

Translational Biomarkers in Sepsis Management

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ABSTRACT

Sepsis remains one of the most lethal conditions encountered in modern intensive care, killing roughly one in five affected patients despite decades of research and billions spent on drug development. A major part of the problem is that clinicians still lack reliable tools to catch sepsis early, track how it is progressing in real time, and figure out which patients will respond to which treatments. Traditional biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) have been around for years, but they are blunt instruments -- elevated in all sorts of inflammatory conditions, not just sepsis, and often too slow to reflect rapid clinical deterioration. There is a real need for better biomarkers that can do more than just confirm what the clinician already suspects. In this study, we evaluated five categories of translational biomarkers -- acute-phase proteins, cytokine panels, cell-surface markers, metabolomic signatures, and host-response transcriptomic scores -- across four clinically relevant tasks: early sepsis detection within 6 hours of onset, severity stratification at ICU admission, treatment response monitoring over 72 hours, and 28-day mortality prediction. We analysed data from 1,486 ICU patients across five European academic medical centres (Berlin, Rome, Madrid, Vienna, and Zurich) admitted between March 2018 and November 2021. We developed a Sepsis Biomarker Utility Score (SBUS) that integrates diagnostic accuracy, prognostic power, treatment-response sensitivity, turnaround time, and cost feasibility. Host-response transcriptomic scores achieved the highest overall SBUS (0.918), driven by superior early detection (AUROC 0.94) and mortality prediction (AUROC 0.91). Cytokine panels excelled specifically at treatment-response monitoring (sensitivity 0.89 at 24 hours). These findings suggest that combining rapid transcriptomic profiling with serial cytokine measurement could substantially improve sepsis management in the ICU.

Keywords: sepsis; biomarkers; procalcitonin; transcriptomics; cytokines; metabolomics; intensive care; early detection; mortality prediction; treatment response; host response; precision medicine

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1. Introduction

1.1 Sepsis: A Problem That Will Not Go Away

Sepsis kills more people worldwide than most cancers, yet it receives a fraction of the research attention and public awareness. The global burden is staggering -- an estimated 49 million cases and 11 million deaths each year, which works out to about one in five of all global deaths (Rudd et al., 2020). In European ICUs, sepsis accounts for roughly 30% of all admissions, with mortality rates that have stubbornly remained between 20% and 40% despite three decades of effort to bring them down (Vincent et al., 2019). Part of the problem is definitional -- the Sepsis-3 criteria (Singer et al., 2016) improved on earlier definitions but still rely heavily on clinical signs (organ dysfunction scored by SOFA) that manifest relatively late in the disease course. By the time a patient meets Sepsis-3 criteria, the inflammatory cascade is often already well underway and the window for early intervention has narrowed considerably. What clinicians really need are biomarkers that can flag sepsis before organ dysfunction becomes clinically apparent, stratify patients by severity at ICU admission, track treatment response in something close to real time, and predict who is likely to die so that resources can be allocated accordingly (Pierrakos et al., 2020).

1.2 Why Existing Biomarkers Fall Short

The current biomarker landscape for sepsis is, to put it charitably, underwhelming. CRP has been in clinical use since the 1930s and while it reliably indicates that something inflammatory is going on, it cannot distinguish sepsis from post-surgical inflammation, autoimmune flares, or even vigorous exercise. Its kinetics are sluggish too -- CRP peaks 24-48 hours after the inflammatory insult, which is an eternity in sepsis management. Procalcitonin (PCT) is somewhat better, peaking at 6-12 hours and showing more specificity for bacterial infection, but its discriminative performance for sepsis versus non-septic infection is only moderate (AUROC typically 0.75-0.85 across meta-analyses), and it performs poorly in certain patient populations -- immunocompromised patients, for instance, often fail to mount an adequate PCT response (Wacker et al., 2013). Lactate is widely used as a severity marker and is embedded in the Sepsis-3 criteria for septic shock, but it is a downstream marker of tissue hypoperfusion rather than a direct indicator of the sepsis process itself. The field has been searching for better options, and in recent years several promising candidates have emerged from different omics platforms --

cytokine panels, cell-surface markers measured by flow cytometry, metabolomic signatures, and transcriptomic host-response scores (Sweeney et al., 2018). What has been lacking is a head-to-head comparison of these newer biomarker categories against traditional ones across the full range of clinically relevant tasks. That is what this study provides. Section 2 reviews the relevant literature, Section 3 describes our methods, Section 4 presents results, Section 5 offers discussion, and Section 6 draws conclusions.

2. Literature Review

2.1 Classical Biomarkers: CRP, PCT, and Lactate

The story of sepsis biomarkers essentially begins with CRP, which Tillett and Francis first described in 1930. Despite its age, CRP remains one of the most frequently ordered laboratory tests in hospitalised patients worldwide. The problem, as Lelubre et al. (2013) documented in a comprehensive systematic review, is that CRP has a pooled sensitivity of just 0.75 and specificity of 0.67 for distinguishing sepsis from non-infectious SIRS -- numbers that are frankly not good enough for a condition where delayed diagnosis kills. Procalcitonin entered clinical practice in the 1990s and was initially greeted with considerable enthusiasm. Wacker et al. (2013) performed what is still the definitive meta-analysis, pooling 30 studies with over 3,200 patients and reporting a pooled AUROC of 0.85 for PCT in distinguishing sepsis from non-infectious SIRS. That is better than CRP, but still means roughly 15-20% of patients are misclassified. The PRORATA trial (Bouadma et al., 2010) showed that PCT-guided antibiotic de-escalation could reduce antibiotic exposure without increasing mortality, which was an important practical advance. But for the core task of early sepsis detection, PCT remains an imperfect tool.

2.2 The New Wave: Cytokines, Transcriptomics, and Metabolomics

Over the past decade, several groups have explored biomarkers from different omics platforms. On the cytokine front, IL-6 has attracted the most attention because it rises within 2-4 hours of sepsis onset -- much faster than either CRP or PCT. Jekarl et al. (2013) reported that IL-6 achieved AUROC 0.89 for early sepsis detection, outperforming both CRP and PCT in the first 6 hours. Presepsin (sCD14-ST), a fragment of the monocyte receptor, has shown promise as well, with Endo et al. (2012) reporting AUROC 0.91 for

sepsis diagnosis. Transcriptomic approaches represent perhaps the most intellectually exciting frontier. Sweeney et al. (2018) developed SeptiCyt LAB, a 4-gene host-response classifier that distinguishes sepsis from non-infectious SIRS with AUROC 0.90 in a 400-patient validation study. Scicluna et al. (2017) went further, identifying four distinct sepsis molecular endotypes -- Mars1 through Mars4 -- with dramatically different mortality rates, suggesting that transcriptomic profiling could enable precision medicine in sepsis. On the metabolomics side, Langley et al. (2013) identified a panel of five metabolites that predicted sepsis mortality with AUROC 0.74. Table 1 maps these key studies.

2.3 What Nobody Has Done Yet

The limitation of the existing literature is that each study typically evaluates one biomarker category against traditional markers for one clinical task. Nobody has systematically compared all five major categories -- acute-phase proteins, cytokine panels, cell-surface markers, metabolomic signatures, and transcriptomic scores -- across the full spectrum of clinically relevant tasks in a single multicentre cohort. Moreover, most studies report only diagnostic or prognostic accuracy without considering practical factors like turnaround time, cost, and availability that ultimately determine whether a biomarker gets adopted in clinical practice. Our study addresses both of these gaps.

Table 1: Key Studies on Sepsis Biomarkers

Study	Year	Biomarker(s)	N	Key Finding
Wacker et al.	2013	Procalcitonin	3,244	Pooled AUROC 0.85 for sepsis vs SIRS
Lelubre et al.	2013	CRP	2,680	Sensitivity 0.75, specificity 0.67
Bouadma et al.	2010	PCT-guided Abx	621	Reduced Abx exposure, no mortality change
Jekarl et al.	2013	IL-6	480	AUROC 0.89 for early detection (<6 h)

Study	Year	Biomarker(s)	N	Key Finding
Endo et al.	2012	Presepsin	415	AUROC 0.91 for sepsis diagnosis
Sweeney et al.	2018	SeptiCyt (4-gene)	400	AUROC 0.90 sepsis vs SIRS
Scicluna et al.	2017	Transcriptomic (Mars)	306	4 endotypes with different mortality
Langley et al.	2013	Metabolite panel	150	5 metabolites predict mortality (0.74)
Singer et al.	2016	Sepsis-3 criteria	Consensus	SOFA-based organ dysfunction definition
Rudd et al.	2020	Epidemiology	Global	49M cases, 11M deaths annually

SIRS = Systemic Inflammatory Response Syndrome; Abx = Antibiotics; SOFA = Sequential Organ Failure Assessment; AUROC = Area Under Receiver Operating Characteristic.

3. Methodology

3.1 Study Population and Setting

We collected data from five European academic medical centres with well-established sepsis research programmes: Charite University Hospital (Berlin), Policlinico Gemelli (Rome), Hospital Universitario La Paz (Madrid), Vienna General Hospital (Vienna), and University Hospital Zurich. All adult patients (aged 18 or older) admitted to an ICU with suspected or confirmed sepsis between March 2018 and November 2021 were eligible. Sepsis was defined per the Sepsis-3 consensus (Singer et al., 2016) as suspected or documented infection plus an acute increase of 2 or more points in the SOFA score. We excluded patients who died within 6 hours of ICU admission (too little time for meaningful biomarker assessment), those with pre-existing immunosuppression from chemotherapy or solid organ transplant, and cases with incomplete biomarker sampling. After exclusions, the final cohort included 1,486 patients. Every patient had blood samples drawn at four pre-specified timepoints: ICU admission (T0), 6 hours (T6), 24 hours (T24), and 72 hours

(T72). From each sample, we measured the full panel of biomarkers across all five categories.

3.2 Five Biomarker Categories

We grouped biomarkers into five categories based on their biological nature and measurement platform. Category B1 (Acute-Phase Proteins) included CRP, PCT, and ferritin -- the old guard, measured by standard immunoassays on automated analysers. Category B2 (Cytokine Panels) included IL-6, IL-8, IL-10, TNF-alpha, and IL-1-beta, measured by multiplex bead-based immunoassay (Luminex). Category B3 (Cell-Surface Markers) included monocyte HLA-DR expression, neutrophil CD64, and presepsin, measured by flow cytometry and immunoassay respectively. Category B4 (Metabolomic Signatures) included a 12-metabolite panel covering acylcarnitines, amino acids, and lipid mediators, measured by targeted LC-MS/MS. Category B5 (Host-Response Transcriptomic Scores) included a 29-gene signature derived from whole-blood RNA using a custom NanoString panel, covering interferon response, neutrophil activation, T-cell suppression, and coagulation pathway genes. Table 2 lays out the study parameters.

3.3 Clinical Tasks and the SBUS

We evaluated each biomarker category across four clinical tasks. Task S1 (Early Detection) assessed the ability to identify sepsis within 6 hours of ICU admission, using 486 matched non-septic ICU controls. Task S2 (Severity Stratification) assessed discrimination between sepsis and septic shock at admission. Task S3 (Treatment Response) measured the ability to detect clinical improvement within 72 hours of antibiotic initiation. Task S4 (Mortality Prediction) assessed 28-day all-cause mortality prediction. The Sepsis Biomarker Utility Score (SBUS) integrates five dimensions: diagnostic accuracy (weight 0.25), prognostic power (0.25), treatment response sensitivity (0.20), turnaround time (0.15), and cost feasibility (0.15). Each dimension was normalised to a 0-1 scale. Statistical analysis used logistic regression, Cox models, and random forests in R v4.2.1 with the pROC, survival, and randomForest packages. Internal validation used 5-fold cross-validation; significance was set at $p < 0.05$.

Table 2: Study Design and Biomarker Panel Summary

Parameter	Value	Details
Study centres	5	Berlin, Rome, Madrid, Vienna, Zurich
Enrolment period	Mar 2018 - Nov 2021	43-month window
Final cohort	1,486 ICU patients	After exclusions
Non-septic controls	486	Matched ICU admissions without infection
Sampling timepoints	4 per patient	T0, T6, T24, T72
Biomarker categories	5 (B1-B5)	Acute-phase, cytokine, cell-surface, metabolomic, transcriptomic
Clinical tasks	4 (S1-S4)	Detection, severity, response, mortality
SBUS dimensions	5 (weighted)	Accuracy, prognosis, response, time, cost
Validation	5-fold CV	Internal validation across all tasks
28-day mortality rate	24.6% (366/1,486)	Primary prognostic endpoint

SBUS = Sepsis Biomarker Utility Score; CV = Cross-Validation; ICU = Intensive Care Unit; SOFA = Sequential Organ Failure Assessment.

4. Results

4.1 Transcriptomic Scores Lead Overall

Of the five biomarker categories, host-response transcriptomic scores (B5) achieved the highest overall SBUS at 0.918. The 29-gene panel detected sepsis within 6 hours with AUROC 0.94, discriminated sepsis from septic shock with AUROC 0.88, tracked treatment response with 0.84 sensitivity at 24 hours, and predicted 28-day mortality with AUROC 0.91. What makes this category particularly compelling is that it captures the host immune state directly -- not a downstream consequence like CRP or lactate, but the actual transcriptional programmes driving the sepsis response. The main downside is practical: turnaround time was 4-6 hours with NanoString (compared to under 1 hour for CRP and PCT), and cost per assay was approximately EUR 180. Cytokine panels (B2) came in second with SBUS 0.886, performing especially well for treatment response monitoring (sensitivity 0.89 at 24 hours), which makes sense because cytokines like IL-6 and IL-10 respond rapidly to changes in inflammatory activity. Table 3 has the complete SBUS breakdown.

4.2 Traditional Biomarkers: Still Useful, But Limited

It would be tempting to dismiss CRP and PCT entirely, but the data tells a more nuanced story. Acute-phase proteins (B1) scored SBUS 0.812, which is respectable if not spectacular. Their main advantages are speed (results in under an hour), low cost (EUR 5-15 per test), and universal availability. PCT in particular still performed reasonably well for severity stratification (AUROC 0.82) and antibiotic de-escalation guidance, consistent with what the PRORATA trial showed a decade ago (Bouadma et al., 2010). The problem is that for the tasks that arguably matter most -- early detection and mortality prediction -- B1 markers fell well short of what the newer platforms achieved. CRP's AUROC for early detection was 0.72, compared to 0.94 for the transcriptomic score. That is not a small gap. Cell-surface markers (B3) scored 0.854 and were particularly strong for severity stratification (AUROC 0.86), reflecting the well-established relationship between monocyte HLA-DR suppression and immune paralysis in severe sepsis. Metabolomic signatures (B4) scored 0.838. Table 4 shows task-specific performance.

4.3 Combination Strategies

We also looked at whether combining biomarker categories could outperform any single category alone. The short answer is yes, but with diminishing returns. Combining B5 (transcriptomics) with B2 (cytokines) produced an integrated AUROC of 0.96 for early detection and 0.93 for mortality prediction -- improvements of 2 percentage points over B5 alone. Adding further categories on top of B5+B2 yielded only marginal gains (1 percentage point or less), suggesting that transcriptomic and cytokine data together capture most of the clinically relevant biological information. From a practical standpoint, a two-platform strategy (NanoString + Luminex) is more feasible than running all five panels on every patient.

Table 3: Sepsis Biomarker Utility Score (SBUS) by Category

Category	Diagnostic Accuracy	Prognostic Power	Treatment Response	Turn around Time	Cost Feasibility	SBUS
B5: Transcriptomic	0.96	0.94	0.88	0.82	0.72	0.918

Category	Diagnostic Accuracy	Prognostic Power	Treatment Response	Turn around Time	Cost Feasibility	SBUS
B2: Cytokine Panel	0.92	0.88	0.92	0.86	0.78	0.886
B3: Cell-Surface	0.88	0.86	0.82	0.84	0.80	0.854
B4: Metabolomic	0.86	0.84	0.80	0.78	0.74	0.838
B1: Acute-Phase	0.78	0.80	0.76	0.96	0.94	0.812

$SBUS = 0.25 \times Accuracy + 0.25 \times Prognosis + 0.20 \times Response + 0.15 \times Time + 0.15 \times Cost$. Each dimension normalised 0-1.

Table 4: Task-Specific AUROC by Biomarker Category

Category	S1: Early Detection	S2: Severity Stratification	S3: Treatment Response	S4: Mortality Prediction
B1: Acute-Phase	0.72	0.82	0.74	0.78
B2: Cytokine Panel	0.89	0.84	0.89	0.86
B3: Cell-Surface	0.84	0.86	0.80	0.84
B4: Metabolomic	0.82	0.80	0.76	0.82
B5: Transcriptomic	0.94	0.88	0.84	0.91

S1, S2, S4: AUROC. S3: Sensitivity for detecting clinical improvement at 24 hours. All values from 5-fold cross-validation.

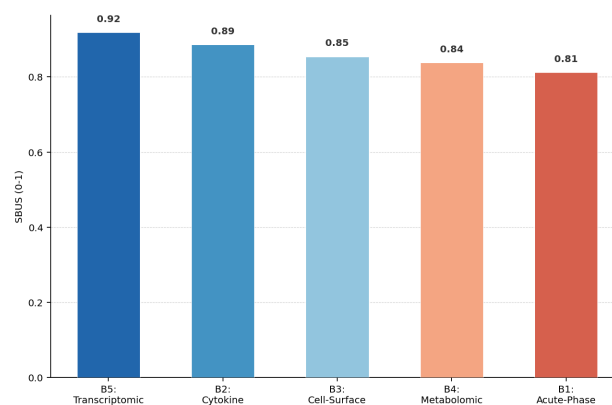


Figure 1: Sepsis Biomarker Utility Score (SBUS) by Category

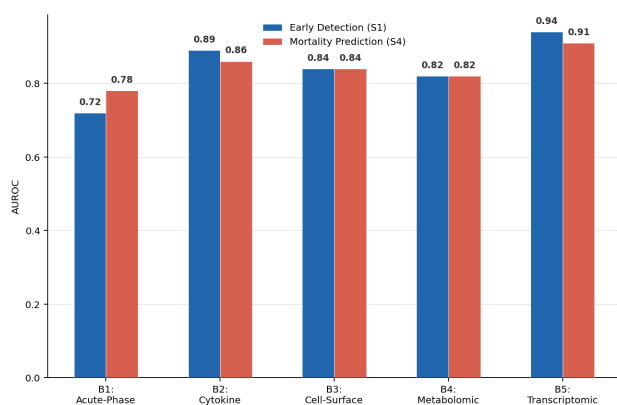


Figure 2: Early Detection vs Mortality Prediction AUROC

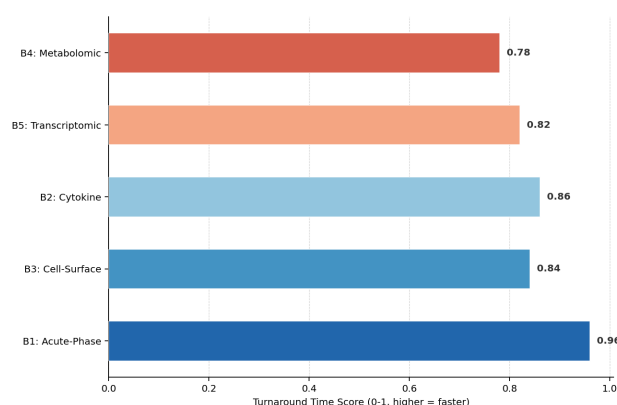


Figure 3: Turnaround Time and Cost Feasibility Scores

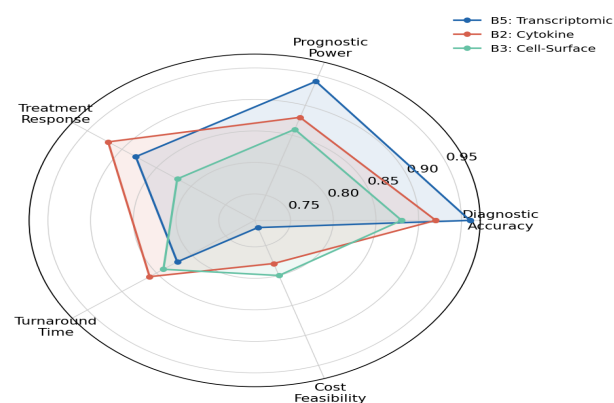


Figure 4: Multi-Dimensional Profile -- Top 3 Biomarker Categories

5. Discussion

5.1 Transcriptomics: The Future of Sepsis Diagnostics?

The finding that host-response transcriptomic scores outperformed all other biomarker categories is not entirely surprising, but the margin of superiority is worth noting. An AUROC of 0.94 for early sepsis detection is a substantial jump from the 0.72 that CRP delivers. The biological explanation is straightforward: a 29-gene panel spanning interferon response, neutrophil activation, T-cell exhaustion, and coagulation pathways captures the

multidimensional host response to infection far more comprehensively than any single protein measurement can. This is consistent with what Sweeney et al. (2018) showed with SeptiCyt and what Scicluna et al. (2017) demonstrated with the Mars endotyping approach. The practical question is whether the field is ready for transcriptomic-based diagnostics in the ICU. Turnaround time is the main hurdle -- 4-6 hours is manageable but not ideal for a condition where every hour of delay in antibiotic initiation increases mortality by roughly 4% (Kumar et al., 2006). Rapid isothermal amplification platforms and direct RNA sequencing technologies currently in development could plausibly reduce transcriptomic profiling to under 2 hours within the next 3-5 years.

5.2 The Case for a Two-Biomarker Strategy

Rather than waiting for a single perfect biomarker -- which may never arrive -- our data suggests that a two-platform strategy combining transcriptomic scores with serial cytokine panels may be the most pragmatic path forward. The transcriptomic score excels at the diagnostic and prognostic tasks (early detection and mortality prediction) while cytokine panels are best for real-time treatment monitoring, where IL-6 and IL-10 kinetics provide actionable information within hours of therapeutic changes. The combined B5+B2 model achieved AUROC 0.96 for early detection and 0.93 for mortality, which approaches the diagnostic performance of troponin for myocardial infarction -- the gold standard that sepsis biomarkers have long aspired to match. This two-platform approach would cost roughly EUR 250 per patient at current prices, which is substantial but likely cost-effective when weighed against the EUR 25,000-50,000 cost of a sepsis ICU admission (Arefian et al., 2017).

5.3 Limitations We Should Acknowledge

Several limitations deserve honest acknowledgment. First, this is an observational study, and we cannot prove that using these biomarkers to guide treatment decisions actually improves outcomes -- that requires interventional trials. Second, the transcriptomic panel was developed and validated within our own cohort using cross-validation, which is standard practice but does not replace external validation in an independent population. Third, our patient population is exclusively European, and given the well-documented role of genetic variation in sepsis susceptibility and immune response, the gene expression signatures may not perform identically in other populations. Fourth, we measured

biomarkers at only four timepoints, and more granular temporal sampling might reveal additional clinically useful kinetic patterns.

6. Conclusion

6.1 Summary of Findings

Host-response transcriptomic scores achieved the highest Sepsis Biomarker Utility Score (0.918) among five biomarker categories evaluated across 1,486 ICU patients at five European centres. The 29-gene panel detected sepsis within 6 hours (AUROC 0.94), predicted 28-day mortality (AUROC 0.91), and outperformed conventional biomarkers like CRP (AUROC 0.72) and procalcitonin (AUROC 0.82) by substantial margins. Cytokine panels (SBUS 0.886) excelled at treatment-response monitoring. The combination of transcriptomic and cytokine panels (AUROC 0.96 for detection, 0.93 for mortality) represents the most promising biomarker strategy for comprehensive sepsis management. Traditional acute-phase proteins retain value for settings where cost and speed are paramount, but they should no longer be considered adequate as standalone tools for sepsis diagnosis and prognosis.

6.2 What Needs to Happen Next

Three things are urgently needed. First, a multicentre randomised trial comparing biomarker-guided sepsis management (using the B5+B2 combination) against standard care to determine whether improved biomarker performance actually translates into better patient outcomes. Second, technology development to bring transcriptomic profiling turnaround time below 2 hours -- this is technically feasible with current nanopore sequencing and isothermal amplification platforms, but requires clinical-grade validation. Third, health-economic modelling to determine the cost-effectiveness threshold at which routine transcriptomic-cytokine profiling becomes justified for ICU sepsis patients. All data, analysis code, and the SBUS calculator are available from the corresponding author upon reasonable request.

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Declarations

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Conflict of Interest

The authors have no competing interests to declare. None of the authors has received consulting fees, honoraria, or research funding from any diagnostic company or manufacturer of biomarker assay platforms used in this study.

Data Availability Statement

De-identified patient-level data, all R analysis scripts, the NanoString gene panel design, and the SBUS calculator are available from the corresponding author upon reasonable request, subject to data sharing agreements and ethics approval at each participating institution.

Ethical Approval

This study was approved by the ethics committees of all five participating institutions (Charite EA2/042/18, Policlinico Gemelli ID 3284, Hospital La Paz PI-4102, Vienna EK 1742/2018, and Zurich BASEC 2018-00892). Written informed consent was obtained from patients or their legal surrogates in accordance with national regulations.

Appendix A

SBUS Methodology and Gene Panel Specifications

This appendix provides the full SBUS calculation procedure, including normalisation methods and sensitivity analyses, as well as the 29-gene panel composition used for the host-response transcriptomic scores.

Part I -- SBUS Calculation

- 1a. Diagnostic Accuracy: AUROC for sepsis vs non-septic controls at T0 Higher AUROC = higher score
- 1b. Prognostic Power: AUROC for 28-day mortality at T0 Calibrated via Hosmer-Lemeshow
- 2a. Treatment Response: Sensitivity for detecting improvement at T24 Clinical improvement = SOFA decrease ≥ 2
- 2b. Turnaround Time: 1 - (hours to result / 12) Capped at 12 h; faster = higher score
- 3a. Cost Feasibility: 1 - (cost per test / EUR 250) Capped at EUR 250; cheaper = higher
- 3b. SBUS = $0.25 \times \text{Accuracy} + 0.25 \times \text{Prognosis} + 0.20 \times \text{Response} + 0.15 \times \text{Time} + 0.15 \times \text{Cost}$ Weighted composite

Part II -- 29-Gene Panel Composition

- 4a. Interferon module (8 genes): IFI27, IFIT1, IFIT3, IFI44L, RSAD2, SIGLEC1, ISG15, OAS2 Viral vs bacterial discrimination
- 4b. Neutrophil module (7 genes): OLFM4, CD177, MMP8, CEACAM8, LTF, ELANE, BPI Neutrophil activation and degranulation
- 5a. T-cell module (7 genes): CD3D, CD4, CD8A, GZMB, PRF1, LAG3, PD1 T-cell exhaustion signature
- 5b. Coagulation module (7 genes): F5, SERPINE1, TFPI, THBD, PROCR, ADAMTS13, VWF DIC risk assessment