity. The mean ISS score was not significantly different in the high-LBP vs. the low-LBP group (Table 3).

Correlation of LBP with outcome

Having established that plasma LBP concentrations were significantly higher in trauma patients on admission and at 24 h after injury, we sought to correlate LBP with outcome. The admission LBP concentration was significantly greater in patients who did not survive than in survivors by *t*-test (p = 0.0244; Fig. 5). Using a cutoff of >20 mg/L (which represented the best discrimination, as derived from receiver operator characteristic curves), LBP as a predictor of death had a sensitivity 86.4% and a specificity of 59.5%. Logistic regression analysis confirmed that nonsurvivors had significantly higher plasma LBP concentrations on admission. There was a 1.02-fold increase in the odds of death for every unit increase in LBP at admission (p = 0.042; Table 4).

Further analysis of admission LBP (high vs. low) by logistic regression revealed that the high-LBP group had a >2-fold higher risk of

death than the low-LBP group. However, given the small sample size, this difference did not reach statistical significance (p = 0.297; Table 4). Because age and ISS were confirmed previously as independent predictors of outcome in trauma, we performed a multiple logistic regression analysis with age and ISS as covariates. In this analysis, the LBP group was no longer an independent predictor of death.

Correlation of LBP with SIRS and organ dysfunction

No correlation of plasma LBP concentration (admission or 24 h) with the presence of SIRS or organ failure (as measured by admission and daily SOFA score and MODS) was identified. The time courses of serial daily scores are depicted in Figure 6 for patients in the high-LBP vs. low-LBP group; no significant differences were identified.

DISCUSSION

Lipopolysaccharide-binding protein is an acute-phase protein that enhances the responsiveness of immune cells to LPS by virtue of its capacity to transfer it to CD14. The protein plays an integral part in the LPS-mediated release of inflammatory cytokines. Both LBP and the LPS receptor CD14 represent key molecules in the pathophysiologic alterations induced by
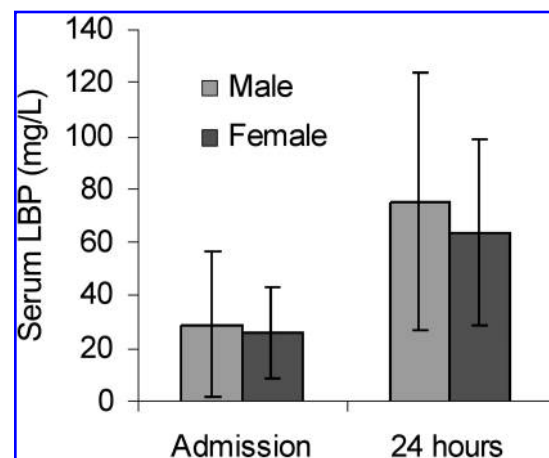

FIG. 4. Concentration of lipopolysaccharide-binding protein in trauma patients by sex (n = 96). No difference was identified.
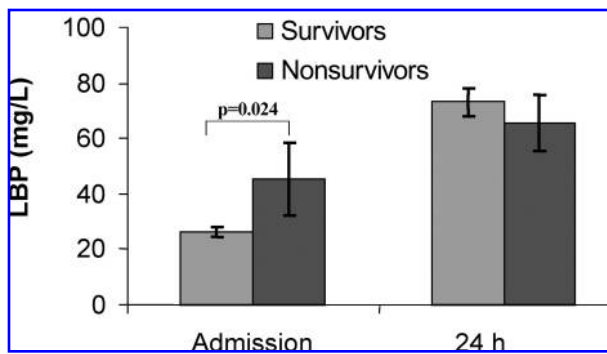
FIG. 5. Concentration of lipopolysaccharide-binding protein (LBP) according to outcome (n = 96). Nonsurvivors had significantly higher LBP concentrations on admission.

low concentrations of endotoxin after trauma. Although LBP is synthesized predominantly by the liver, the protein is also produced in multiple extrahepatic locations, including the lung. Fang et al. [25] examined endotoxin concentrations and LBP and CD14 mRNA expression after burns in a rat model. Endotoxin concentrations in the liver, spleen, and lung increased markedly after the injury, with the highest concentration in the liver. The expression of both tissue LBP and CD14 mRNA also rose significantly, peaking at 12 h post-burn and then decreasing gradually. Expression of the LBP gene had returned to baseline by 48 h. This study also identified a correlation between high LPS and expression of LBP/CD14 mRNA and TNF-α mRNA in tissues. The authors postulated that excessive LBP and CD14 mRNA expression might be associated with enhanced synthesis and release of TNF-α stimulated by endotoxin translocation after major burns.

Upregulation of LBP mRNA expression in liver, lungs, and kidney also was documented in a rat model after hemorrhagic shock and resuscitation without direct tissue injury [30]. The administration of LPS after hemorrhagic shock was associated with significantly higher concentrations of TNF-α than were found in the experimental groups exposed to either shock or LPS alone. These data suggest that upregulation of LBP expression is a major molecular mechanism increasing the sensitivity to endogenous endotoxin after trauma or hemorrhagic shock. In contrast, studies in human trauma have documented reduced responsiveness of peripheral blood monocytes to LPS and decreased secretion of proinflammatory cytokines, and this endotoxin/LPS tolerance may be associated with changes in the intracellular signals that link monocyte membrane LPS receptors to protein kinase C [31] and to soluble serum factors released systemically after trauma [32].

Other investigators have hypothesized that greater local expression of LBP primes tissues to secondary LPS-mediated damage. Klein et al. [33] documented that local pulmonary LBP and CD14 mRNA were both upregulated after either systemic or local (intratracheal) LPS exposure in a rat model. Intratracheal LPS administration also was associated with a significant increase in TNF-α. There is concern that upregulation of LBP may render the lung more susceptible to local immune overactivation and injury during subsequent exposure to LPS.

Similarly, Martin et al. showed that immunoreactive LBP was detectable in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome [34]. Furthermore, purified LBP enhanced the response of human and rabbit alveolar macrophages to LPS, with earlier onset and greater TNF-α production at an LPS threshold dose that was as much as 1,000-fold lower. These authors concluded that LBP accumulates in the lungs of patients with lung injury and plays an important role in augmenting LPS-stimulated TNF-α gene expression in alveolar macrophages by a pathway that depends on the CD14 receptor.

TABLE 4. TIME-DEPENDENT CHANGES IN LIPOPOLYSACCHARIDE-BINDING PROTEIN IN TRAUMA: LOGISTIC REGRESSION ANALYSIS

	Mortality	
Variable	Odds ratio (95% CI)	P
Admission concentration	1.02 (1.00, 1.04)	0.042
24-h concentration	0.99 (0.98, 1.01)	0.62
Admission concentration ≥20 mg/L	2.13 (0.52, 8.77)	0.297

Difference did not achieve statistical significance, likely because of size of sample.

Those who died had significantly higher values on admission, with a 1.02-fold increase in odds of death for every unit increase in LBP.
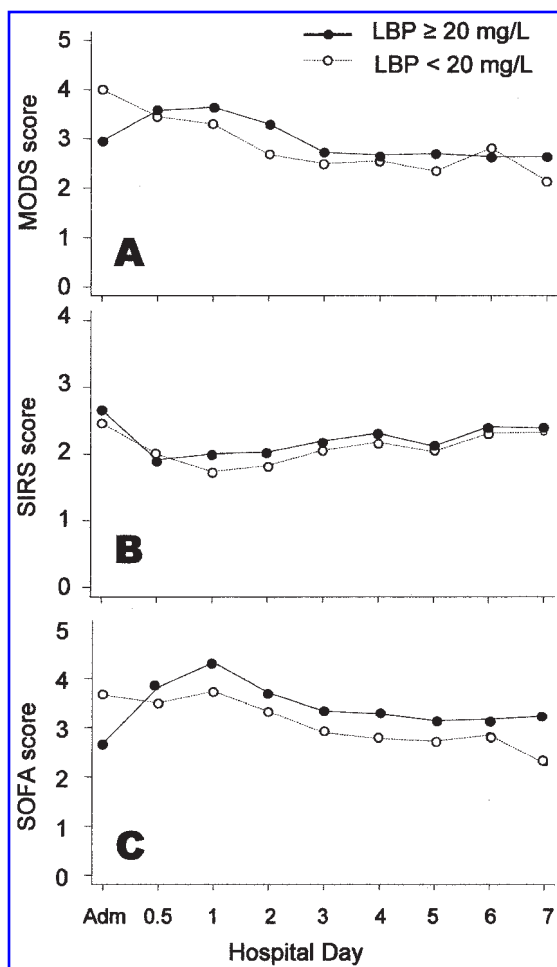
FIG. 6. Admission lipopolysaccharide-binding protein concentration and serial systemic inflammation response score, multiple organ dysfunction score, and sequential organ failure assessment score (n = 96).

Lipopolysaccharide-binding protein also is an essential component of an effective innate immune response to infection. Mice deficient in the LBP gene (LBP$^{-/-}$) are highly susceptible to *E. coli* peritonitis, as indicated by earlier death, faster bacterial dissemination to the blood, impaired bacterial clearance from the peritoneal cavity, and more severe remote organ damage than are seen in wild-type mice [35]. Fan et al. observed a significant increase in the mortality rate, earlier onset of bacteremia, and greater pulmonary bacterial loads in LBP$^{-/-}$ mice compared with controls challenged with direct intratracheal inoculation of *Klebsiella pneumoniae* [36]. Furthermore, total lung myeloperoxidase activity, neutrophil recruitment to the alveolar space, and concentrations of KC (a chemokine involved in neu-

trophil recruitment) in bronchoalveolar lavage fluid and lung homogenates were significantly diminished in LBP$^{-/-}$ mice compared with control animals. Together, these findings suggest that LBP is essential to the pulmonary innate immune response to bacteria.

Early studies in humans documented that LBP serum concentrations range from 1–24 mcg/mL and increase significantly in the presence of bacterial infection [37,38]. Compared with healthy controls, LPS-challenged volunteers and patients with sepsis exhibit significantly higher plasma concentrations of LBP (p < 0.01). Three additional studies have examined plasma concentrations of LBP in patients with severe sepsis and septic shock. Opal et al. performed the largest study to date, with measurements of plasma endotoxin and LBP in 253 patients at the onset of severe sepsis or septic shock [39]. The concentration of LBP was elevated in 97% of the patients: median, 31.2 mcg/mL (range 4.1–162 mcg/mL; interquartile range, 22.5–47.7 mcg/mL) compared with a normal value of 4.1 ± 1.65 mcg/mL. The LBP concentrations were lower in nonsurvivors than survivors (28.0 vs. 33.2 mcg/mL; p < 0.05) over the 28-day study period. This finding was in contrast to those of other studies, in which elevated plasma concentrations of LBP were associated with adverse patient outcomes [40,41].

More recently, Zweigner et al. analyzed serum LBP concentrations in 63 patients with severe sepsis or septic shock [42]. For the entire study cohort, the median LBP concentration at the onset of sepsis was 46.2 mg/L (range 3.74–155 mg/L), significantly higher than that of healthy volunteers (7.94 mg/L; range 1.85–17.4 mg/L). Peak LBP concentrations were reached after a median of 40 h (range 1–120 h) from the onset of severe sepsis. No significant difference in serum LBP concentration was observed in survivors compared with nonsurvivors (44.2 vs. 55.5 mg/L). Multivariate analysis including severity of infection as a covariate revealed that LBP was not a significant independent predictor of death. Blairon et al. [43] also examined LBP serum concentrations in 24 patients with severe sepsis. The concentration was significantly higher in the septic patients (46.4 ± 28.3 mcg/mL) than in healthy volunteers (5.7 ± 1.9 mcg/mL; p < 0.0001), but

no difference was noted between survivors and nonsurvivors.

To our knowledge, no prior study has investigated time-dependent alterations in LBP concentrations in human trauma victims. The mean LBP concentrations on admission and at 24 h after admission were similar to the concentrations previously reported in septic patients. It should be recognized, however, that none of these trauma patients had infection at the time of hospital admission. This finding—that plasma LBP concentrations are increased to the same degree as in patients with severe sepsis and septic shock—is interesting, but the underlying mechanism is not known. We can postulate that gut-derived endotoxin may stimulate the LBP increase, because high plasma endotoxin concentrations have been identified in human trauma victims. For example, in a series of 20 patients with multiple injuries, plasma endotoxin concentrations were at their peak at admission, decreasing thereafter to almost normal values within five days [44].

Importantly, we found that admission LBP concentrations in trauma patients were significantly greater in nonsurvivors than in survivors. Studies in septic patients have yielded conflicting data in this regard, with one study documenting lower LBP concentrations and two studies higher LBP concentrations associated with death. We also identified a correlation between age and admission LBP concentrations. That is, older trauma patients (age ≥ 65 years) had higher admission LBP concentrations than younger patients. This correlation of LBP with age has not been identified in studies in septic patients.

We attempted to categorize trauma patients as low or high LBP on the basis of their admission LBP concentration in an effort to define a concentration that could identify a patient as being at high risk for an adverse outcome. We found that the mortality rate was doubled (13.5% vs. 6.8%) in patients with admission plasma LBP >20 mg/L. Additional studies with a larger sample will be required to validate this assay as a rational approach to determining prognosis.

Laboratory biomarkers for outcome in trauma are not available currently but would be helpful to identify patients at high risk of death. The ad-

mission LBP concentration is promising, despite the fact that the independent prognostic value of LBP was not incremental to clinical outcome predictors (including age and ISS) in logistic regression analysis. We currently use abnormal cardiac troponin concentrations to diagnose acute myocardial damage, but in acute coronary syndromes, elevation of cardiac troponin at admission does not increase the prognostic capacity of a clinical risk model that includes baseline clinical variables and quantitative electrocardiographic ischemia data [45]. Therefore, quantitative biomarkers would be of great utility in clinical medicine.

It has recently been documented that the response to LPS is highly variable as a result of genetic diversity. Single-nucleotide polymorphisms in the gene encoding Toll-like receptor 4 (the principal receptor for LPS) are associated with systemic inflammatory hyporesponsiveness or hyperresponsiveness to inhaled LPS in healthy volunteers [46]. Low responders have significantly lower white blood cell counts and lower blood concentrations of C-reactive protein and LBP than high responders. No studies to date have examined similar genetic polymorphisms for LPS responsiveness in trauma victims, but such differences likely exist. Future studies should aim to correlate such polymorphisms with plasma LBP concentrations in trauma patients.

There are substantial limitations to this study. First, this is a single-institution study with a small sample. Second, the majority of the study population sustained moderate to severe injury (mean ISS, 23); we did not have a control group that sustained less severe injury. Therefore, the statistical analyses that evaluated the correlation between plasma LBP concentration and injury severity may not have had an adequate range of ISS values to assess this association fully. Additional studies will need to enroll patients with lower injury severity. Third, the majority of the study cohort had evidence of SIRS and organ dysfunction, with only a small number (n = 22) having a MODS of 0 on admission. Future studies will need to examine trauma patients without SIRS or organ dysfunction on admission in order to characterize fully the plasma LBP response to acute injury. Fourth, we examined plasma LBP concentrations at

only two time points. The kinetics of LBP expression in response to trauma in humans have not been established. Neither the rate of change of LBP over time nor the maximum value of LBP production after injury is known. Further studies will be required to determine the peak and nadir LBP concentrations after trauma. Furthermore, whether it is the rate of change in LBP concentration or the peak concentration of LBP that has pathophysiologic or prognostic significance is not yet known. In this initial study, we have demonstrated that plasma concentrations of LBP in trauma victims soon after injury have prognostic significance, and further studies are warranted. Lipopolysaccharide-binding protein should be examined critically as an early biomarker of adverse outcome after traumatic injury.

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