HHS Public Access

Author manuscript

Crit Care Med. Author manuscript; available in PMC 2019 July 01.

Published in final edited form as:

Crit Care Med. 2018 July ; 46(7): 1106–1113. doi:10.1097/CCM.0000000000003137.

Combined Biomarkers Predict Acute Mortality Among Critically Ill Patients with Suspected Sepsis

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Abstract

Objective—Sepsis is associated with high early and total in-hospital mortality. Despite recent revisions in the diagnostic criteria for sepsis that sought to improve predictive validity for mortality, it remains difficult to identify patients at greatest risk of death. We compared the utility of nine biomarkers to predict mortality in subjects with clinically suspected bacterial sepsis.

Design—Cohort study.

Setting—The medical and surgical intensive care units at an academic medical center.

Subjects—We enrolled 139 subjects who met two or more systemic inflammatory response syndrome (SIRS) criteria and received new broad-spectrum antibacterial therapy.

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CONFLICTS OF INTEREST: None

The remaining authors have disclosed that they do not have any potential conflicts of interest.

LIST OF ABBREVIATIONS:

A2M, ALT, AST, AUROC, CRP, FER, FIB, HAP, HIV, ICU, MICU, PCT, SAA, SAP, SICU, SIRS, SOFA, TPA, WBC

Interventions—We assayed nine biomarkers (α-2 macroglobulin, C-reactive protein, ferritin, fibrinogen, haptoglobin, procalcitonin, serum amyloid A, serum amyloid P [SAP], and tissue plasminogen activator [TPA]) at onset of suspected sepsis and 24-, 48-, and 72-hours thereafter. We compared biomarkers between groups based on both 14-day and total in-hospital mortality and evaluated the predictive validity of single and paired biomarkers via area under the receiver operating characteristic curve (AUROC).

Measurements and Main Results—14-day mortality was 12.9%, and total in-hospital mortality was 29.5%. SAP was significantly lower (4 of 4 timepoints) and TPA significantly higher (3 of 4 timepoints) in the 14-day mortality group, and the same pattern held for total in-hospital mortality (Wilcoxon p <= 0.046 for all timepoints). SAP and TPA demonstrated the best individual predictive performance for mortality, and combinations of biomarkers including SAP and TPA achieved greater predictive performance (AUROC greater than 0.76 for 14-day and 0.74 for total mortality).

Conclusions—Combined biomarkers predict risk for 14-day and total mortality among subjects with suspected sepsis. SAP and TPA demonstrated the best discriminatory ability in this cohort.

Keywords

sepsis; biomarkers; serum amyloid P; tissue plasminogen activator; procalcitonin

INTRODUCTION

Sepsis, defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection,” is counted among the leading causes of critical illness and mortality worldwide (1–3). But it has proven difficult to develop clinical and laboratory criteria that accurately predict risk for mortality, particularly in the early period of sepsis. A recent large cohort study, performed to validate new clinical criteria for sepsis, found that the recommended criteria, called the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score, achieved moderate predictive performance for acute mortality, with an area under the receiver operating characteristic curve (AUROC) of 0.74 for in-hospital mortality among intensive care unit (ICU) encounters, and an AUROC of 0.79 for in-hospital mortality among non-ICU encounters. No other sepsis criteria outperformed the SOFA score among ICU encounters; an abbreviated quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) score outperformed SOFA among non-ICU encounters, but the difference was minimal (4).

In the setting of imperfect diagnostic and prognostic tools for sepsis, novel methods for recognizing a dysregulated inflammatory response and predicting associated mortality must be developed. The SOFA score integrates clinical signs and laboratory values, including the PAO2/FIO2 ratio, platelet count, serum bilirubin, mean arterial pressure, Glasgow Coma Scale, serum creatinine, and urine output. The new consensus definition of septic shock incorporates a biomarker, serum lactate, in addition to SOFA criteria (1, 4, 5). Procalcitonin, a peptide precursor of the hormone calcitonin, has also been proposed as a tool to improve sepsis diagnosis and prognosis. Procalcitonin, which increases in response to microbial toxins and systemic inflammation, demonstrated value in discriminating infectious and

noninfectious causes of sepsis in critical illness (6–8). A recent large randomized controlled trial that de-escalated antibiotics prescribed as empiric sepsis therapy if an 80% decrease in procalcitonin occurred demonstrated a survival benefit at 28 days and a significant reduction in antibiotic use (9). However, the application of procalcitonin and other novel biomarkers requires validation. For this reason, procalcitonin received only a weak recommendation in the Surviving Sepsis Campaign Guidelines, and the recently revised international consensus definitions for sepsis and septic shock exclude procalcitonin, preferring instead serum lactate and the other laboratory values listed above (1, 4, 5, 10).

We sought to identify novel biomarkers that better characterize a dysregulated immune response and predict sepsis-related mortality by comparing predictive validity for acute and total in-hospital mortality among patients with clinically suspected bacterial sepsis. We investigated nine biomarkers associated with a systemic inflammatory response, assayed longitudinally at 24-hour intervals, in a cohort of subjects with suspected bacterial sepsis recruited from both medical (MICU) and surgical intensive care units (SICU) at an academic medical center.

MATERIALS & METHODS

Study Design and Setting

Patients admitted to the MICU or SICU at the Hospital of the University of Pennsylvania were prospectively enrolled from January 2012 through May 2014, with the approval of the institutional review board of the University of Pennsylvania. Methods were identical in the MICU and SICU, as described in more detail in prior work (7, 8). The study protocol was approved by the Institutional Review Board of the University of Pennsylvania. A waiver of informed consent was granted.

Study Population

Eligibility for study enrollment required 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 at ICU admission or at any time during the ICU stay (11, 12). 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. New empiric antibiotic therapy required either the initiation of new antibiotic therapy in a patient previously not on any antibiotics or the broadening of antibiotic therapy in a patient already receiving an antibiotic regimen. Antibiotic review was performed by two physicians trained in infectious diseases (EL, JHH). Patients were excluded if new or broadened empiric antibiotic therapy had been given for greater than four hours prior to the timepoint when baseline biomarkers were measured because of the potential for antibiotic therapy to impact baseline biomarker measures (13).

Exclusion criteria included (1) code status of “do not resuscitate,” (2) cardiopulmonary arrest from which patients 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 (or the equivalent) for two or more weeks in the preceding three months, or cystic fibrosis).

Biomarker Measurements

Residual blood samples obtained during the course of routine medical care were stored at -70C until biomarker assays could be performed (as per assay manufacturer instructions). Nine biomarkers were assayed: α-2 macroglobulin (A2M), C-reactive protein (CRP), ferritin (FER), fibrinogen (FIB), haptoglobin (HAP), procalcitonin (PCT), serum amyloid A (SAA), serum amyloid P (SAP), and tissue plasminogen activator (TPA). Biomarker measurements were performed at the time a patient met all eligibility criteria, and then repeated daily for three days (24-hour, 48-hour, and 72-hour timepoints). The sample closest to the precise timepoint of interest was chosen in cases of multiple available clinical samples. Samples for each patient over the four timepoints were assayed in the same testing run. 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 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. 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

At baseline, we recorded relevant demographic information, length of hospital and ICU stay prior to enrollment, and comorbidities with specific attention to 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). For all subjects with documented parameters, APACHE II scores were calculated at enrollment (14).

Definition of Mortality

14-day mortality was defined by a time of death documented as within 14 days of the time of enrollment during the hospital stay. Total in-hospital mortality was defined by a time of death at any time during the index hospital admission. 14-day mortality was chosen as an outcome measure to capture mortality likely related to the index episode of suspected bacterial sepsis; total in-hospital mortality was chosen to validate associations observed with 14-day mortality.

Statistical Analysis

We first visually explored the temporal trends in biomarker values in aggregate, stratified by 14-day mortality, and stratified by total in-hospital mortality, using LOESS regression with a least-squares estimator and Tukey's biweight M-estimator (the latter to limit the impact of outliers). We then compared the median biomarkers values between mortality versus no-mortality groups at each timepoint using the Wilcoxon rank-sum test. We characterized the clinical characteristics of ICU patients with 14-day and in-hospital mortality 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.

Area under the receiver operating characteristic curves (AUROC) was calculated for each individual biomarker and timepoint, and for logistic regression models incorporating all pairwise combinations of the biomarkers and timepoints (with and without an interaction term) (15–17). We then compared the performance of the best individual biomarkers and pairwise combinations to logistic regression models based on the APACHE II score (14, 18, 19) and the criterion of 80% decrease in procalcitonin, which has been used in a recent large randomized trial and found to be a significant predictor of severe sepsis-related mortality (9, 20). APACHE II score was available for 127 of the 139 enrolled subjects (12 had insufficient data recorded in the electronic medical record to calculate APACHE II score and were excluded from the analysis). 80% decrease in procalcitonin was defined as decrease from maximal value at any point during the 72-hour observation period. Finally, we compared the performance of the best combined biomarker prediction tools across the MICU and SICU groups. Statistical analyses were performed using R v3.2.1 (21). Figures were produced using R's ggplot2 package v1.0.1 (22).

RESULTS

Clinical Features Associated with 14-Day and Total In-Hospital Mortality in Suspected Sepsis

A total of 485 patients were screened for eligibility, with 139 (28.6%) enrolled. Reasons for exclusion included: not meeting SIRS criteria (n=15); antibiotics broadened more than 4 hours prior to initial biomarker measurement (n=18); ongoing antibiotic treatment for a known infection (n=53); immunosuppression (n=199); DNR status (n=7); cardiopulmonary arrest (n=6); and unavailable or incomplete laboratory samples (n=48).

Of the 139 enrolled subjects, 70 were enrolled from the MICU and 69 from the SICU. Eighteen subjects (12.9%) died within 14 days of enrollment, and 41 subjects (29.5%) died during the index hospital admission.

We evaluated clinical features of the full enrolled cohort, and we compared features between acute mortality (within 14 days of meeting SIRS criteria) and total in-hospital mortality groups. Table 1 shows the clinical features in the entire cohort, and features stratified by 14-day and total in-hospital mortality. Older age, higher APACHE II score on enrollment, non-white race, and cirrhosis were significant risks for 14-day mortality. Older age, higher APACHE II score on enrollment, malignancy, and cirrhosis were significantly associated with total in-hospital mortality.

Biomarker Differences to Discriminate 14-Day and Total In-Hospital Mortality in Suspected Sepsis

We began our evaluation of biomarkers to discriminate risk for acute (14-day) and in-hospital mortality after suspected sepsis by visualizing biomarker change over time via LOESS regression (Figures 1 and 2). For both acute and total in-hospital analyses, SAP and TPA demonstrated the best separation between mortality versus no mortality.

We then compared biomarker values between mortality and no-mortality groups at 4 categorical timepoints. Supplemental Table 1 presents the median (interquartile range) of each biomarker at the time of meeting SIRS criteria, 24-hours, 48-hours, and 72-hours thereafter. For 14-day mortality, Wilcoxon rank-sum testing identified significant differences in FER at a single timepoint; SAP at all timepoints; and baseline, 48-hour, and 72-hour TPA. For total in-hospital mortality, the same approach identified significant differences in SAP and TPA across all timepoints, as well as FER and FIB at two timepoints. Concordant with LOESS regression (Figures 1 and 2), Wilcoxon rank-sum testing highlighted SAP and TPA as the biomarkers that differed most consistently between mortality and no-mortality groups.

To evaluate the ability of individual biomarkers to predict 14-day and total in-hospital mortality, we developed logistic regression models based on each biomarker and compared the model AUROC. The top seven highest AUROC values for 14-day mortality came from SAP or TPA; the top five highest AUROC values for total in-hospital mortality came from SAP or TPA. 72-hour TPA achieved the highest AUROC for 14-day mortality (0.726). 48-hour SAP achieved the highest AUROC for total mortality (0.696). Baseline SAP achieved an AUROC of 0.657 for 14-day mortality, and of 0.608 for total in-hospital mortality. Baseline TPA achieved an AUROC of 0.651 for 14-day mortality, and of 0.680 for total in-hospital mortality. In comparison, a model based on APACHE II score alone achieved an AUROC of 0.694 for 14-day mortality and an AUROC of 0.680 for total in-hospital mortality (14, 18, 19). A model based on an 80% decrease in PCT achieved an AUROC for 14-day mortality of 0.666 and an AUROC for total in-hospital mortality of 0.6028 (9, 20), and baseline PCT achieved an AUROC of 0.574 for 14-day mortality and 0.566 for total in-hospital mortality. Supplemental Table 2 presents the AUROC of logistic regression models for 14-day and total in-hospital mortality based on each biomarker at each timepoint.

Because SAP is produced by the liver and because we observed high mortality in subjects with cirrhosis (Table 1), we performed a sub-group analysis restricted to subjects without cirrhosis to address the possibility that cirrhosis confounds the relationship between SAP and mortality. The restricted cohort, which included 116 of the total 139 subjects, demonstrated significantly lower 48-hour SAP and 72-hour SAP in the mortality versus the no-mortality group (Supplemental Table 3). In the restricted cohort, 48-hour SAP remained the second-best predictor of total in-hospital mortality, with a model AUROC of 0.672. The findings from the restricted cohort thus recapitulated those from the full cohort.

Biomarker Combinations to Improve 14-Day and Total In-Hospital Mortality Prediction

We further evaluated the performance of logistic regression models based on combined biomarkers to predict both 14-day and total in-hospital mortality. Figure 3 displays the

AUROC achieved by each pairwise combination of biomarkers. Each model was evaluated with and without an interaction term. Of 630 unique pairwise combinations, the top 46 AUROCs for 14-day mortality included either SAP, TPA, or both. The top 119 AUROCs for total in-hospital mortality included either SAP, TPA, or both. The combination of 24-hour and 72-hour TPA achieved the best performance predicting 14-day mortality (AUROC 0.761 without interaction term, AUROC 0.765 with interaction term). The combination of 48-hour SAP and 72-hour FER achieved the best performance predicting total in-hospital mortality (AUROC 0.738 without interaction term, AUROC 0.739 with interaction term).

At baseline (time of meeting two SIRS criteria) SAP and TPA achieved an AUROC of 0.657 (with or without interaction term) for 14-day mortality. For total in-hospital mortality, a model based on the same baseline combination achieved an AUROC of 0.689 without interaction term, and an AUROC of 0.693 with interaction term. The combination performed better than baseline SAP or TPA alone, which achieved respective AUROCs of 0.657 and 0.651 for 14-day mortality, 0.608 and 0.680 for total in-hospital mortality.

Differences Between Surgical Intensive Care and Medical Intensive Care

Given the potential for recent surgery to impact biomarkers of inflammation (7, 8), we compared the performance of biomarker combinations to predict 14-day and total in-patient mortality stratified by whether subjects were admitted to the MICU or SICU (Supplemental Figure 1). We found that models incorporating SAP and TPA performed among the best for MICU 14-day mortality, MICU total mortality, and SICU total mortality. However, there was no clear pattern of model performance for SICU 14-day mortality, and FER at all timepoints performed well in the prediction of SICU in-hospital mortality, particularly when combined with SAP or TPA.

DISCUSSION

We evaluated nine biomarkers to predict acute and total in-hospital mortality early in suspected bacterial sepsis, and we found that SAP and TPA had the best predictive performance, both individually and in pairwise combinations. The performance of SAP and TPA matched or exceeded the performance of clinical criteria (APACHE II score) and other, more extensively studied biomarkers (e.g., PCT and CRP) used for diagnosis and mortality prediction in the setting of sepsis.

SAP is a glycoprotein member of the pentraxin superfamily, which serves as a component of the innate immune system, binding to chromatin, apoptotic and necrotic cells, as well as microbes, in a calcium-dependent fashion (23–26). We found SAP consistently reduced in subjects who would experience acute (within 14-days) mortality or in-hospital mortality, relative to surviving subjects. Other pentraxins (particularly pentraxin-3) have been shown to predict mortality in the setting of infection and sepsis (27, 28), but to the best of our knowledge this is the first report of SAP’s utility in predicting mortality associated with sepsis.

TPA is a serine protease produced by endothelial cells to catalyze the conversion of plasminogen to plasmin. We found TPA consistently elevated in subjects who would

experience 14-day or in-hospital mortality. TPA has previously been shown to increase in the setting of sepsis (29), and its level has been correlated with clinical outcomes in hemorrhagic fever (30), but it has not previously been evaluated as a biomarker to predict sepsis-associated mortality.

The predictive performance of SAP and TPA was striking in that it exceeded the performance of PCT, which has been studied far more extensively. Single, absolute PCT levels have exhibited variable performance in the prediction of sepsis-associated mortality. PCT change has shown more promise as a prognostic tool and has been used successfully as the basis for antibiotic stewardship interventions in sepsis (9, 31–33). As shown above, SAP and TPA alone and in combination outperformed absolute PCT in our cohort. Furthermore, a model based on baseline SAP and TPA values exceeded the performance of PCT change (80% decrease) for the prediction of total in-hospital mortality.

The predictive performance of SAP and TPA also matched the performance of the APACHE II score, which incorporates clinical and common laboratory measures and is well validated as a tool to predict the mortality of critically ill patients (14, 18, 19). In our cohort, the APACHE II score achieved AUROC of 0.680 for total in-hospital mortality, versus the AUROC of 0.693 achieved by baseline SAP and TPA. Our findings suggest that serum SAP and TPA, when combined with the clinical SIRS criteria that defined eligibility for enrollment, may prove a valuable tool to predict mortality in sepsis.

Several limitations must be noted: (1) The study was performed at a single center, and (2) enrollment excluded immunocompromised patients, thus limiting its external validity. In addition, (3) there was significant heterogeneity among the subjects enrolled, and (4) we did not assess the appropriateness of antibiotic therapy. Specifically, we found that the performance of SAP and TPA was greatest among subjects in the MICU, and FER performed particularly well predicting total in-hospital mortality among subjects in the SICU. The difference in the predictive validity of inflammatory biomarkers between patients who have or have not experienced surgery is an important target for future investigation, as is the difference between patients who are or are not prescribed appropriate antibiotic therapy.

Further limitations include (5) the use of SIRS criteria, which are no longer recommended for the diagnosis of sepsis, to determine eligibility for enrollment, and (6) the possibility that liver disease confounded that observed association between SAP and mortality. Given that SAP is produced by the liver, the observed association between low SAP and increased mortality risk may have been driven by subjects with cirrhosis, who had high mortality in this cohort (Table 1). As detailed above, we repeated analyses excluding all subjects with cirrhosis, and still found significant differences in 48-hour SAP and 72-hour SAP between mortality and no-mortality groups. Furthermore, 48-hour SAP remained the second-best predictor of total in-hospital mortality in the restricted cohort. Finally, it must be noted that (7) the combination of SAP and TPA performed comparably to APACHE II and SOFA but was not clearly superior.

Despite the above limitations, the finding that, when assayed in subjects who meet SIRS criteria, SAP and TPA have predictive validity for 14-day and total in-hospital mortality, merits close follow-up. Models developed from SAP and TPA performed as well or better than more established clinical and biomarker-based tools in this cohort. It is essential to better characterize the dysregulated immune response that defines sepsis and its attributable mortality. The finding that SAP and TPA predict mortality risk early in the course of suspected bacterial sepsis may contribute to improved models of sepsis-related immune dysregulation, novel risk stratification strategies, and personalized antibiotic-treatment strategies.

CONCLUSIONS

SAP and TPA together provide good predictive ability for both 14-day and total in-hospital mortality among subjects with suspected sepsis. The performance of SAP and TPA in this cohort rivals established clinical and biomarker-based tools for mortality risk stratification in sepsis. Further study should be directed towards validating SAP and TPA for sepsis prognosis, evaluating SAP and TPA for sepsis diagnosis, better defining the differences in biomarker performance between subjects with and without recent surgery, and assessing the additive value of SAP or TPA in combination with predictive clinical features.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the CDC Healthcare-Associated Infection Prevention Epicenters Program (U54 CK000485), of which EL is principal investigator. In addition, BJK and JHH were supported by career development awards from the National Institute of Allergy and Infectious Diseases (K23 AI121485 and K01 AI103028, respectively). The funding bodies had no role in the study design; in the collection, analysis, or interpretation of data; or in manuscript preparation. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

FUNDING: This work was supported by the CDC Healthcare-Associated Infection Prevention Epicenters Program (U54 CK000485), of which EL is principal investigator. In addition, BJK and JHH were supported by career development awards from the National Institute of Allergy and Infectious Diseases (K23 AI121485 and K01 AI103028, respectively). The funding bodies had no role in the study design; in the collection, analysis, or interpretation of data; or in manuscript preparation.

Copyright form disclosure: Drs. Kelly, X. Han, and J.H. Han received support for article research from the National Institutes of Health (NIH). Drs. Lautenbach and Nachamkin received support for article research from the Centers for Disease Control (CDC). Dr. Coffin's institution received funding from the CDC, NIH, and Agency for Healthcare Research and Quality, and she received funding from SHEA/IDSA (participation on working group and medical legal consulting). Dr. Bilker's institution received funding from the NIH, and he disclosed government work.

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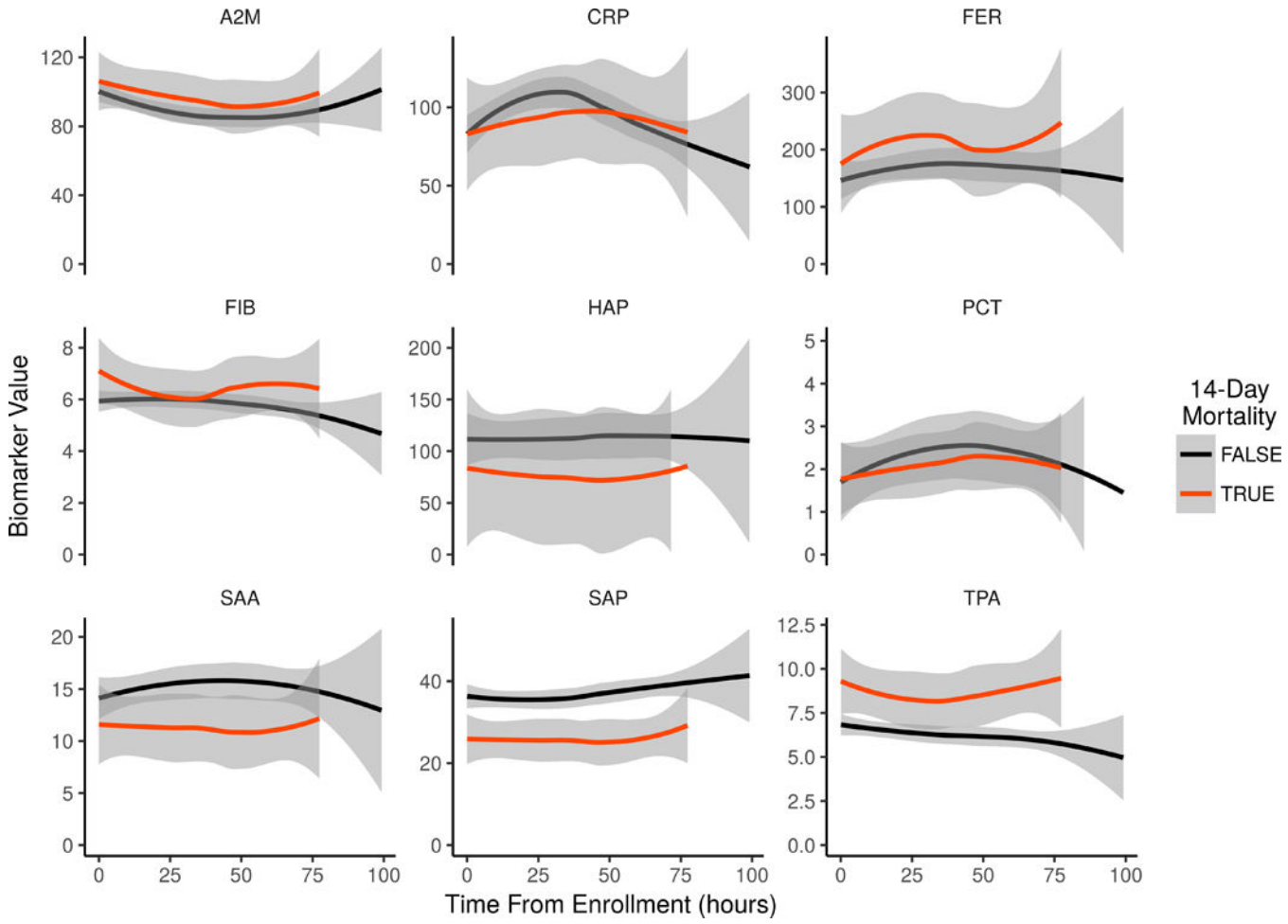

Figure 1. Longitudinal biomarker change from time of suspected sepsis and 14-day mortality

LOESS regression was performed for the 9 biomarkers using the actual time of sample collection, with fitting performed by a redescending M-estimator (Tukey's biweight function) to minimize the impact of outliers. Biomarker values were compared between acute 14-day mortality groups. The line indicates the point estimate at each timepoint, and the grey shading indicates the 95% confidence interval. In both analyses, SAP and TPA demonstrated the best separation between mortality versus no mortality.

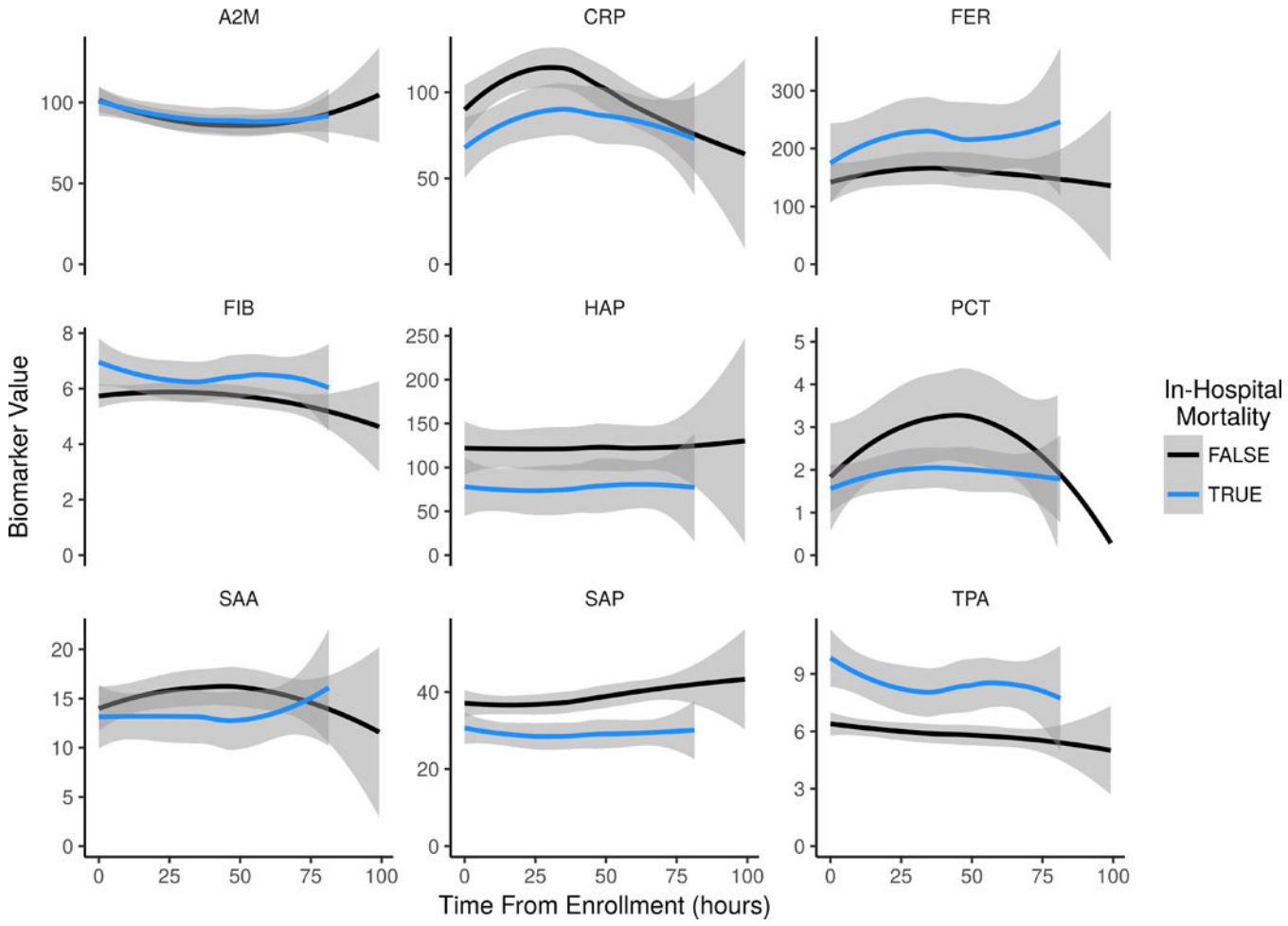

Figure 2. Longitudinal biomarker change from time of suspected sepsis and in-hospital mortality

LOESS regression was performed for the 9 biomarkers using the actual time of sample collection, with fitting performed by a redescending M-estimator (Tukey's biweight function) to minimize the impact of outliers. Biomarker values were compared between total in-hospital mortality groups. The line indicates the point estimate at each timepoint, and the grey shading indicates the 95% confidence interval. In both analyses, SAP and TPA demonstrated the best separation between mortality versus no mortality.

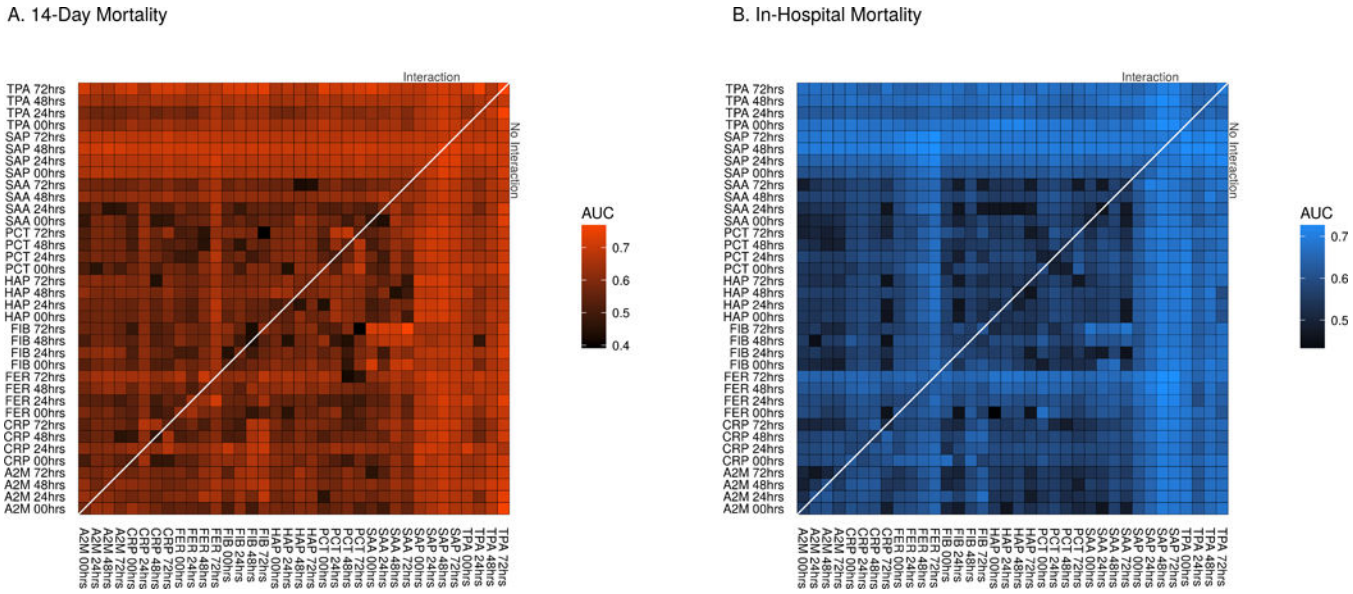

Figure 3. Biomarker combinations to discriminate acute and total in-hospital mortality

The color intensity shows the AUROC achieved by logistic regression models based on each pairwise combination of biomarkers. (A) The intensity of orange shows the AUROC for acute (14-day) mortality. (B) The intensity of blue shows the AUROC for total in-hospital mortality. Each model was evaluated with an interaction term (upper triangle) and without an interaction term (lower triangle). The matrix diagonal depicts the AUROC for single biomarkers. Combinations with SAP and TPA improved the AUROCs for single biomarkers.

Table 1

Clinical features associated with acute and total in-hospital mortality in suspected sepsis.

	All Subjects	Acute 14-Day Mortality			Total In-Hospital Mortality		
		Yes	No	p-value	Yes	No	p-value
Subject Number	**139**	**18**	**121**		**41**	**98**	
MICU	70 (50.4%)	11 (61.1%)	59 (48.8%)	0.450	24 (58.5%)	46 (46.9%)	0.265
SICU	69 (49.6%)	7 (38.9%)	62 (51.2%)	0.450	17 (41.5%)	52 (53.1%)	0.265
Age (years)	62.1 (23.2)	70.2 (24)	60.6 (26)	0.022 *	70.4 (17)	58.1 (26.7)	<0.001 *
APACHE II	23 (9.5)	25 (9.5)	21 (10)	0.009 *	25 (10.5)	21 (9)	0.001 *
Male Sex	51 (36.7%)	9 (50%)	42 (34.7%)	0.294	13 (31.7%)	38 (38.8%)	0.563
Black	48 (39.7%)	3 (16.7%)	48 (39.7%)	0.069	10 (24.4%)	41 (41.8%)	0.056
Asian	6 (4.3%)	0 (0%)	6 (5%)	1.000	3 (7.3%)	3 (3.1%)	0.360
White	64 (46%)	14 (77.8%)	50 (41.3%)	0.005 *	23 (56.1%)	41 (41.8%)	0.139
Unknown Race	18 (12.9%)	1 (5.6%)	17 (14%)	0.468	5 (12.2%)	13 (13.3%)	1.000
Non-white Race	63 (45.3%)	3 (16.7%)	60 (49.6%)	0.010 *	15 (36.6%)	48 (49%)	0.196
Malignancy	35 (25.2%)	6 (33.3%)	29 (24%)	0.393	16 (39%)	19 (19.4%)	0.019 *
Diabetes Mellitus	41 (29.5%)	3 (16.7%)	38 (31.4%)	0.272	10 (24.4%)	31 (31.6%)	0.423
CHF	9 (6.5%)	0 (0%)	9 (7.4%)	0.605	4 (9.8%)	5 (5.1%)	0.449
Lung Disease	15 (10.8%)	1 (5.6%)	14 (11.6%)	0.692	6 (14.6%)	9 (9.2%)	0.375
Cirrhosis	23 (16.5%)	9 (50%)	14 (11.6%)	<0.001 *	14 (34.1%)	9 (9.2%)	<0.001 *
Renal Insufficiency	33 (23.7%)	6 (33.3%)	27 (22.3%)	0.373	13 (31.7%)	20 (20.4%)	0.190
Hemodialysis	8 (5.8%)	2 (11.1%)	6 (5%)	0.277	4 (9.8%)	4 (4.1%)	0.235
Bacteremia	89 (64%)	14 (77.8%)	75 (62%)	0.292	30 (73.2%)	59 (60.2%)	0.177

For continuous variables, median value and (interquartile range) are shown; for categorical variables, subject number and (percentage of total subjects in group) are shown. P-values are based on the Wilcoxon rank sum test for continuous variables, Fisher's exact test for categorical variables. APACHE II score was calculable for 127 of the 139 enrolled subjects (missing blood gas for 12 subjects); missing data was excluded from APACHE II analysis.

* Significant p-values are highlighted.