

Heparin-Binding Protein Measurement Improves the Prediction of Severe Infection With Organ Dysfunction in the Emergency Department

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Clinical trial number: ClinicalTrials.gov NCT01392508 (the IMPROVED Prediction of Severe Sepsis in the Emergency Department study).

Drs. Linder, Arnold, Christensson, Pritchard, and Åkesson conceived and designed the study. Dr. Linder, Dr. Arnold, Mr. M. Zindovic, Dr. I. Zindovic, Dr. Lange, Dr. Paulsson, Dr. Nyberg, Dr. Boyd, and Dr. Russell did sample and collected data. All the authors analyzed and interpreted the data. Drs. Linder, Arnold, Boyd, Russell, Christensson, Pritchard, and Åkesson drafted the article for important intellectual content.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccmjjournal>).

Supported, in part, by the Swedish Government Funds for Clinical Research (ALF), the University Hospital in Lund, and by Axis-Shield Diagnostics, Dundee, United Kingdom.

Presented, in part, at the 6th International Sepsis Forum, Rio de Janeiro, Brazil, November 2013.

Dr. Linder has a patent with Hansa Medical (inventor of HBPAssay). Dr. Arnold received support from Axis Shield Diagnostics. His institution received support for travel from Axis Shield Diagnostics. Drs. I. Zindovic, Lange, Paulsson, and Nyberg received grant support and compensation for costs for biochemical analyses from Axis-Shield Diagnostics. Dr. Russell served as a board member for Cyon Therapeutics; consulted for Cubist Pharmaceutical, Ferring Pharmaceutical, Grifols, Leading Biosciences, Cytovalle, and Sirius Genomics; has patents (owned by the University of British Columbia that are related to PCSK9 inhibitor[s] and sepsis and related to the use of vasopressin in septic shock. He is an inventor on these patents); and has stock in Cyon Therapeutics. His institution received grant

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DOI: 10.1097/CCM.0000000000001265

support from Sirius Genomics and Ferring Pharmaceutical. Dr. Pritchard is employed by Axis-Shield Diagnostics. Dr. Christensson has a patent with Hansa Medical (inventor of HBPAssay). Dr. Åkesson has a patent with Hansa Medical (inventor of HBPAssay). The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: Early identification of patients with infection and at risk of developing severe disease with organ dysfunction remains a difficult challenge. We aimed to evaluate and validate the heparin-binding protein, a neutrophil-derived mediator of vascular leakage, as a prognostic biomarker for risk of progression to severe sepsis with circulatory failure in a multicenter setting.

Design: A prospective international multicenter cohort study.

Setting: Seven different emergency departments in Sweden, Canada, and the United States.

Patients: Adult patients with a suspected infection and at least one of three clinical systemic inflammatory response syndrome criteria (excluding leukocyte count).

Intervention: None.

Measurements and Main Results: Plasma levels of heparin-binding protein, procalcitonin, C-reactive protein, lactate, and leukocyte count were determined at admission and 12–24 hours after admission in 759 emergency department patients with suspected infection. Patients were defined depending on the presence of infection and organ dysfunction. Plasma samples from 104 emergency department patients with suspected sepsis collected at an independent center were used to validate the results. Of the 674 patients diagnosed with an infection, 487 did not have organ dysfunction at enrollment. Of these 487 patients, 141 (29%) developed organ dysfunction within the 72-hour study period; 78.0% of the latter patients had an elevated plasma heparin-binding protein level (> 30 ng/mL) prior to development of organ dysfunction (median, 10.5 hr). Compared with other biomarkers, heparin-binding protein was the best predictor of progression to organ dysfunction (area under the receiver operating characteristic curve = 0.80). The performance of heparin-binding protein was confirmed in the validation cohort.

Conclusion: In patients presenting at the emergency department, heparin-binding protein is an early indicator of infection-related organ dysfunction and a strong predictor of disease progression to severe sepsis within 72 hours. (*Crit Care Med* 2015; 43:2378–2386)

Key Words: circulatory failure; heparin-binding protein; organ dysfunction; prognostic biomarker; sepsis; severe sepsis

The underlying pathogenesis of sepsis is complex and dependent on the etiologic microorganism, site of infection, and host factors (1, 2). As a result of the non-specific diagnostic criteria of sepsis, patients at risk of becoming more seriously ill are often not identified for resuscitation until they develop overt signs of organ failure. Indeed, almost a quarter of patients presenting with uncomplicated sepsis in an emergency department (ED) developed severe sepsis or septic shock within 72 hours (3). Delayed in-hospital progression to increased organ dysfunction was associated with increased transfer to the ICU and increased hospital length of stay (4). Furthermore, the progression to severe sepsis and organ failure is associated with increased mortality (5–7). The early identification of high-risk patients can lead to earlier initiation of resuscitation that could reduce morbidity and mortality (8–10). In addition, septic shock is associated with impaired quality of life and increased mortality for several years after the initial incident (11–13). Also, less severe organ dysfunction is associated with increased long-term mortality among survivors (14, 15).

Heparin-binding protein (HBP) resides in the secretory and azurophilic granulae of neutrophils and can be released in the presence of bacteria (16–18). HBP has several functions, such as a chemoattractant and an activator of monocytes and macrophages (19). Also, it induces vascular leakage by interacting with the capillary endothelium and breaking cell barriers (20). In vivo studies have demonstrated that HBP released by the complex formed by the group A streptococcal M1 protein and fibrinogen induces massive tissue edema contributing to severe organ damage (16–18). In clinical investigations, the release of HBP has been demonstrated in various infectious diseases caused by a wide array of bacteria (21–24). A recent single-center study of patients admitted for suspected infection and fever showed that plasma levels of HBP were significantly higher among patients who presented with or developed severe sepsis (21).

The objectives of this study were to 1) validate the utility of a threshold concentration of plasma HBP to predict the development of organ dysfunction and 2) to compare the performance of HBP relative to currently used sepsis biomarkers in ED patients.

MATERIALS AND METHODS

Study Design and Settings

This was a prospective, multicenter, observational, convenience sample study of ED patients with suspected infection

(ClinicalTrials.gov NCT01392508), conducted at five Swedish academic centers and one center in the United States. In Sweden, two Infectious Diseases Clinics with separate EDs (Skåne University Hospital, Lund, and Örebro University Hospital, Örebro) and three general EDs (Skåne University Hospital in Lund and in Malmö, and Linköping University Hospital) participated, and in the United States, the study center was a tertiary care academic medical center (Cooper University Hospital, Camden, NJ). The size of the catchment areas of the respective hospital varied from 140,000 to 400,000 inhabitants and the annual visits of the EDs from 45,000 to 84,000 per year. The study was conducted over a 15-month period between April 2011 and June 2012.

A validation cohort was composed of patients who had sepsis from the ED of St. Paul's Hospital, a tertiary referral hospital with 40,000 annual visits, in Vancouver, Canada. Patients were recruited between January 2011 and July 2013. The Institutional Review Board for Human Research approved the trial at each center.

Patient Population

Patients were enrolled upon presentation to the ED when fulfilling the following inclusion criteria: 1) age 18 years old or older; 2) a suspected infection after evaluation by the attending clinician; and 3) at least one of three clinical criteria for the systemic inflammatory response syndrome (SIRS) (25). SIRS was defined as a) temperature more than 38°C or less than 36°C or self-reported fever/chills within the past 24 hours; b) respiration rate more than 20 breaths/min; and c) heart rate more than 90 beats/min. The fourth criterion commonly used in SIRS definition, the WBC count, was not used as an inclusion criterion because the WBC count was not available when the patient presented to the ED. There were no exclusion criteria.

Data Collection

Patient data collected at enrollment included demographics, comorbid conditions, concomitant medication, vital signs (heart rate, respiratory rate, blood pressure, arterial oxygen saturation [SaO_2]), and mental status. Laboratory testing (WBC, platelets, C-reactive protein [CRP], international normalized ratio [INR], bilirubin, serum creatinine, and serum lactate) was performed, and the suspected source of infection was noted. Vital signs were documented at enrollment and later as often as available from the medical record. In addition, blood pressure was measured regularly (at least every fourth hour) during the first 24 hours. All signs of organ dysfunction including hypotension were collected from the medical records, and mortality within the 72-hour study period was assessed.

Sample Collection and Biomarker Assays

Venous blood samples for the determination of biomarkers were drawn from patients at enrollment (sample 1) and again 12–24 hours after the initial sample (sample 2). Samples were processed locally at each site, centrifuged, stored at -80°C within 2 hours of collection and subsequently shipped on dry ice to a centralized laboratory for analysis of HBP and

procalcitonin (PCT). HBP was analyzed blinded and in duplicate using the Axis-Shield HBP microtiter plate enzyme-linked immunosorbent assay (Axis-Shield Diagnostics, Dundee, United Kingdom) and PCT by the ADVIA Centaur BRAHMS PCT assay (Siemens Healthcare Diagnostics, Surrey, United Kingdom). WBC, CRP, and lactate analyses were performed at the clinical chemistry laboratories at each site. HBP and WBC were analyzed across the entire study population.

Definition of Outcomes

The primary outcome was the progression to infection-related organ dysfunction (severe sepsis) within the 72-hour time period from enrollment. A secondary outcome was the presence of severe sepsis at any time during the study period. The criteria for organ dysfunction were adapted from consensus criteria for sepsis syndrome (25, 26) and the current surviving sepsis guidelines (27). It was defined as present when any of the following criteria were met in the absence of preexisting pathology that could explain the abnormal results: acute neurologic dysfunction such as a confused, drowsy, or unconscious state; cardiovascular dysfunction defined as systolic blood pressure less than 90 mmHg, a mean arterial pressure less than 70 mmHg, a decrease in systolic blood pressure of more than 40 mmHg, or the need for vasopressors; respiratory dysfunction defined as SaO_2 less than 90% at any time or the need for mechanical ventilation; renal dysfunction defined as a creatinine increase more than 44 $\mu\text{mol/L}$ between any two measurements; hematologic dysfunction defined as any platelet count less than $100 \times 10^9/\text{L}$ or INR more than 1.5; and hepatic dysfunction defined as a total bilirubin more than 32 $\mu\text{mol/L}$. Serum lactate elevation was not included as a criterion for organ dysfunction as its utility was evaluated as a marker in the study. If patients were discharged from the hospital before the 72-hour period and there was no evidence of organ dysfunction during the hospitalization, they were assumed to have no subsequent organ dysfunction. Septic shock was defined as sepsis plus hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 70 mmHg) refractory to fluid resuscitation or the administration of vasopressors (27).

After review of the medical records including clinical, microbiological, laboratory, and radiological findings, the study physician at each site determined the infection status of each patient based on a standard algorithm in the *Clinical Record Form*. Similarly, data collected in the study and from the medical charts were used to determine the presence and time of onset of organ dysfunction at each site. For patients not clearly meeting the criteria for infection or organ dysfunction, three of the investigators (A.L., B.C., P.Å.), unaware of the biomarker results, reviewed the data and decided on the final classification. Patients with infections were divided into two groups: 1) infection with organ dysfunction, that is, patients with septic shock or severe sepsis and 2) infection without organ dysfunction.

Statistical Methods

Means, medians, SDs, and interquartile ranges (IQRs) were reported as appropriate. Spearman rank correlation was used

to assess the relationship between pairs of continuous variables. Areas under the receiver operating characteristic curves (AUC) were calculated to assess the diagnostic power of each marker, and significant differences were determined using a two sample Z test with a Bonferroni adjusted p value. To account for the wide distribution of data and potential nonlinear associations, markers values were transformed into quartiles based on the distribution within the study population when calculating odds ratios (OR). SPSS software system version 20.0 (SPSS, Armonk, NY) and Graphpad Prism 6 (GraphPad Software, La Jolla, CA) software were used for statistical calculations.

RESULTS

Patient Characteristics

A total of 806 ED patients with a suspected infection and at least one SIRS criterion were prospectively enrolled. Forty-seven patients (5.8%) were excluded, leaving 759 patients for further evaluation (Fig. 1). An infection diagnosis was established in 674 patients (88.8%). Of these 674 patients, 328 (48.7%) had signs of organ dysfunction (severe sepsis) within the 72-hour study period, including 29 patients with septic shock (4.3%); 52.7% of these patients had one organ dysfunction, 28.4% had two organ dysfunctions, and 18.9% had three or more organ dysfunctions. Cardiovascular (80.2%) and respiratory dysfunction (36.9%) were most common. Of the 85 patients who were not diagnosed with an infection, 22 (25.9%) had an organ dysfunction. Common diagnoses in these patients were autoimmune disorder, pancreatitis, and cancer. The overall mean age was 58 years (range, 18–101), 46.0% were women, and 89.7% were Caucasians. Patients with infection and organ dysfunction were older and had more comorbidities, such as cardiovascular and malignant diseases and diabetes mellitus, than patients with infection without organ dysfunction. Details on patient characteristics are presented in Table 1. Four patients died within the 72-hour study period, all with an infection with organ dysfunction.

Accuracy of Biomarkers as Predictors of Risk of Severe Sepsis

To determine the potential of the candidate biomarkers to identify patients who progressed to severe sepsis, plasma from the 487 infected patients without organ dysfunction at presentation was analyzed. Of these, 141 patients (29.0%) progressed to severe sepsis within the study period. To increase the likelihood of detecting patients who might deteriorate several hours after admission, biomarkers were measured twice, at enrollment and 12–24 hours later when clinically convenient. The highest biomarker value before detection of organ failure was used for analyses of the predictive capacity. The diagnostic accuracy for the identification of patients progressing to severe sepsis was highest for HBP, with an AUC value of 0.80 (Fig. 2). HBP was significantly better in identifying patients who developed organ dysfunction compared with the other markers ($p < 0.01$). When using only data from patients where all five markers had been measured, the AUC value for HBP increased to 0.82, still

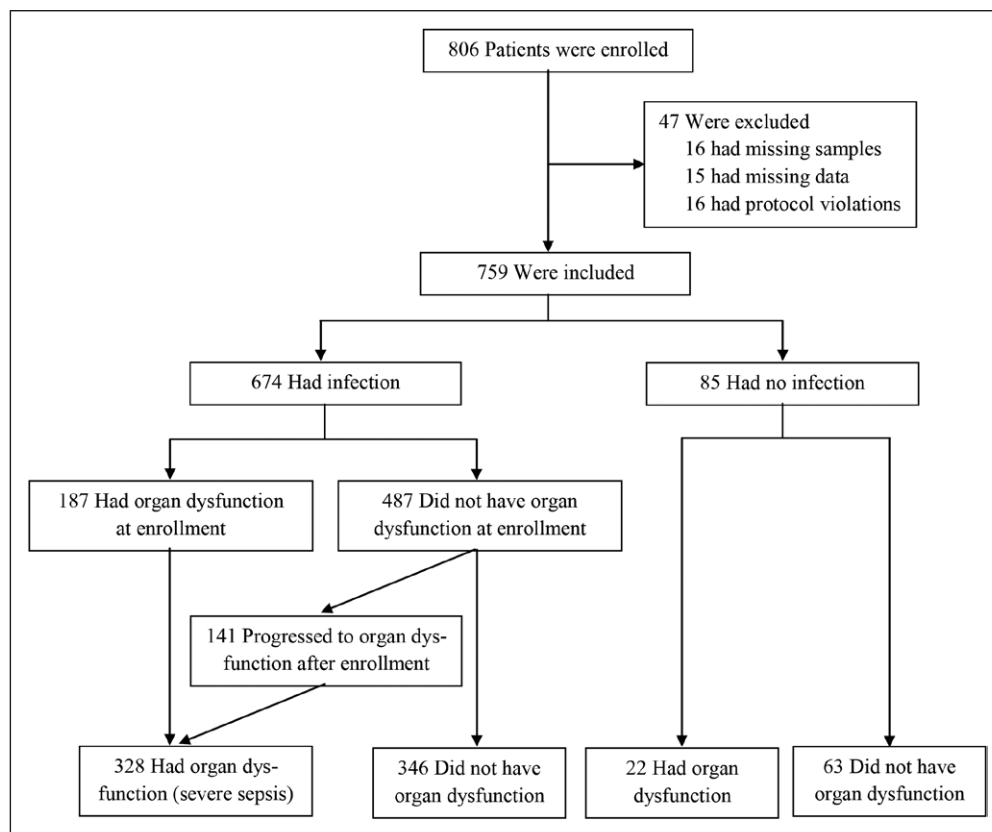


Figure 1. Flow chart of patients in the study cohort and subsequent patient outcomes.

significantly higher than for the other markers ($p < 0.01$). A combination of all five investigated markers improved the prediction of progression to organ dysfunction (AUC, 0.85).

For discriminatory analyses of HBP, a threshold value of 30 ng/mL was applied. One hundred ten of the 141 patients (78.0%) had an increased plasma HBP concentration more than 30 ng/mL before developing organ dysfunction. This elevated HBP was detected several hours before fulfilling any of the criteria for organ dysfunction (median, 10.5 hr) (Fig. 3). When using suggested cutoff values for other biomarkers, PCT (> 0.5 ng/mL) was increased in 73 of 139 patients (52.5%), WBC ($> 12 \times 10^9/L$) in 57.4%, CRP (> 130 μ g/mL) in 59.3%, and lactate (> 2.0 mmol/L) in 28.1%, before the onset of organ dysfunction. HBP predicted progression to organ dysfunction with a sensitivity of 78.0% and a specificity of 76.3%, outperforming other biomarkers (Table 2).

Among patients who progressed to severe sepsis within the first 24 hours, nine had plasma levels below the cutoff for HBP at admission but were positive at the second sampling, which was at the time of or after detection of organ failure. Including these patients in the analysis by using the highest HBP value in the two samples increased the AUC to 0.85, suggesting that more frequent testing might further increase the utility of plasma HBP for prediction of severe sepsis.

Unadjusted ORs of progression to organ dysfunction for infected patients increased continuously across quartiles for all biomarkers (Table 3). The OR in the top quartile was highest for HBP (20.5; 95% CI, 9.92–42.4), indicating that a patient with elevated

HBP has a greatly increased risk of developing severe sepsis.

Biomarker Distribution in Relation to the Final Diagnosis of Organ Dysfunction

In addition to the analysis of biomarkers as predictors, their ability to identify severe sepsis at any time (present at enrollment or developing during the study period) was investigated. For this, all 674 infected patients, including the ones who presented with organ dysfunction, were analyzed. The highest biomarker values obtained either at admission or in the 12- to 24-hour sample were used. The concentrations of all biomarkers were significantly higher in patients who had (at ED admission) or developed severe sepsis (Fig. 4). The median HBP plasma concentration was 63.5 ng/mL (IQR, 35.1–114.1) in the group with organ failure versus 18.8 ng/mL

(IQR, 10.6–29.7) among patients without organ failure. Receiver operating characteristic curves for the identification of severe sepsis at any time demonstrated that HBP had an AUC of 0.85 (95% CI, 0.82–0.88), significantly higher than all other biomarkers ($p < 0.01$): PCT, 0.78 (0.74–0.81); WBC, 0.74 (0.70–0.77); CRP, 0.76 (0.72–0.80); and lactate, 0.70 (0.66–0.74).

In the total study cohort of 759 patients, 85 patients were not diagnosed with an infection. Of these, 22 had signs of organ dysfunction. The median plasma HBP concentration was significantly higher in these organ dysfunction patients (27.6 ng/mL; IQR, 17–49) compared with the 63 noninfected patients without organ dysfunction (11.1 ng/mL; IQR, 7–19).

Performance of HBP in an Independent Validation Cohort

Plasma samples from 104 patients from a prior prospective study of endotoxin tolerance in sepsis (28) were used to validate the HBP assay in an independent cohort (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCM/B419>). Of the 21 patients with severe sepsis, nine presented without signs of organ dysfunction at enrollment. The diagnostic accuracy for HBP in predicting severe sepsis in this cohort was higher than in the larger prospective cohort with an AUC of 0.89 (95% CI, 0.74–1.03). The AUC for determining the final diagnosis of severe sepsis (i.e., severe sepsis at any time) was 0.91 (0.82–0.99). The AUC for lactate was 0.53 (0.31–0.76) for predicting and 0.72 (0.57–0.86) for diagnosing severe sepsis. When the plasma HBP threshold of

TABLE 1. Characteristics of the Study Population

Characteristics	Infection With Organ Dysfunction (<i>n</i> = 328)	Infection Without Organ Dysfunction (<i>n</i> = 346)	No Infection (<i>n</i> = 85)	<i>p</i>
Age, mean years (range)	65 (18–101)	52 (18–94)	59 (18–92)	< 0.001
Gender, % female	45	44	58	
Race, <i>n</i> (%)				
White	297 (91)	307 (89)	77 (91)	
Black	13 (4)	17 (5)	1 (1)	
Other	18 (5)	22 (6)	7 (8)	
Comorbidities, <i>n</i> (%)				
Cardiovascular disease	119 (36)	55 (16)	13 (15)	< 0.001
Diabetes mellitus	69 (21)	45 (13)	8 (9)	< 0.01
Renal disease	39 (12)	25 (7)	5 (6)	
Liver disease	7 (2)	6 (2)	4 (5)	
Malignancy	52 (16)	24 (7)	17 (20)	< 0.001
Respiratory disease	44 (13)	42 (12)	6 (7)	
Immunocompromised	14 (4)	13 (4)	0	
No comorbidities	127 (39)	212 (61)	52 (61)	< 0.001
Source of infection, <i>n</i> (%)				
Lower respiratory	125 (38)	102 (29)	0	< 0.05
Upper respiratory	7 (2)	29 (8)	0	< 0.001
Urogenital	75 (23)	59 (17)	0	
Skin/soft tissue	40 (12)	63 (18)	0	< 0.05
Intra-abdominal	42 (13)	48 (14)	0	
Other	19 (6)	24 (7)	0	
Unknown	20 (6)	21 (6)	0	
Vital signs at entry, mean (range)				
Temperature, °C	38.3 (35.0–41.4)	37.8 (34.5–40.3)	37.4 (34.7–39.6)	< 0.001
Heart rate, beats/min	96 (50–156)	92 (53–141)	93 (55–152)	< 0.01
Respiratory rate, per min	23 (12–52)	20 (9–45)	21 (10–38)	< 0.001
Systolic BP, mm Hg	131 (69–248)	134 (80–222)	133 (92–230)	
Diastolic BP, mm Hg	71 (25–175)	77 (48–120)	77 (44–125)	< 0.001
Blood cultures (%)				
Obtained, number of patients	303 (92)	238 (69)	49 (58)	< 0.001
Positive, number of patients	83 (27)	23 (10)	0	< 0.001

BP = blood pressure.

p values refer only to comparisons between patients with infection, with or without organ dysfunction, respectively. Only *p* values < 0.05 are indicated.

30 ng/mL was applied to this cohort, the sensitivity was 78% and the specificity 95% in predicting severe sepsis among infected patients presenting without organ dysfunction. Among the 41 patients without an established infection diagnosis, HBP levels were low (median, 3.6 ng/mL; range, 1–25). None of these patients had a HBP level above the threshold of 30 ng/mL.

DISCUSSION

In this ED-based multicenter study, plasma HBP was a robust predictor of disease progression to infection-related organ dysfunction, that is, severe sepsis. A prognostic biomarker with high clinical utility should predict outcomes before clinical signs of the primary outcome become apparent. In the present

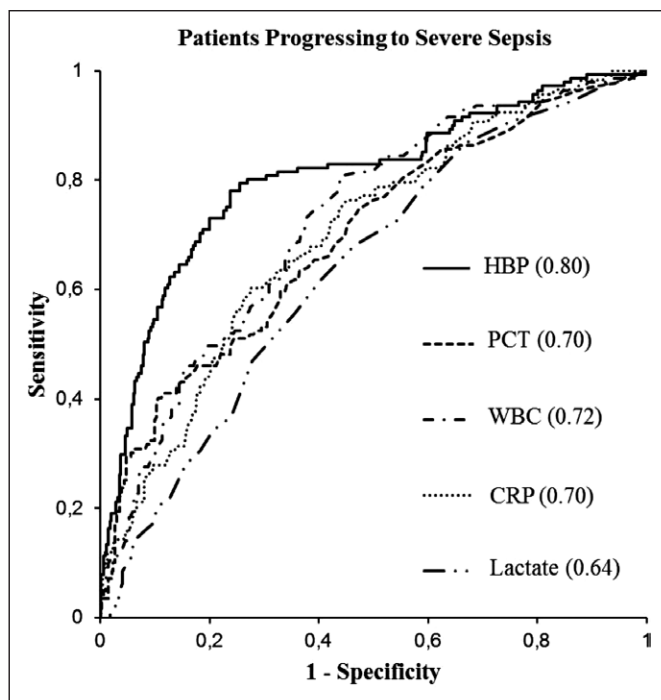


Figure 2. Diagnostic accuracy of biomarker testing for infection-related organ dysfunction, that is, severe sepsis. Receiver operating characteristic curves are shown comparing heparin-binding protein (HBP), procalcitonin (PCT), C-reactive protein (CRP), lactate, and leukocyte count in discriminating between patients with infection who progressed to organ dysfunction and those who did not. The highest biomarker value before onset of organ dysfunction was used. The area under the receiver operating characteristic curve values (95% CI) for the progression to organ dysfunction were as follows: HBP, 0.80 (0.76–0.85); PCT, 0.70 (0.64–0.75); WBC, 0.72 (0.66–0.77); CRP, 0.70 (0.65–0.75); and lactate, 0.64 (0.58–0.69). HBP was significantly better than all the other markers in discriminating between patients who progressed to organ dysfunction and those who did not ($p < 0.01$).

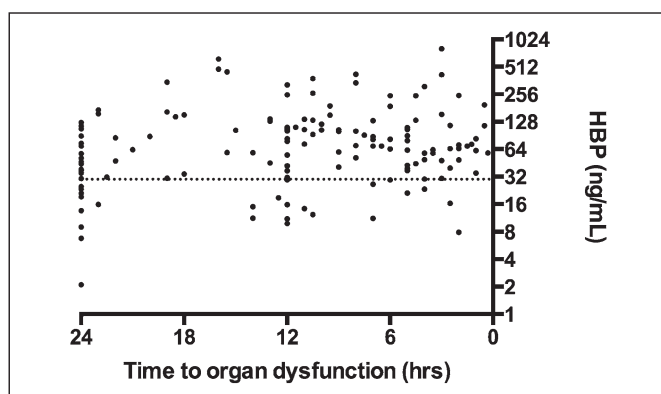


Figure 3. Analysis of infected patients progressing to organ dysfunction after enrollment. Plasma heparin-binding protein (HBP) levels and times from plasma sampling to the development of organ dysfunction are indicated. Each dot represents one of the 141 patients. Patients with organ dysfunction detected at 24 hr or later after sampling are marked at 24 hr.

study, 29% of the patients with infection who presented without signs of organ dysfunction progressed to severe sepsis within 72 hours, a proportion that is similar to the results of some other recent ED studies (3, 21, 29). In this important but diagnostically challenging group, HBP was the best biomarker

with increased plasma levels several hours before circulatory failure or organ dysfunction developed. In this respect, HBP seems to elevate prior to the other investigated markers. The rapid increase of HBP can be explained by its location within the secretory granulae, which are the first to be mobilized upon neutrophil activation. After release, HBP contributes to the neutrophil-mediated permeability changes of the endothelium leading to vascular leakage. The likelihood of an elevated HBP is probably increased if the patient sample is obtained closer to the onset of organ dysfunction. This tendency was seen in the current study. The results also aligns with a previous single-center study that showed increased plasma HBP in over 90% of the patients with infection who developed severe sepsis after inclusion (21). Furthermore, the negative predictive value of 89.5% for HBP indicates a high probability for excluding the progression to a more severe disease in an otherwise clinically stable patient with infection. The data also suggest that repeated HBP analysis during the initial time period is beneficial in improving detection of the development of organ dysfunction.

The inclusion criteria, suspected infection, and one clinical SIRS criterion were selected to enroll broad range of ED patients. Of note, 49% of the infected patients were diagnosed with organ dysfunction. This is comparable to the occurrence rate in another large ED study (29) but higher than in a previous epidemiological study (3). Difficulties in the classification of infection severity and the identification of organ dysfunctions could explain the differences between studies (30, 31). In a recent sepsis study based in an ICU, the frequency of organ failure in the same cohort differed from 10% to 36% depending on the use of liberal or restrictive settings of criteria and on the timing of measurements (31). A post hoc analysis of the patients without organ dysfunction who had an elevated HBP (false positives) showed that there was a tendency to treat this group with more IV fluids and antibiotics than other patients with uncomplicated infections (data not shown). Many of these “false-positive” patients had organ dysfunction variables just below threshold for classifying as organ dysfunction.

The strengths of the study include the large study population with a broad range of clinical presentations and diagnoses, the careful blinded and accurate measurements of HBP, and the careful monitoring of organ dysfunction. The distributions of most common diagnoses, microbiological findings, and types of organ dysfunctions are similar to recent reports (32). Samples were handled at independent hospital laboratories, and HBP was analyzed by an assay reproduced outside of the laboratory where it was developed. Some limitations of the study are the incomplete sample size for comparative biomarkers (i.e., CRP), the lack of data on long-term mortality, and the limited number of patients in the validation cohort. Also, the presented cutoff value for HBP was higher than in previous studies of HBP as a sepsis marker (21, 23). The threshold value was selected to give the best combined sensitivity and specificity. However, it is unclear if transportation and handling of samples outside the research laboratory is an explanation for varying cutoffs or if it reflects different patient cohorts.

TABLE 2. Discriminatory Value of Biomarkers for the Final Diagnosis of Severe Sepsis in Patients Who Did Not Have Organ Dysfunction at Sampling (*n* = 487)

Variable	Heparin-Binding Protein	Procalcitonin	WBC	C-Reactive Protein	Lactate
Cutoff Value	30 ng/mL	0.5 ng/mL	$12 \times 10^9/L$	130 $\mu\text{g/mL}$	2.0 mmol/L
Sensitivity	78.0	52.5	57.4	59.3	28.1
Specificity	76.3	71.1	71.7	72.5	84.3
Positive predictive value	57.3	42.7	45.2	45.8	41.4
Negative predictive value	89.5	78.6	80.5	82.0	74.9

TABLE 3. Quartile Ranges and Odds Ratios for Progression to Organ Dysfunction Among Patients With Infection Who Presented Without Organ Failure (*n* = 487) in the Emergency Department

Variable	Reference Group	Level	OR	95% CI
Heparin-binding protein (ng/mL)	0.0–12.2			
		12.3–23.1	1.30	0.56–2.98
		23.2–48.0	3.86	1.85–8.06
		48.1–807.3	20.5	9.92–42.37
Procalcitonin (ng/mL)	0.0–0.16			
		0.17–0.32	1.56	0.80–3.04
		0.33–0.75	2.07	1.08–3.97
		0.76–69.2	6.25	3.33–11.74
WBC ($10^9/L$)	0.0–7.7			
		7.8–10.1	2.95	1.35–6.45
		10.2–13.8	5.53	2.62–11.68
		13.9–57.9	13.0	6.21–27.22
C-reactive protein ($\mu\text{g/mL}$)	0.0–42			
		43–96	2.56	1.18–5.54
		97–175	4.01	1.9–8.48
		176–474	7.85	3.77–16.3
Lactate (mmol/L)	0.0–1			
		1.1–1.3	2.31	1.16–4.62
		1.4–1.8	3.25	1.73–6.1
		1.9–5.3	4.17	2.21–7.89

OR = odds ratios.

The highest biomarker value before onset of organ dysfunction was used. The reference group represents the first (lowest) heparin-binding protein quartile (*n* = 122).

The results from the validation of the HBP assay in patients independent from the multicenter cohort suggested a robust reproducible performance of plasma HBP to predict progression to severe sepsis.

In conclusion, the host response to sepsis involves numerous mediators, many of which have been proposed as sepsis biomarkers (33, 34). HBP represents one such mediator with an important role in a central sepsis mechanism, the

induction of vascular leakage. Targeting HBP release has shown dramatic effects on organ damage in animal experiments (16). HBP was the best single marker predictive of progression to organ dysfunction (i.e., severe sepsis) in patients with infection in the ED setting. Accordingly, we suggest that measurement of plasma HBP may facilitate decisions on early management to potentially prevent progression to severe sepsis in the ED. Furthermore, plasma HBP may be a predictive

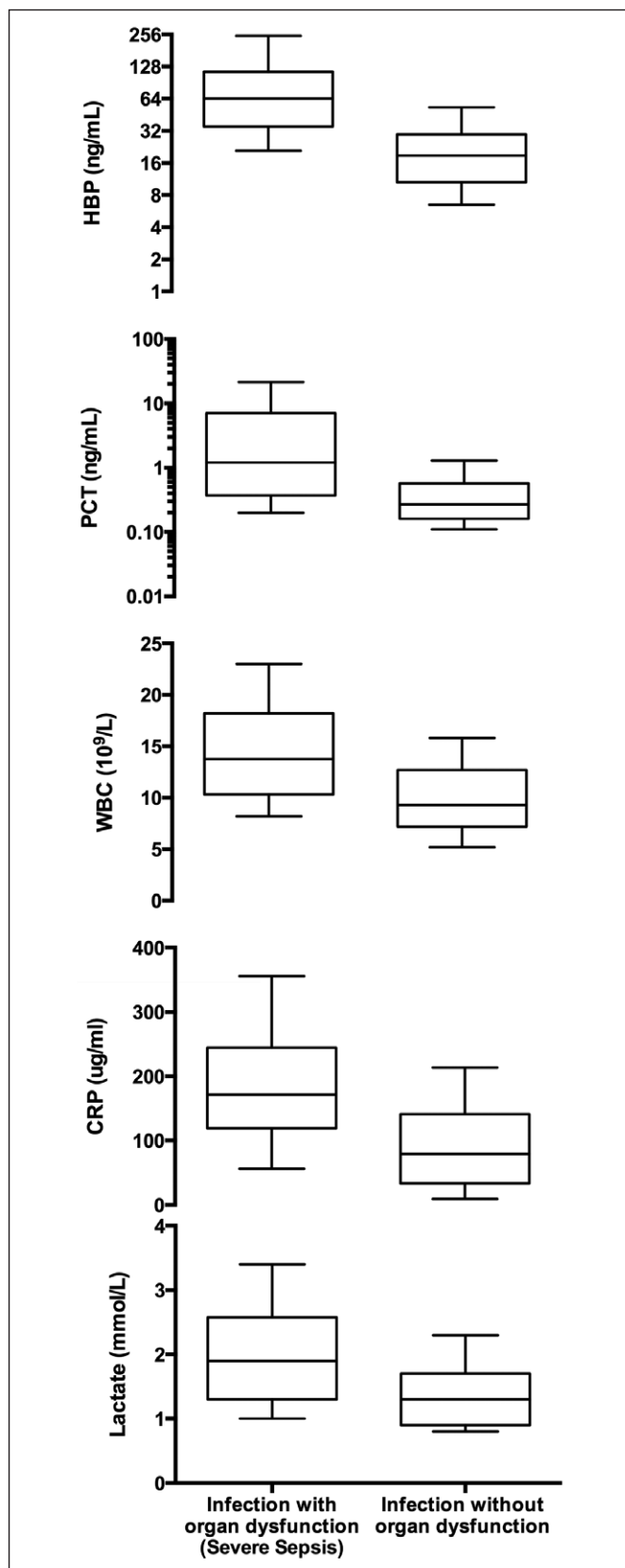


Figure 4. Analysis of peak biomarker values in infected patients. Two plasma samples were collected in the study: one at enrollment and one after 12–24 hr. The maximal value obtained for each biomarker was used to calculate the median values (line), interquartile range (boxes), and the 10–90% ranges (whiskers) for patients in each patient group. CRP = C-reactive protein, HBP = heparin-binding protein, PCT = procalcitonin.

biomarker for patient stratification in future therapeutic sepsis trials.

ACKNOWLEDGMENTS

We thank the physician, nursing, and other staff from the participating institutions, Ann Åkesson and Britt-Marie Hansson for excellent technical assistance, and Rasmus Hermansson and Fredrik Lindahl for help with sampling. In addition, we thank the Randall Scholarship Fund and Pepperdine University for the support of the Shock Research Internship students who assisted with the study.

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