Ardabili *et al. Clinical Proteomics* (2026) 23:22
https://doi.org/10.1186/s12014-026-09597-1

Clinical Proteomics

RESEARCH Open Access

Clinic-first sepsis recognition in the ICU: a proteomics-guided, parsimonious model with independent validation

A. Khaleghi Ardabili[1,2], S. Rice[1], A. Samuelsen[1], Ruth-Ann Brown[3] and Anthony S. Bonavia[2,3,4*]

Abstract

Background Sepsis recognition in the ICU remains variable and relies on consensus clinical criteria rather than biomarker-defined rules. Routine laboratory and physiologic data often overlap with noninfectious critical illness, obscuring early identification. We evaluated whether discovery proteomics could prioritize a concise set of routinely obtainable clinical variables, yielding a practical, clinic-first model that distinguishes sepsis from other critical illness.

Methods In a prospective, single-center pilot at an academic medical center, we enrolled adults within 48 h of critical illness onset (sepsis and non-sepsis comparators). Plasma proteomics by LC-MS/MS with diaPASEF identified proteins differentiating groups and guided selection of proteome-enriched routine variables for modeling. A Random Forest classifier was trained in a Discovery cohort ($n = 55$) and evaluated in an independent Validation cohort ($n = 59$), with prespecified attention to discrimination, parsimony, and feasibility for electronic health record (EHR) deployment.

Results Twelve plasma proteins differed between groups at FDR < 0.10, supporting biological separation. A parsimonious model using routine predictors ± CCL3 achieved AUC 0.73 in Discovery and AUC 0.76 in the independent Validation cohort. Recursive feature elimination demonstrated a parsimony plateau at ~ 9 variables; beyond this threshold, further reduction degraded accuracy. Notably, blood urea nitrogen, CCL3 (measured by multiplex immunoassay), and creatinine were the final features retained before performance declined, aligning with renal stress and inflammatory signaling. Figures present ROC curves and the parsimony profile, highlighting a minimal variable set compatible with typical ICU workflows and decision-support systems.

Conclusions A proteomics-informed, clinic-first strategy produced a parsimonious set of routine variables that discriminated sepsis from other ICU critical illness with clinically meaningful accuracy and an immediately actionable footprint. Because most predictors are routinely captured in the EHR, the model is EHR-compatible; CCL3 is readily measurable on standard immunoassay platforms if adopted locally. These findings justify multicenter studies to confirm generalizability and calibration, evaluate real-time integration into ICU workflows, and test whether an early recognition adjunct improves timeliness of sepsis care and patient outcomes.

Keywords Sepsis, Pilot study, Proteomics, Machine learning, Feasibility, Random forest

*Correspondence:
Anthony S. Bonavia
abonavia@pennstatehealth.psu.edu
[1]Penn State College of Medicine, Hershey, PA, USA
[2]Penn State Critical Illness and Sepsis Research Center (CISRC), Hershey, PA, USA
[3]Department of Anesthesiology and Perioperative Medicine, Penn State Hershey Medical Center, 500 University Dr, Mailbox H-187, Hershey 17033, PA, USA
[4]Division of Critical Care Medicine, Department of Anesthesiology and Perioperative Medicine, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

Background

Sepsis is a clinical syndrome characterized by organ dysfunction resulting from a dysregulated host immune response to infection. Despite decades of investigation, the clinical and immunologic heterogeneity of sepsis has prevented the identification of a single biomarker that is pathognomonic for the condition. Consequently, recognition remains clinical and is based on a consensus definition [1].

Organ dysfunction in sepsis is currently operationalized using the Sequential (or Sepsis-Related) Organ Failure Assessment (SOFA) score, which pre-dates the current sepsis definitions and was not originally developed as a recognition tool for this syndrome [2]. The SOFA score is a composite measure of dysfunction across six, equally weighted organ systems: respiratory, coagulation, hepatic, cardiovascular, central nervous system, and renal. It is designed to be easily used in the clinical setting, facilitating the rapid identification of septic patients for timely medical management. Under Sepsis-3 criteria, sepsis is defined by suspected infection and an increase in SOFA score of two points or more from baseline, independent of the organ system(s) involved.

We asked whether a proteomics-informed machine-learning approach could prioritize a concise, clinically accessible variable set for sepsis recognition. We integrated high-dimensional proteomics with established clinical measures (SOFA components plus routinely obtained laboratories, physiologic parameters, and biomarkers) to capture non-linear associations that conventional statistics might miss. Related work by Pimienta et al. [3] identified a functionally connected plasma protein network in murine sepsis using quantitative mass spectrometry, supporting our discovery-to-clinic strategy. Because comprehensive proteomic profiling is costly and impractical at the bedside, we leveraged proteomic signatures distinguishing sepsis from other critical illness to identify rapid, clinically measurable variables in a Discovery cohort, then evaluated their predictive value in an independent Validation cohort.

Methods

Study design and participants

This prospective, single-center pilot was conducted between October 2021 and July 2024 under IRB approval (Penn State University Human Subjects Protection Office/Institutional Review Board, protocol #15328, 7/30/2020). We adhered to STROBE [4] recommendations for cohort studies (Supplementary Materials). We used a prespecified Discovery/Validation split with feasibility-based accrual over the study period. We report discrimination with 95% confidence intervals and parsimony profiles to provide effect-size estimates that guide sample-size planning for a forthcoming multicenter validation.

Eligibility

Eligible ICU adults with critical illness and suspected sepsis were identified by an electronic health record (EHR)-based modified early warning system (MEWS) algorithm [5] and confirmed by two clinicians. Adults (≥ 18 years) enrolled within 48 h of developing critical illness were included. Critical illness required respiratory support or vasopressors. Sepsis diagnosis followed Sepsis-3 criteria (SOFA increase ≥ 2 with suspected/confirmed infection) [5, 6]. Exclusions were major immune-modifying conditions (active hematologic malignancy, immunosuppressive therapy, chronic corticosteroids unless sepsis-related, chemotherapy/radiation within the prior 30 days, HIV with low CD4, solid organ transplant, autoimmune diseases).

Data collection

Clinical data (demographics, APACHE II [7–9], Charlson index [10], SOFA score (on day 1 and maximum score), laboratory measurements, physiologic parameters, infection characteristics) were drawn from the institutional Critical Illness Biorepository (Supplementary Table S1). Shock was defined as lactate > 2 mmol/L after adequate fluids, with concurrent vasopressor use.

Sample collection and processing

Whole venous blood was collected in EDTA tubes within 4 h of the clinical enrollment window. Plasma was isolated from whole blood by centrifugation (2000 xg for 10 min at 4 °C), then frozen at -80 °C. Plasma was thawed and processed at a later date in two, matched batches. The first batch of plasma samples was used to measure concentrations of common inflammatory markers (CCL3, CCL7, IL-10, PD-L1, CXCL9, CXCL10, FasL, TRAIL, IL-8, IL-18, leptin, TNFR1, IFNg, IL-6, TNF) were measured on the Proteinsimple (Bio-techne) multiplexing platform. These analytes were treated as clinically measured variables distinct from proteomic measurements.

The second batch of matched plasma samples from each patient was thawed in the presence of protease inhibitors. Proteins were extracted and digested from these samples using a KingFisher Flex magnetic-bead workflow (see Supplementary Methods), before undergoing proteomic analysis as detailed below.

Proteomic analysis

Proteins were analyzed by liquid chromatography-mass spectrometry (LC-MS) using data-independent acquisition parallel accumulation-serial fragmentation (diaPASEF) on a timsTOF platform (see Supplementary Methods). Raw files were then processed using DIA-NN

(a neural-network-based software platform for DIA proteomics data processing; Aptila Biotech GmbH, Berlin, Germany), which performs automated alignment and correction of chromatographic retention time and ion-mobility drift across samples, improving peptide identification consistency and quantitative reproducibility. In practical terms, this alignment step ensures that the same peptides are consistently identified and quantified across samples despite minor run-to-run variability inherent to high-throughput LC-MS experiments.

All plasma was processed in a single batch with randomized plate positions and equine-myoglobin QC spike-ins; dia-PASEF/DIA-NN alignment-controlled retention-time and ion-mobility variance. Proteomic tables were filtered to ≥ 75% non-missing globally and per group, followed by k-nearest-neighbor imputation prior to differential testing. Differentially expressed proteins between sepsis and non-sepsis groups were identified using Ingenuity Pathway Analysis (QIAGEN Silicon Valley, Redwood City, CA).

Outcomes

The primary pilot outcomes were feasibility, assessed as completeness of clinical and proteomic data (missingness), and adherence to prespecified proteome quality-control metrics. The key analytic outcome was model discrimination, quantified by the area under the receiver-operating characteristic curve (AUC) for the proteome-informed clinical model in the Discovery cohort and evaluated in the independent Validation cohort. Secondary outcomes focused on model parsimony, examined using recursive feature elimination (RFE) to identify the smallest predictor set that maintained stable performance.

Statistical analysis and machine learning

In Discovery (n = 55), Random-Forest models assessed whether differentially expressed proteins could predict clinical variables. We used an FDR threshold < 0.1 at the protein level to balance false discovery risk against type II error (signal loss) in this discovery-oriented proteomics screen. This choice follows common practice in exploratory, high-dimensional proteomics when the goal is signal prioritization rather than definitive biomarker confirmation. Importantly, protein intensities were not used directly as model inputs; instead, proteomic signals were used to prioritize clinically obtainable variables, which were subsequently evaluated in an independent validation cohort, mitigating downstream false-positive risk [11–13].

For visualization in volcano plots, adjusted p-values were transformed as -log10(adjusted p-value), such that higher values correspond to greater statistical significance after multiple-testing correction.

Variables with proteomic support were used to predict sepsis and then evaluated in an independent Validation cohort (n = 59, Fig. 1). Discovery performance used leave-one-out cross-validation (LOOCV) with 10 repetitions; Validation performance was estimated by 10 repeated applications at the fixed Youden J threshold learned in Discovery. RFE iteratively removed least-important variables to examine parsimony.

Features with high missingness (procalcitonin 73%, CRP 63%, infection type 29%) were excluded a priori; remaining clinical variables were imputed with MICE (predictive mean matching; m = 5; 50 iterations, Supplementary Table S1), stratified by cohort. Proteomic matrices used KNN imputation after filtering as above.

Results

Patient characteristics

Discovery included 38 sepsis and 17 critically ill but non-septic (CINS) patients; Validation included 31 different sepsis and 28 CINS patients with comparable acute illness severity (APACHE II) and sex distribution (Table 1).

Proteome depth and quality

LC-MS detected 696 protein groups; after filtering, 507 proteins were consistently quantified. In 90% of samples, median CV was < 20%, supporting feasibility of batched LC-MS in an ICU pipeline. These metrics, together with the single-batch randomized layout and QC spike-ins, suggest minimal residual batch effect (Supplementary Fig. S1).

Differential expression

In exploratory analyses, 12 proteins differed between sepsis and CINS with clear group separation on clustering and expected acute phase/inflammatory patterns (Fig. 2; Table 2). Many of the differentially expressed proteins identified (e.g., CRP, SAA1/2, LCN2, LBP) are well-established markers of inflammation and sepsis, supporting the biological validity of the proteomic analysis rather than representing novel biomarker discovery.

Sepsis classification models

Using a clinic-first, proteome-informed set of 26 clinical/laboratory features (Supplementary Table S2), mean AUCs were 0.73 ± 0.01 (Discovery; repeated LOOCV) and 0.76 ± 0.01 (independent Validation, Fig. 3). Creatinine was the most strongly associated with the sepsis proteomic signature (R^2=0.558), followed by PD-L1 (0.387) and IL-8 (0.363).

We selected Random Forest modeling given its robustness to non-linearities and interactions, tolerance to correlated inputs, and straightforward variable importance profiles for RFE. In exploratory checks we also fit gradient-boosted trees (XGBoost) and a linear SVM using

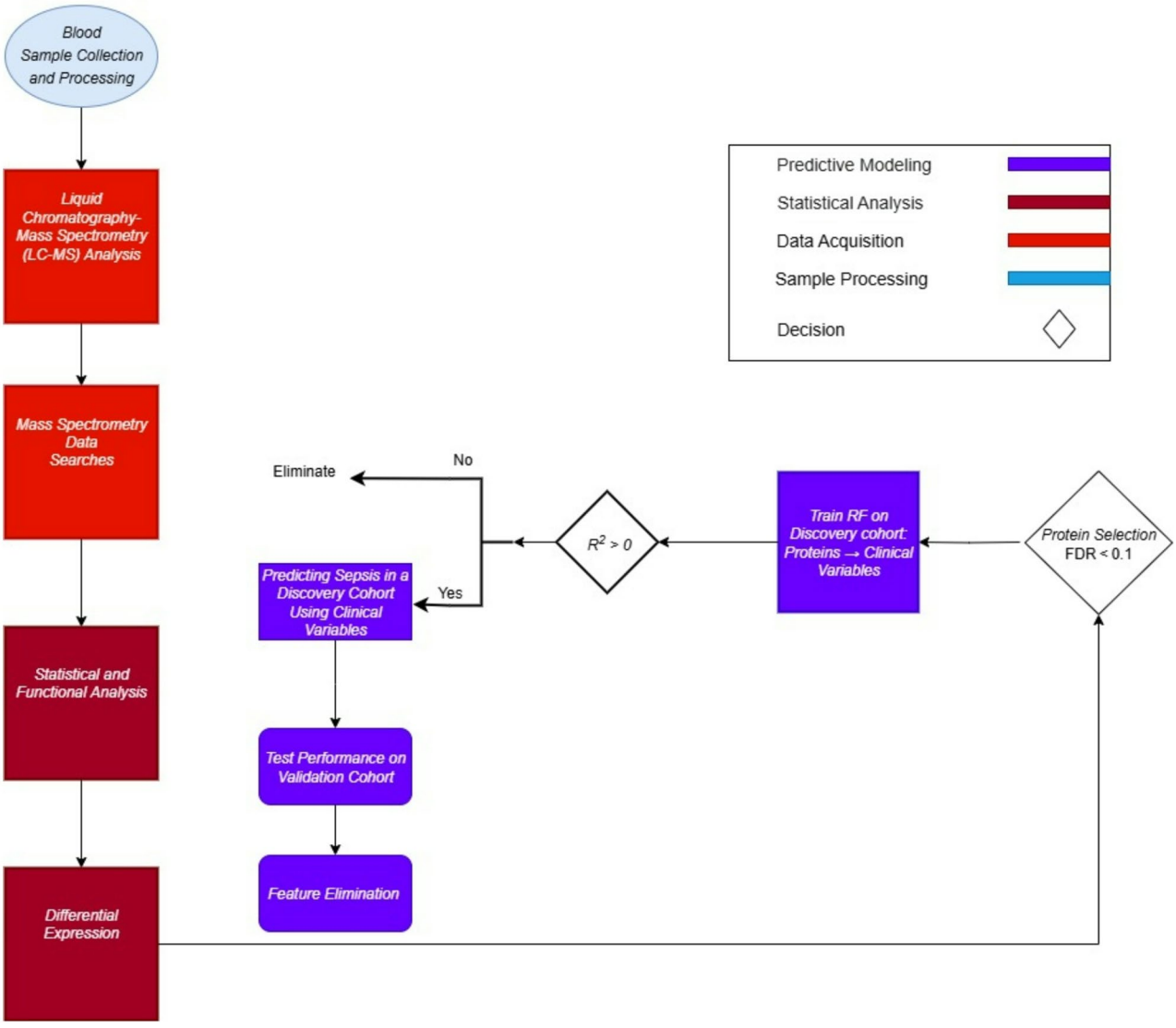

Fig. 1 Flow diagram summarizing the proteomics-informed predictive modeling approach. Blood samples from critically ill patients underwent sample processing and proteomic data acquisition using Liquid Chromatography-Mass Spectrometry (LC-MS). Proteins were identified and quantified through mass spectrometry data searches. Subsequent statistical and functional analyses identified differentially expressed proteins between sepsis and non-sepsis critical illness groups. These proteins (FDR < 0.1) were then used in Random Forest predictive modeling to predict clinical variables in a Discovery cohort. Clinical variables successfully predicted by proteomic profiles ($R^2 > 0$) were retained and subsequently used to predict sepsis status in an independent Validation cohort. Recursive Feature Elimination further identified a minimal set of the most predictive clinical variables

the same feature set and CV scheme; results were qualitatively similar (AUC within < ΔAUC range > of Random Forest). We proceeded with Random Forest to maintain a single, transparent pipeline across discovery, validation, and parsimony analyses.

Feature minimization

Recursive feature elimination (RFE) showed a performance plateau ~ 0.75 with ≥ 9 variables, peaking at 0.78; accuracy declined below seven variables. Blood urea nitrogen (BUN), chemokine ligand 3 (CCL3), and creatinine (Cr) were the last features retained before decline, underscoring the diagnostic influence of renal function and inflammatory signaling (Fig. 4; Supplementary Table S3).

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Discussion

Our analysis identifies a proteomic signature distinguishing sepsis from other critical illness that maps onto routine clinical measures. Among bedside variables, creatinine showed the strongest proteome-guided association and, with BUN and CCL3, remained in the final minimal set, consistent with the central role of kidney

Table 1 Comparison between Discovery and Validation Cohorts

	Discovery cohort (*n* = 55)	**Validation cohort (*n* = 59)**
Sepsis (*n*, %)	40 (71.4%)	31 (52.5%)
Age, years	70.5 [60.0, 76.0]	70.0 [61.0, 77.5]
APACHE II score	22.9 ± 8.0	21.1 ± 6.7
Lactate, plasma (mmol/dl)	3.1 [2.0, 5.0]	2.10 [0.8, 3.9]
Shock (n, %)	29 (51.8%)	50 (84.7%)
Absolute lymphocyte count (K/μl)	0.75 [0.46, 1.06]	0.99 [0.78, 1.15]
SOFA (day 1 of illness)	8.0 [6.8, 11.0]	6.0 [4.5, 10.0]
SOFA (maximum score)	9.0 [6.8, 11.0]	7.0 [5.0, 10.5]
CCL3, plasma (pg/ml)	99.4 [54.6, 133.0]	55.0 [33.6, 78.1]
CXCL10, plasma (pg/ml)	379.0 [164.0, 767.0]	213.0 [118.5, 428.0]
TNFR1, plasma (ng/ml)	5.3 [3.6, 8.6]	4.0 [2.2, 7.9]
Temperature, deg C	36.3 [36.0, 38.2]	36.2 [35.9, 38.1]
Diastolic blood pressure, mm Hg	44.0 [38.0, 49.0]	46.00 [41.0, 51.0]
Mechanically ventilated (n, %)	23 (41.1%)	31 (52.5%)
Glasgow Coma Score	11.5 [6.8, 15.0]	11.0 [7.0, 15.0]
LPS-stimulated IL-6 production (ng/ml)	115.8 [39.0, 328.5]	348.9 [188.6, 743.0]
LPS-stimulated TNF production (ng/ml)	43.1 [14.9, 88.5]	76.2 [35.5, 147.9]
BUN, plasma (mg/dl)	29.0 [18.0, 47.8]	25.0 [16.0, 43.5]
Albumin, plasma (g/dl)	2.79 ± 0.57	3.03 ± 0.68
Total bilirubin, plasma (mg/dl)	1.20 [0.60, 2.08]	0.90 [0.40, 1.60]
Creatinine, plasma (mg/dl)	1.48 [1.01, 2.35]	1.46 [0.86, 2.58]
Hematocrit, %	31.4 ± 5.5	31.5 ± 6.1

dysfunction in sepsis [14, 15]. These findings suggest that readily available renal indices, complemented by targeted immune-inflammatory signals, may capture much of the information conveyed by costly and time-consuming, higher-dimensional proteomic analysis. Because the model relies primarily on routine blood analysis, it is readily implementable; adding CCL3 is feasible where institutions elect to enable a simple immunoassay.

Similarly, declining absolute lymphocyte counts and rising inflammatory chemokines (IL-18) converged in our parsimonious nine-variable model, echoing reports that lymphopenia and chemokine storms independently portend worse outcomes [16]. By integrating these easily obtainable laboratory tests with organ-specific scores (e.g., SOFA score), clinicians may additionally capture the immune-metabolic state signaled by proteomic assays without needing them at the bedside. Furthermore, a proteomics-informed, clinic-first strategy can refine existing scores by selectively re-weighting routinely collected predictors and is well suited for EHR-embedded early recognition and risk estimation. Analogous to lactate's role in cardiovascular scoring, assigning greater influence to creatinine and BUN within renal components may better capture underlying biology while preserving workflow simplicity. In this pilot, a classifier using routine EHR variables ± CCL3 achieved AUCs of 0.73 (Discovery) and 0.76 (Validation), indicating clinically useful discrimination with minimal additional testing.

CCL3 (macrophage inflammatory protein-1α) has been extensively studied in infection and sepsis [17, 18], with prior work demonstrating its role in leukocyte recruitment, endothelial permeability, and inflammatory injury in both experimental models and human disease. Accordingly, we do not propose CCL3 as a novel sepsis biomarker. Rather, its relevance in the present study arises from its emergence as a parsimonious, clinically measurable variable within a proteomics-informed modeling framework. The novelty of this work lies in demonstrating how discovery proteomics can be used to *prioritize and re-weight existing clinical variables*, rather than introduce new assays, to support early sepsis recognition using EHR-deployable models with independent validation.

Among the proteins identified, insulin-like growth factor binding protein 6 (IGFBP6) is notable because its role in sepsis has only recently been described [19]. It has been shown to be an active mediator of immune dysfunction in sepsis, with experimental evidence demonstrating that IGFBP6 exacerbates infection and organ injury through suppression of macrophage recruitment and antibacterial responses. In this clinic-first framework, IGFBP6 emerges as a supportive inflammatory signal that complements routine laboratory data and illustrates the translational value of proteomics for improving early sepsis risk stratification.

Study limitations include single-center design, modest sample size, with feasibility-based accrual over the study

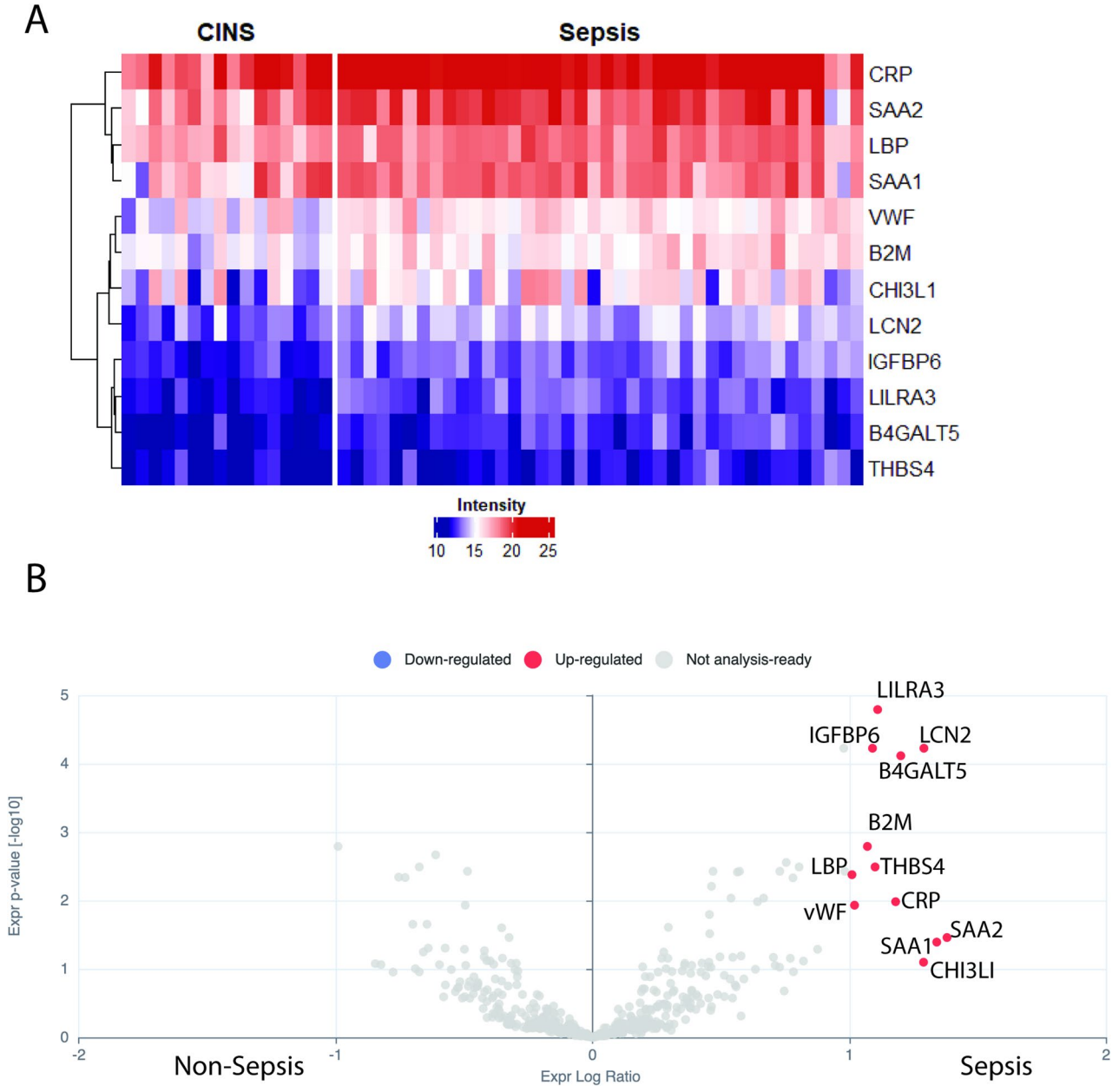

Fig. 2 The Plasma Proteome Signature Associated with Acute Sepsis. (**A**) Heat map with hierarchical clustering of 55 Discovery-cohort plasma samples (columns) and 12 differentially expressed proteins (rows; FDR < 0.1). Log2-scaled intensities are z-standardized per protein. Sepsis samples exhibit uniformly higher expression (red) of acute-phase proteins (e.g., SAA1/2, CRP) and immune mediators (LCN2, LILRA3) relative to critical-illness non-sepsis (CINS) controls. (**B**) Volcano plot of differential plasma protein expression. Each dot represents a quantified protein ($n = 507$). The x-axis shows log2 fold-change (sepsis vs. CINS); the y-axis shows –log10 of the false discovery rate–adjusted p-value, a standard transformation used to visualize statistical significance after multiple-testing correction. Proteins meeting FDR < 0.1 and |log2-fold change| > 1 are colored red (up-regulated). B2M = beta-2-microglobulin, B4GALT = beta-1,4-galactosyltransferase 5, CHI3L1 = chitinase 3 like 1, CRP = C-reactive protein, IGFBP6 = insulin-like growth factor binding protein 6, LBP = liposaccharide-binding protein, LCN2 = lipocalin 2, LILRA3 = leukocyte immunoglobulin-like receptor 3, SAA1 = serum amyloid A1, SAA2 = serum amyloid A2, THBS4 = thrombospondin 4, VWF = Von Willebrand Factor

period, exclusion of CRP and procalcitonin due to missingness, and potential circularity from Sepsis-3 (though the final model used independent variables). Consistent with the exploratory aim of the proteomic screen, we adopted a permissive FDR threshold to reduce the risk of discarding biologically relevant signals. However, all downstream modeling and performance estimates were evaluated on clinical variables in an independent cohort, providing protection against overfitting and false discovery inflation.

Imputation bias was mitigated by excluding highly missing features, using MICE with predictive mean

Table 2 Protein expression levels in critically ill, septic patients relative to those in non-septic patients

Protein ID	Gene name	Log2-fold change	*P*-value	Bonferroni-adjusted *P*-value
P0DJI9	SAA2	1.38	0.0026	0.035
P0DJI8	SAA1	1.34	0.0031	0.041
P36222	CHI3L1	1.29	0.0097	0.082
P80188	LCN2	1.29	4.3×10^{-7}	6.0×10^{-5}
O43286	B4GALT5	1.20	7.6×10^{-7}	7.7×10^{-5}
P02741	CRP	1.18	5.8×10^{-4}	0.010
Q8N6C8	LILRA3	1.11	3.2×10^{-8}	1.6×10^{-5}
P35443	THBS4	1.10	7.7×10^{-5}	0.0032
P24592	IGFBP6	1.09	2.5×10^{-7}	6.0×10^{-5}
P61769	B2M	1.07	2.2×10^{-5}	0.0016
P04275	VWF	1.02	7.0×10^{-4}	0.012
P18428	LBP	1.01	1.7×10^{-4}	0.0042

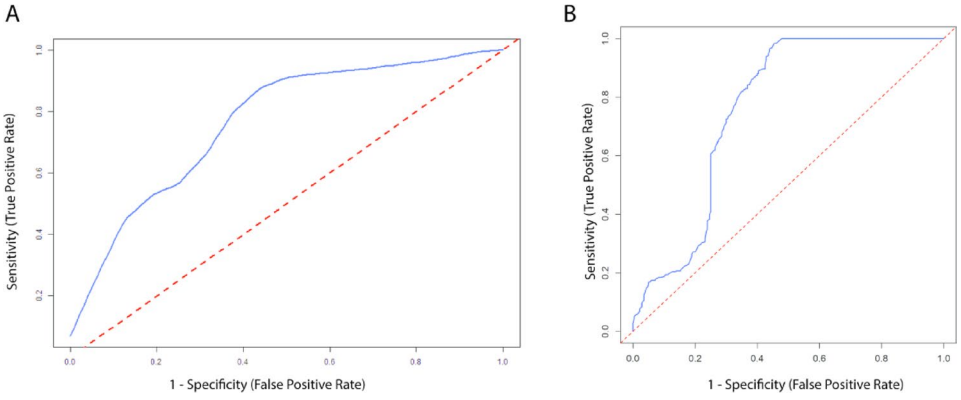

Fig. 3 Receiver-operating Characteristic Curves for Sepsis Recognition. (**A**) Discovery cohort - The Random Forest model trained on 26 proteome-enriched clinical/laboratory features (Supplementary Table S2) was evaluated with leave-one-out cross-validation (10 repeats). Mean area under the ROC curve (AUC) = 0.73; dashed line indicates chance (AUC = 0.50). (**B**) Validation cohort - The model and fixed decision threshold derived from the Discovery cohort were applied to 59 new patients. Mean AUC = 0.76 over 10 repeated runs, demonstrating robust generalizability. Discovery ($n = 55$): AUC 0.73 ± 0.01; Validation ($n = 59$): AUC 0.76 ± 0.01; dashed line indicates chance (AUC = 0.50).

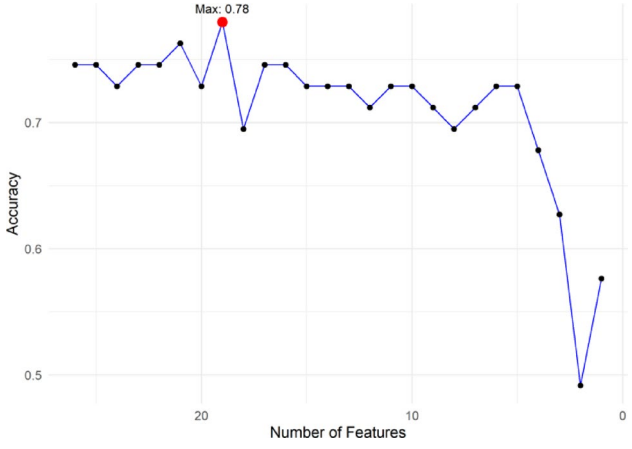

Fig. 4 Recursive Feature Elimination (RFE) Performance Curve. Cross-validated classification accuracy (y-axis) as a function of the number of retained clinical variables (x-axis). Peak accuracy is achieved with nine variables, beyond which performance plateaus, indicating an optimal minimal feature set for rapid bedside implementation. Nine variables marked the practical parsimony plateau suitable for EHR-ready implementation. Routine predictors are EHR-compatible; inclusion of CCL3 is a feasible single-analyte addition where available

matching, and confirming similar rankings in complete-case analyses. Results were similar in complete-case analyses, supporting robustness to missingness patterns. Ongoing work will test organ-specific weighting against standard SOFA and selected biomarker panels, evaluate calibration and net clinical benefit, and assess generalizability across settings and case-mix.

Conclusions

A concise set of routine variables, centered on renal function (creatinine, BUN) and supported by inflammatory mediators (e.g., CCL3, IL-18), captures key elements of the sepsis-associated proteomic signal and provides clinically meaningful discrimination between sepsis and other causes of critical illness. Translating omics insights into selective re-weighting of existing frameworks offers a practical path to earlier recognition and more informative risk assessment without additional assays. Future work should verify performance across diverse populations, compare against biomarker panels, and integrate

these models within EHR workflows to support timely, consistent bedside decisions.

Abbreviations

ALC	Absolute lymphocyte count
AMC	Absolute monocyte count
APACHE II	Acute physiology and chronic health evaluation II
AUC	Area under the receiver operating characteristic curve
BUN	Blood urea nitrogen
CCL3	Chemokine (C-C motif) ligand 3
CINS	Critically ill, non-sepsis
CRP	C-reactive protein
CV	Coefficient of variation
DIA-NN	DIA-NN proteomics analysis software (for DIA data)
dia-PASEF	Data-independent acquisition parallel accumulation–serial fragmentation
EDTA	Ethylenediaminetetraacetic acid
EHR	Electronic health record
FDR	False discovery rate
ICU	Intensive care unit
IGFBP6	Insulin-like growth factor-binding protein 6
IL-7/IL-8/IL-18	Interleukin-7 / Interleukin-8 / Interleukin-18
IPA	Ingenuity Pathway Analysis
IRB	Institutional Review Board
KNN	k-nearest neighbors (imputation)
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
LOOCV	Leave-one-out cross-validation
MEWS	Modified Early Warning Score
MICE	Multiple imputation by chained equations
PD-L1	Programmed death-ligand 1
QC	Quality control
R^2	Coefficient of determination
RFE	Recursive feature elimination
RF	Random Forest
ROC	Receiver operating characteristic
SAA1/SAA2	Serum amyloid A1 / Serum amyloid A2
SOFA	Sequential (Sepsis-related) Organ Failure Assessment
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVM	Support vector machine
THBS4	Thrombospondin-4
VWF	von Willebrand factor
XGBoost	Extreme gradient boosting
Youden J	Youden's J index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12014-026-09597-1.

Supplementary Material 1

Acknowledgements

Mass Spectrometry and Proteomics Core (RRID: SCR_017831) services and instruments used in this project were funded, in part, by the Pennsylvania State University College of Medicine via the Office of the Vice Dean of Research and Graduate Students and the Pennsylvania Department of Health using Tobacco Settlement Funds (CURE). The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions.

The Penn State Critical Illness and Research Center (RRID: SCR_026307) is a multidisciplinary consortium of investigators sharing data and resources related to critical illness research within the Penn State system. The content is solely the responsibility of the authors and does not necessarily represent the official views of the University or College of Medicine.

Author contributions

AKA and ASB conceived the study. AKA, SR, and ASB designed the methods. AS and RB curated the data while AKA and SR developed software. AKA performed the formal analyses. AKA and ASB prepared figures and drafted the manuscript, and all authors reviewed and edited the final version. ASB supervised the project and secured funding.

Funding

This study was funded by the National Institute of General Medical Sciences grant #R35GM150695 (ASB), of the National Institutes of Health.

Data availability

Analysis code, and a data dictionary are available on [Github](https://urldefense.com/v3/__https://github.com/ahad1361/proteoimic_validation/tree/main__;!!Ls64Rlj6!xdYv5Y-5af0QTxk2c1VPs-pOV78nxMB07L-VF6-hboa8o7w9EeD9UlpHRmLmwSZpxT24t8d-zswUABjnLTwg-gs-M7uGbQ$); additional materials available from the corresponding author on reasonable request. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by Penn State University Human Subjects Protection Office (IRB protocol #15328, 7/30/2020). The study complied with the Declaration of Helsinki (1964) and its later amendments and institutional requirements. The participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 28 October 2025 / Accepted: 26 February 2026
Published online: 14 March 2026

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