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Combined biomarkers discriminate a low likelihood of bacterial infection among surgical intensive care unit patients with suspected sepsis

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Abstract

Among surgical intensive care unit (SICU) patients, it is difficult to distinguish bacterial sepsis from other causes of systemic inflammatory response syndrome (SIRS). Biomarkers have proven useful to identify the presence of bacterial infection. We enrolled a prospective cohort of 69 SICU patients with suspected sepsis and assayed the concentrations of nine biomarkers (α-2 macroglobulin (A2M), C-reactive protein, ferritin, fibrinogen, haptoglobin, procalcitonin (PCT), serum amyloid A, serum amyloid P, and tissue plasminogen activator) at baseline, 24-, 48-, and 72-hours. 42 patients (61%) had bacterial sepsis by chart review. A2M concentrations were significantly lower and PCT concentrations significantly higher in subjects with bacterial sepsis at

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three of four timepoints. Using optimal cutoff values, the combination of baseline A2M and 72-hour PCT achieved a negative predictive value of 75% (95% CI, 54%–96%). The combination of A2M and PCT discriminated bacterial sepsis from other SIRS among SICU patients with suspected sepsis.

Keywords

sepsis; systemic inflammatory response syndrome; biomarker; procalcitonin; alpha-2-macroglobulin; surgical intensive care unit

Introduction

It is difficult to distinguish bacterial sepsis from other causes of systemic inflammatory response syndrome (SIRS) in critically ill patients. The presence of two or more SIRS criteria with suspected infection has become the standard for sepsis diagnosis (Mouncey et al.; 1992; Sprung et al. 2008; COIITSS Study Investigators et al. 2010; Perner et al. 2012; Ranieri et al. 2012; Opal et al. 2013; ARISE Investigators et al. 2014; Holst et al. 2014). However the SIRS criteria have been criticized for lacking specificity for infection (Vincent 1997; Levy et al. 2003; Sprung et al. 2006; Vincent et al. 2013; Liao et al. 2014). Given the morbidity and mortality associated with bacterial sepsis, as well as evidence that early antibiotic therapy improves mortality in severe sepsis, guidelines recommend that empiric, broad-spectrum antibacterial agents be administered to patients who meet the two-SIRS-criteria standard (Kaukonen et al.; Brun-Buisson et al. 2004; Gaieski et al. 2010, 2013; Dellinger et al. 2013; Ferrer et al. 2014). The poor specificity of the SIRS criteria may thus contribute to excess use of broad, empiric antibiotics.

Surgical intensive care unit (SICU) patients, in particular, represent a population in whom SIRS criteria may demonstrate poor specificity for bacterial infection. The incidence of SIRS in the SICU exceeds the incidence in medical and cardiovascular ICUs. Prior studies have shown that greater than 90% of SICU patients meet SIRS criteria during their ICU stay (Pittet et al. 1995; Sigfrido Rangel-Frausto et al. 1995). The SICU has a higher proportion of culture-negative SIRS and sepsis than do medical or cardiovascular intensive care units (Sigfrido Rangel-Frausto et al. 1995; Andersson and Tracey 2011; Vincent et al. 2013).

Biomarkers have proven to be useful tools to distinguish the presence or absence of bacterial infection in specific patient populations. Procalcitonin (PCT) in particular has shown promise as a component of diagnostic and antibiotic stewardship strategies for respiratory tract infection and sepsis (Assicot et al. 1993; Schuetz et al. 1996, 2009, 2012, 2013; Christ-Crain et al. 2004; Simon et al. 2004; Uzzan et al. 2006; Tang et al. 2007; Nobre et al. 2008). A combination of biomarkers may be even more useful than a single biomarker by increasing specificity for infection and improving the ability to discriminate true bacterial sepsis from other causes of SIRS (Meisner et al. 1999; Harbarth et al. 2001; Castelli et al. 2004). To date, studies of biomarkers in sepsis have been limited in the number of biomarker combinations evaluated, and few studies have restricted analysis to SICU patients, a population in whom bacterial sepsis may be more difficult to discriminate (Hensel et al. 1998; Meisner et al. 1998; Uzzan et al. 2006; Castelli et al. 2009; Prkno et al. 2013; Wacker

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et al. 2013). The identification of SICU patients in whom antibacterial therapy can be safely stopped has the potential to aid antibiotic stewardship efforts, avoid adverse drug effects, and combat the evolution of drug-resistant pathogens (Fishman 2006; Dellit et al. 2007; Roberts et al. 2009; Luyt et al. 2014). We designed this study in companion with a study of biomarker performance in MICU patients with suspected sepsis (Han et al. 2015), with the hypothesis that optimal biomarker combinations and cutoffs may be specific to the SICU population.

We sought to systematically evaluate the ability of nine biomarkers, individually and in combination, to distinguish bacterial sepsis from other causes of SIRS in SICU patients. We further sought to define optimal biomarker cutoffs and sampling times to identify SICU patients with a low likelihood of bacterial infection.

Materials and Methods

Study Design and Setting

We prospectively enrolled patients admitted to the SICU of the Hospital of the University of Pennsylvania from February 2012 through May 2014. The study was approved by the institutional review board of the University of Pennsylvania. Because residual blood from routine clinical samples was used for biomarker analysis, a waiver of informed consent was granted.

Study Population

Patients were deemed eligible for study enrollment if they were identified as having presumed bacterial sepsis, defined by meeting two or more SIRS criteria and having new empiric antibiotic therapy initiated and blood cultures ordered within a four-hour window (Bone et al. 1992; Levy et al. 2003), at SICU admission or at any time during the SICU stay. Two or more SIRS criteria (body temperature > 38C or <36C; heart rate >90/minute; respiratory rate >20/minute; or white blood cell count (WBC) > 12,000 cells/uL or <4,000 cells/uL) had to be met within four hours of the enrollment blood culture. Patients were ineligible if new or broadened empiric antibiotic therapy had been given for greater than four hours past the timepoint when baseline biomarkers were measured given the potential for antibiotic therapy to impact baseline procalcitonin (PCT) measures (Meisner 2014). New empiric antibiotic therapy was defined as the initiation of new antibiotic therapy in a patient previously not on any antibiotics or broadening of antibiotic therapy in a patient already receiving an antibiotic. Antibiotic review was performed by a physician trained in infectious diseases (E.L.).

SICU patients with presumed bacterial sepsis, defined as above, were excluded from enrollment if they had (1) a code status of “do not resuscitate,” (2) cardiopulmonary arrest from which they had been resuscitated, (3) documented bacterial infection treated with antibacterial therapy in the five days prior to enrollment, or (4) evidence of immune compromise (including human immunodeficiency virus (HIV) infection with CD4 cell count <200 cells/mm^3, immunosuppressive therapy after organ transplantation, neutropenia (<500 neutrophils/mm^3), chemotherapy, receipt of >=20mg/day of prednisone for two or more

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weeks in the preceding three months, or cystic fibrosis). These exclusions were made because the use of biomarkers to identify low risk for bacterial infection (and potentially discontinue empiric antibiotics) was believed to be less useful in patients in whom antibiotic management would be dictated by code status, established bacterial infection, or an a priori high risk of bacterial infection (i.e., immunocompromise).

Biomarker Measurements

Serum samples for biomarker measurements were obtained from residual blood samples from tests performed for routine clinical care and stored at −70C until testing as previously described (Han et al. 2015). Baseline biomarker measurements were performed at the time a patient met all eligibility criteria. Measurements were repeated daily for three days (24-hour, 48-hour, and 72-hour timepoints). If multiple clinical blood samples were available, the one closest to the precise timepoint of interest was chosen.

Nine biomarkers were measured at each timepoint: PCT using the VIDAS BRAHMS PCT assay (bioMérieux, Durham, NC), a one-step immunoassay sandwich method with fluorescent detection, and the remaining eight (Supplementary Table 1) using the Bio-Plex Pro™ Human Acute Phase 5- and 4-Plex Panel Complete Kit (Bio-Rad Laboratories, Hercules, CA), a bead-based (xMAP technology) multiplex assay that allows for the simultaneous measurement of nine positive acute phase biomarkers in serum. Assays were performed per manufacturer's instructions. The Bio-Plex assay was read using a Luminex 200 reader (Luminex Corporation, Austin, TX), with samples from all four timepoints included in the same measurement test run, using a single lot of reagents, and each analyte measured in duplicate (results recorded as the mean of measurements).

Data Collection

Demographic information, comorbidities, and length of hospital and SICU stay prior to enrollment were recorded at baseline. Comorbidities of interest included hepatic dysfunction (defined as two or more of total bilirubin >2.5mg/dL, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than twice the upper limit of normal), solid or hematologic malignancy, diabetes mellitus, chronic kidney disease (with or without requiring hemodialysis), and pulmonary disease (chronic obstructive pulmonary disease or chronic bronchitis). APACHE II scores were calculated for patients at enrollment for all subjects in whom parameters were documented (Knaus et al. 1985).

Definition of Infection

The diagnosis of bacterial infection was determined retrospectively by the investigators using established Centers for Disease Control and Prevention (CDC) criteria (Horan et al. 2008). Two physicians trained in infectious diseases (E.L. and J.H.H.) independently reviewed the subjects' cumulative medical records, including all vital signs, provider notes, laboratory and radiographic results at 72 hours after enrollment. The reviewers were blinded to the results of biomarker testing. In cases of discordant assessments, the two reviewers discussed the case and made a consensus determination. The determination of bacterial infection by two-physician review served as the gold standard against which biomarker test characteristics were assessed. Two-physician review was chosen as the gold standard rather

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than positive blood cultures given the potential for false-positive or false-negative blood cultures.

Statistical Analysis

We first visually explored the temporal trends in biomarker values, in aggregate and stratified by bacterial sepsis versus other causes of SIRS (i.e., non-bacterial sepsis or non-infectious SIRS) using LOESS regression (with both least-squares estimator and Tukey's biweight M-estimator, the latter to limit the impact of outliers). We then compared the mean biomarkers values between bacterial sepsis versus other SIRS groups at each timepoint using the Wilcoxon rank-sum test. We characterized the clinical characteristics of SICU patients with bacterial sepsis and other causes of SIRS using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables. For all comparisons, a two-tailed p-value < 0.05 was considered significant.

Receiver-operating characteristic (ROC) curves were explored for each biomarker, and the discrimination of each biomarker was quantified using the area under the ROC curve (AUC, or C-statistic). We developed logistic regression models for pairwise combinations of each biomarker at each timepoint and determined each model's discriminatory power (with and without an interaction term) using the AUC (Kleinbaum and Klein 2010; Austin and Steyerberg 2012). We then explored various cutoffs of each biomarker at various timepoints and pairwise combinations of biomarkers to maximize the specificity and negative predictive value (NPV) for bacterial sepsis relative to other SIRS. The goal of the derived algorithm was to maximize the NPV in order to identify patients with presumed sepsis at low likelihood of bacterial infection and the potential for safe discontinuation of empiric antibiotic therapy. Secondarily, we sought to maximize the specificity of the algorithm so that it would characterize a significant number of patients without bacterial infection as negative.

Statistical analyses were performed using Stata v13.0 (StataCorp LP, College Station, TX), SAS v9.3 (SAS Institute, Cary, NC), and R v3.2.1 (R Core Team 2014). Stata was used for data cleaning; SAS for the analysis of biomarker-combination thresholds, sensitivity, specificity, and predictive values; R was used for all other analyses. Figures were produced using R's ggplot2 package v1.0.1 (Wickham 2010).

Results

Study Population Characteristics

A total of 199 patients were screened. Of these 130 were excluded, leaving 69 subjects for analysis. Reasons for exclusion included immunosuppression (52), ongoing treatment for a known infection (28), unavailable or incomplete laboratory samples (26), antibiotics broadened more than 4 hours prior to initial biomarker measurement (13), not meeting SIRS criteria (10), and cardiac arrest (1).

Of the 69 enrolled subjects, 42 (61%) had true bacterial sepsis based on two-physician chart review. (Initial independent review, prior to consensus determination, with Cohen's kappa = 0.76). In 14 (33%), the source was identified as bloodstream infection; in 11 (26%) as intra-

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abdominal infection; in 8 (19%) as pneumonia; in 3 (7%) as hepatobiliary infection; in 3 (7%) as skin or soft-tissue infection; in 2 (5%) as intra-thoracic empyema; and in 2 (5%) as subdural empyema. Of the 42 subjects deemed to have true bacterial sepsis, 16 (38%) had positive blood cultures. Etiologies of SIRS in the absence of true bacterial sepsis included congestive heart failure, non-ST-elevation MI, pulmonary embolism, aspiration pneumonitis, ischemic bowel injury, perisplenic cyst rupture, and candidemia.

Table 1 compares clinical characteristics of subjects with bacterial sepsis versus other causes of SIRS. No significant differences were observed between the groups in age, APACHE II score, duration of hospital or ICU stay prior-to- or post-enrollment. Comorbidities and complications of subjects' critical illness, including acute kidney injury, chronic renal insufficiency, hemodialysis, congestive heart failure, cirrhosis, diabetes mellitus, lung disease, ICU mortality, and overall mortality were also similar between groups. Only subject race, treated as a dichotomous variable (white or non-white), was significantly different between the groups: 43% of subjects with bacterial sepsis had a race categorized as non-white versus 19% of subjects with other causes of SIRS ($p = 0.04$).

Biomarker measurements in SICU patients with bacterial sepsis versus other causes of SIRS

Figure 1 depicts the result of LOESS regression for the nine biomarkers, with fitting performed by least squares. (Supplemental Figure 1 depicts the same with fitting performed by a redescending M-estimator using Tukey's biweight function, which minimizes the impact of outliers (e.g., fibrinogen)). By visual inspection, differences between groups were apparent in α-2 macroglobulin (A2M), ferritin (FER), and procalcitonin (PCT).

The mean times (standard deviation) from baseline biomarker measurement to the repeat "24-hour", "48-hour", and "72-hour" measurements were 23.8 (4.6) hours, 48.6 (5.9) hours, and 72.6 (6.1) hours, respectively. Table 2 shows the comparison of mean biomarker values at each of the measured timepoints between subjects with bacterial sepsis and subjects with other causes of SIRS, which again highlighted A2M, FER, and PCT. Significant differences were observed between groups for A2M at baseline ($p=0.009$), "24-hour" ($p=0.006$), and "48-hour" ($p=0.03$) timepoints; for FER at baseline ($p=0.04$); and for PCT at "24-hour" ($p=0.01$), "48-hour" ($p=0.007$), and "72-hour" ($p=0.002$) timepoints.

Diagnostic value of alpha-2-macroglobulin and procalcitonin

ROC curve analysis of individual biomarkers at each timepoint (Figure 2) showed that the discrimination between bacterial sepsis and other causes of SIRS was greatest for "72-hour" PCT (0.73), "48-hour" PCT (0.70), baseline A2M (0.69), "24-hour" A2M (0.69), and "24-hour" PCT (0.69). Logistic regression models were generated for each pairwise combination of biomarkers, and the model AUC was calculated both with and without an interaction term. This analysis further highlighted the discrimination of A2M and PCT (Supplementary Figure 2). The greatest logistic regression model AUC was 0.76, observed with the combination of "24-hour" A2M and "72-hour" PCT (no interaction). The combination of "baseline" A2M and "72-hour" PCT was the second most discriminatory model, with an AUC of 0.75. The top 43 observed AUC values (ranging from 0.72–0.76) included either

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A2M, PCT, or both. Though the combination of A2M and PCT outperformed single biomarkers, the difference did not achieve statistical significance: the 95% confidence interval of the best combined-biomarker AUC ranged from 0.64 to 0.87, overlapping the AUC 95% confidence interval for some single biomarker measures.

We explored a range of cutoff values for all nine biomarkers at all four timepoints, and we determined the measurement times and cutoff values with maximal negative predictive value (NPV). Table 3 lists the five combinations of A2M and PCT that achieved the greatest NPV in this population of SICU patients. The NPV achieved with a combination of A2M and PCT measurements ranged from 0.72–0.75. Specificity diminished with increasing negative predictive value, ranging from 0.5–0.46 for the combinations of A2M and PCT.

Discussion

In this prospective cohort study of critically ill surgical patients, we found that combinations of biomarkers and repeat measurements of the same biomarker were better able to discriminate true bacterial sepsis from other causes of SIRS than single biomarker measurements. A2M and PCT each demonstrated a good ability to discriminate true bacterial sepsis from other causes of SIRS, but their combination had greater discriminatory ability. The combination of “72-hour” PCT with either “baseline” A2M or “24-hour” A2M both demonstrated good discriminatory ability, with the “24-hour” A2M combination only slightly greater. We further established the measurement times and cutoff values at which combinations of A2M and PCT had maximal NPV. We examined both combinations in the NPV analysis, but favored “baseline” A2M over “24-hour” A2M given the stated aim to optimize an algorithm that might be applicable to cessation of empiric antibiotic therapy. By optimizing cutoff values of A2M and PCT, we were able to achieve an NPV of 0.75. Of note, the combination of A2M and PCT achieved a more favorable balance of NPV and specificity than did any single biomarker.

It is difficult to distinguish bacterial sepsis from other causes of SIRS in critically ill patients, particularly in SICU patients (Pittet et al. 1995; Sigfrido Rangel-Frausto et al. 1995; Andersson and Tracey 2011; Vincent et al. 2013). Meeting SIRS criteria alone is not specific for infection. Nevertheless, in the absence of an alternative cause, infection is often presumed to be the cause for SIRS, and treatment guidelines direct the prescription of broad-spectrum antibacterial therapy to patients who meet this standard because prompt treatment reduces the morbidity and mortality of patients with severe sepsis (Vincent 1997; Levy et al. 2003; Sprung et al. 2006; Vincent et al. 2013; Liao et al. 2014). In this context, biomarkers may play a useful role. Biomarkers or combinations of biomarkers with a high NPV for bacterial sepsis may allow the prompt discontinuation of antibacterial therapy in patients for whom it is unlikely to offer any benefit (Harbarth et al. 2001; BalcI et al. 2002; Meynaar et al. 2011; Prkno et al. 2013; Wacker et al. 2013; Garnacho-Montero et al. 2014). Such antibiotic stewardship interventions are increasingly important as rates of antibiotic resistance rise, particularly among critically ill patients (Carlet et al. 2004; Rice 2009; for Healthcare Epidemiology of America 2012). But the biomarkers and biomarker combinations found to be most informative may depend upon the particular population of critically ill patients studied, given that the diseases of SICU patients (e.g., trauma, bowel

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injury) differ significantly from those of medical or cardiovascular intensive care unit patients.

PCT and A2M stood out among the nine biomarkers we studied in SICU patients with suspected sepsis. The diagnostic utility of PCT, a peptide precursor of calcitonin produced by the thyroid, is well-established. A2M, a large plasma protein with anti-protease activity, which is produced mostly in the liver, is less well studied than PCT as a biomarker that may aid discrimination between bacterial sepsis and other causes of SIRS. However, it has been shown to decline in the setting of pancreatitis, thought in part due its binding plasmin, which is activated in this setting (McMahon et al. 1984; Abbink et al. 1991; Birkenmeier et al. 2006; Pierrakos and Vincent 2010; Wacker et al. 2013; Dalli et al. 2014; Garnacho-Montero et al. 2014; Vandevyver et al. 2014). The breadth of biomarkers evaluated in the present study permitted identification of A2M as a valuable biomarker. The restriction of the present study to SICU patients may also have played a role. We note that in a parallel study of biomarkers to discriminate bacterial sepsis from other SIRS among medical intensive care unit (MICU) patients, CRP proved a useful adjunct to PCT -- but A2M did not discriminate well between bacterial sepsis and other causes of SIRS at any timepoint in the MICU. One hypothesis for the improved discriminatory ability of A2M among SICU patients relative to MICU patients relates to the documented effect of intra-abdominal inflammation upon A2M decline: intra-abdominal sources accounted for few cases of bacterial sepsis in the MICU study, but accounted for 26% of cases in this study (Han et al. 2015).

The strengths of the study we present are (1) the number of biomarkers and biomarker-combinations evaluated, (2) the longitudinal sampling of biomarkers throughout the early period of suspected bacterial sepsis, and (3) the restriction to SICU patients -- a particularly difficult-to-diagnose population. We are unaware of any study to date that has examined multiple biomarkers with a focus on SICU patients.

This study's findings must be interpreted in light of several limitations. (1) Though agreement between physician-reviewers was high (Cohen's kappa = 0.76), and though each review was performed independently and blinded to the biomarker results, there was the potential for misclassification given the complexity of SICU patients and the absence of a gold standard for the determination of bacterial sepsis. (2) Subject race treated as a dichotomous variable (non-white or white) was significantly different between groups, which may account for some of the differences observed in A2M and PCT (though we could not identify literature to support race-based differences in these biomarkers). (3) It is plausible that the observed patterns of biomarkers may differ by source of infection, but the diverse sources we observed (bloodstream, intra-abdominal, pneumonia, hepatobiliary, skin or soft-tissue infection, intrathoracic empyema, and subdural empyema) relative to the number of subjects enrolled precluded stratified analysis. (4) The study was performed at a single, academic medical center, and it excluded immunocompromised patients -- limiting the populations to which our results can be generalized. Finally, (5) though the combination of A2M and PCT demonstrated good discriminatory ability and NPV, the NPV of 0.75 achieved from this combination alone is not sufficient justify cessation of empiric antibiotics directed against bacterial sepsis. The identified biomarker combination must be integrated with other clinical, laboratory, and imaging data to inform antibiotic management.

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Conclusions

In conclusion, A2M and PCT demonstrate good discrimination between bacterial sepsis and other causes of SIRS among SICU patients. The combination of these two biomarkers performs better than either in isolation. Further study should be directed to antibiotic stewardship algorithms based upon this combination of biomarkers to reduce unnecessary antibiotic use among SICU patients with suspected bacterial sepsis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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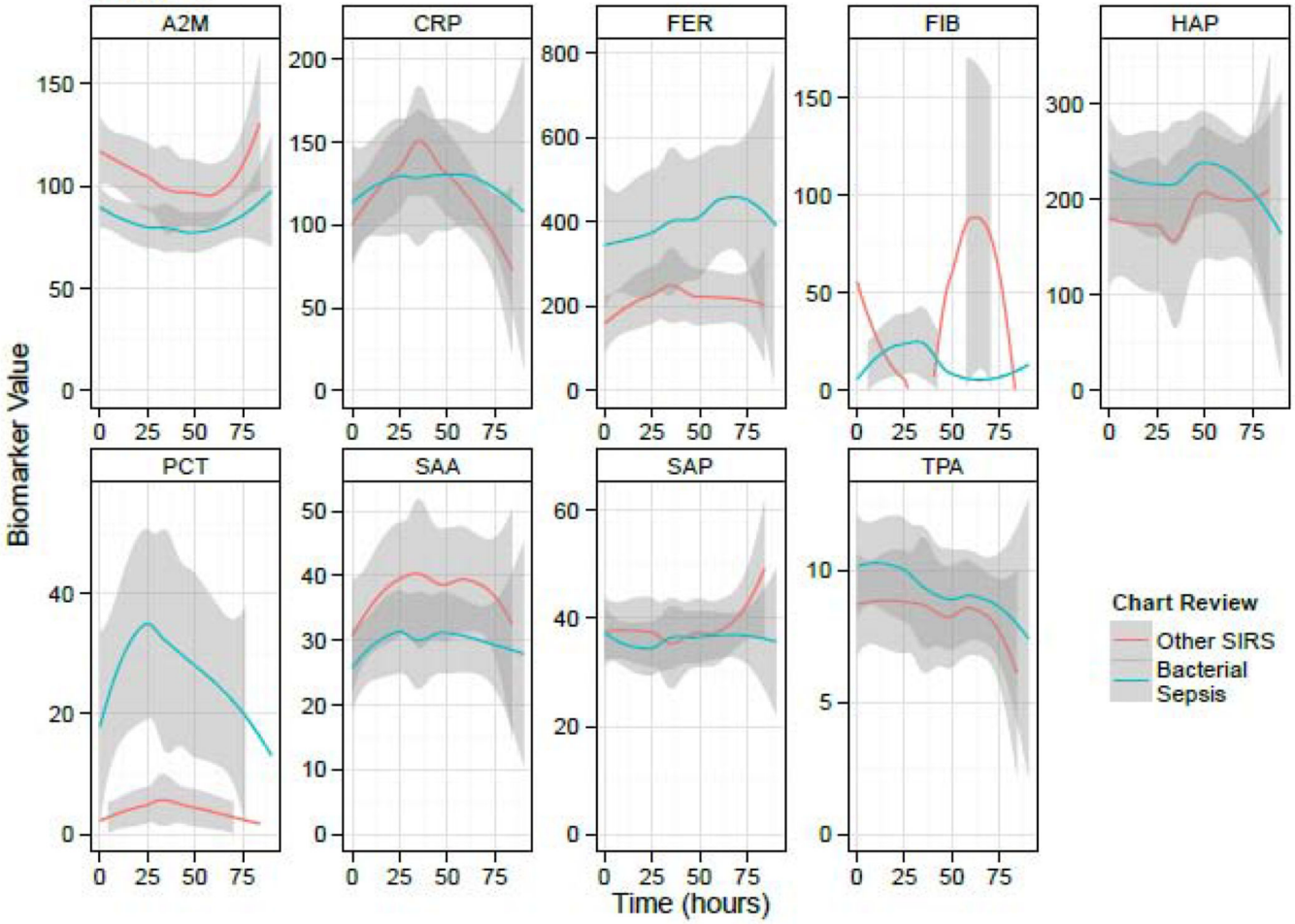

Figure 1.

Longitudinal Biomarker Levels Among Bacterial Sepsis and Other Causes of SIRS. LOESS regression relating biomarker value to actual collection time was performed for each biomarker in each group, with fitting performed by least squares. The line indicates the local mean, colored according to group (bacterial sepsis versus other causes of SIRS); the gray shading indicates the standard error about the mean. A2M, FER, and PCT demonstrate regions of separation between group means. We note that A2M differences are most pronounced at baseline and "24-hours" but diminish at later timepoints. The diminishing difference at later timepoints may reflect A2M synthesis to compensate for a rapid A2M decline in the early phase of sepsis. The FIB local means are highly variable due to outliers.

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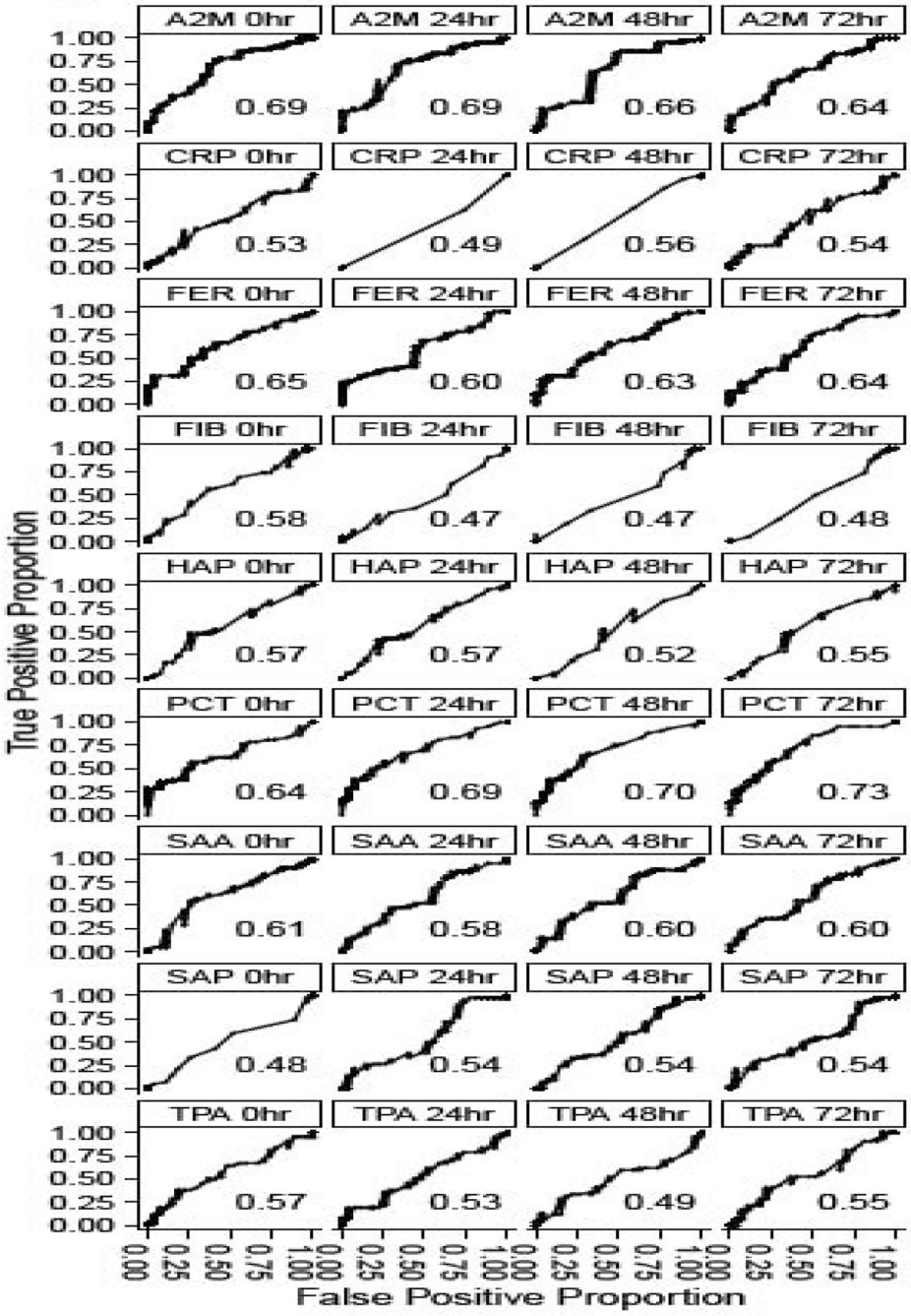

Figure 2.

Individual Biomarker Discrimination Between Bacterial Sepsis and Other Causes of SIRS. Receiver-operating characteristic (ROC) curves are shown for each biomarker at each timepoint. The discrimination of each biomarker, quantified by the C-statistic (equivalent to the area under the ROC curve, AUC) is shown at bottom right of each panel.

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Table 1

Characteristics of Surgical Intensive Care Unit Patients with Suspected Sepsis.

Variable	Bacterial Sepsis (n=42)[a]	Other SIRS (n=27)[a]	p-value[b]
Age (years)	64.2 (26.4)	70.1 (21.2)	0.14
APACHE II Score[c]	23 (9.8)	22 (16)	0.43
Hospital Stay Prior to Enrollment (days)	7.5 (15.2)	6 (7.5)	0.64
ICU Stay Prior to Enrollment (days)	2.5 (8.8)	2 (6)	0.75
Post Enrollment Stay (days)	20.5 (18.2)	15 (18)	0.17
In-Hospital Mortality	8 (19%)	4 (15%)	0.75
ICU Mortality	7 (17%)	3 (11%)	0.73
Malignancy	10 (24%)	10 (37%)	0.28
Diabetes Mellitus	12 (29%)	6 (22%)	0.78
Congestive Heart Failure	0 (0%)	1 (4%)	0.39
Lung Disease	3 (7%)	2 (7%)	>0.99
Cirrhosis	1 (2%)	1 (4%)	>0.99
Chronic Renal Insufficiency	5 (12%)	7 (26%)	0.19
Acute Kidney Injury	16 (38%)	5 (19%)	0.11
Hemodialysis	2 (5%)	1 (4%)	>0.99
Non-white Race	18 (43%)	5 (19%)	0.04*

[a]For continuous variables, table shows median value (interquartile range); for categorical variables, table shows subject number (percentage of total subjects in group).

[b]P-values are based on the Wilcoxon rank-sum test for continuous variables, Fisher's exact test for categorical variables.

[c]APACHE II scores could not be calculated for 18 subjects with bacterial sepsis and 6 subjects with other causes of SIRS because no blood gas testing was performed; missing data was excluded from analysis.

*Significant p-values are highlighted.

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Table 2

Comparison of Biomarkers Between SICU Patients with Bacterial Sepsis and Other Causes of SIRS

Biomarker	Time (hours)	Bacterial Sepsis (n=42)[a]	Other SIRS (n=27)[a]	p-value[b]
α-2 macroglobulin (mg/dL)	0	82.4 (38.6)	112.9 (59.6)	0.009*
	24	75.3 (27.6)	96.2 (53.4)	0.006*
	48	71.9 (26.4)	90.9 (60.6)	0.03*
	72	76.8 (30.1)	89.1 (41)	0.05
C-reactive protein (mg/L)	0	98.5 (81.1)	90.1 (57.2)	0.66
	24	121.2 (109.2)	109.9 (80.8)	0.94
	48	103.2 (84.8)	110.8 (112.9)	0.41
	72	94.6 (75.8)	85.1 (84.3)	0.58
Ferritin (ng/mL)	0	205.8 (305.3)	114.1 (180.6)	0.04*
	24	245.8 (340)	148.6 (270)	0.18
	48	242.6 (418.1)	158.6 (214.4)	0.06
	72	224.1 (295.4)	127.8 (263.7)	0.05
Fibrinogen (μg/mL)	0	5.7 (2.3)	6.5 (2)	0.26
	24	6.2 (3.4)	6.9 (2.9)	0.66
	48	6.3 (3.2)	6.1 (1.8)	0.68
	72	6 (3.4)	5.6 (2.5)	0.81
Haptoglobin (mg/dL)	0	143.4 (359.4)	102 (315.5)	0.36
	24	102 (351.5)	102 (276.4)	0.36
	48	143.6 (359.3)	102 (376.3)	0.81
	72	115.5 (359.7)	101.9 (365.1)	0.53
Procalcitonin (ng/mL)	0	2.2 (13.8)	1 (1.8)	0.05
	24	3.6 (23.2)	1.5 (2.2)	0.01*
	48	2.5 (18.2)	0.8 (1.7)	0.007*
	72	2.3 (12.8)	0.7 (1.6)	0.002*
Serum amyloid A (μg/mL)	0	19.8 (13.8)	24.6 (18.3)	0.12
	24	25.9 (17.8)	27 (39.6)	0.25
	48	23 (18.4)	27.6 (36.9)	0.17
	72	23.9 (20.5)	27.7 (38.2)	0.18
Serum amyloid P (mg/L)	0	34.2 (23.1)	32.7 (15.1)	0.75
	24	33.2 (20.3)	30.1 (25.5)	0.60
	48	33.7 (21.3)	33.4 (21)	0.62
	72	35.8 (22.5)	36.8 (19.2)	0.58
Tissue plasminogen activator (ng/mL)	0	8.3 (4.9)	6.9 (3.5)	0.32
	24	7.9 (5.3)	7.4 (5.9)	0.66

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Biomarker	Time (hours)	Bacterial Sepsis (n=42)[a]	Other SIRS (n=27)[a]	p-value[b]
	48	7.4 (6.2)	7.1 (3.7)	0.94
	72	7.5 (5.8)	6.9 (3.5)	0.45

[a]For each biomarker, in each group, the median value (interquartile range) is presented.

[b]P-values are based upon Wilcoxon rank-sum testing.

[*]Significant p-values are highlighted.

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Table 3

A2M and PCT Threshold Analysis

Biomarker Combination	NPV (95% Confidence Interval)	Number of Negatives	Specificity (95% Confidence Interval)
72-hour PCT ≥0.5 & 48-hour A2M ≤150	0.72 (0.52–0.93)	13	0.5 (0.31–0.70)
72-hour PCT ≥0.5 & 72-hour A2M ≤150	0.72 (0.52–0.93)	13	0.5 (0.31–0.70)
72-hour PCT ≥0.5 & 24-hour A2M ≤150	0.74 (0.54–0.94)	14	0.54 (0.35–0.73)
72-hour PCT ≥0.5 & baseline A2M ≤200	0.75 (0.54–0.96)	12	0.46 (0.27–0.65)
72-hour PCT ≥0.5 & 72-hour A2M ≤200	0.75 (0.54–0.96)	12	0.46 (0.27–0.65)