ACCURATE SEPSIS IDENTIFICATION USING SEPTICYTE® RAPID AND OTHER BIOMARKERS OF SYSTEMIC INFLAMMATION

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INTRODUCTION

Accurate identification of patients with sepsis can be challenging because of vague presenting clinical signs and a lack of timely microbiology results [1]. Improved methods of sepsis identification have included single or combined biomarkers of systemic inflammation [2]. SeptiCyte® RAPID is an RT-qPCR-based host-response gene expression assay that indicates a likelihood of sepsis and is measured on the Biocartis Idylla™ platform with a one-hour turnaround time.

The assay estimates the immune dysregulation underlying sepsis. Given this information, researchers hypothesized that SeptiCyte® RAPID (SeptiScore®), which measures two immune biomarkers to differentiate sepsis from SIRS, could be combined with other biomarkers to improve sepsis identification. The performance of SeptiCyte® RAPID was also evaluated relative to other biomarkers commonly evaluated when identifying and managing sepsis.

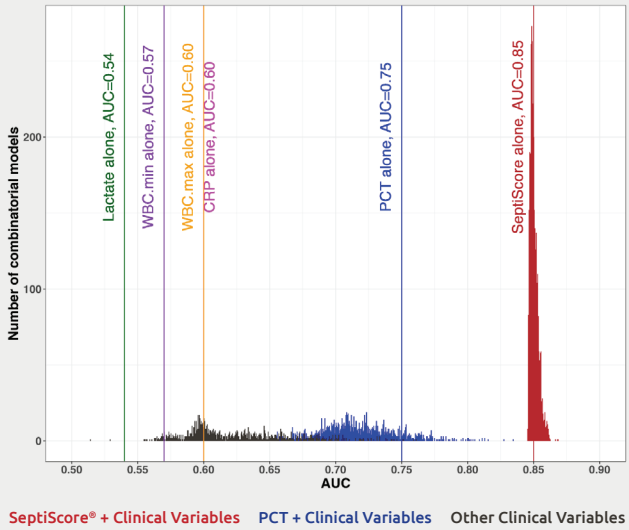
METHODS

The study used data from clinical trials (retrospective and prospective) conducted at ten hospital sites in the USA and Europe comprising adult patients who were critically ill and admitted to the ICU with a suspicion of sepsis. All patients in the cohort had at least two or more Systemic Inflammatory Response Syndrome (SIRS) criteria (NCT01905033, NCT02127502, NCT05469048 on clinicaltrials.gov). A panel of three physicians adjudicated all cases to provide a Retrospective Physician Diagnosis (RPD) of Sepsis or SIRS. The SeptiScore® ranges from 0 to 15 and is interpreted using 4 Bands with scores higher than 7.4 (Band 4), indicating a higher probability of sepsis as compared to scores lower than 5.0 (Band 1). The performance of SeptiScore and five additional biomarkers (ROC-AUC) were compared to an RPD [2] for 378 patients where each panel physician adjudicated either sepsis or SIRS (sepsis, n=154; SIRS, n=224). A permutation analysis of 6 variables (SeptiScore®, C-Reactive Protein (CRP), procalcitonin (PCT), lactate, white blood cell count (WBC Min & Max within 24 hours of ICU admission)), alone, or in any combination, was utilized resulting in 63 logistic regression models. Missing values were imputed using a multivariable imputation algorithm, Amelia [3], for WBC Min (n=9), WBC Max (n=14), PCT (n=68), lactate (n=125) & CRP (n=337). Further analysis of SeptiCyte® RAPID performance included categorization of patients into five groups using a composite score whereby 1 point was given for each biomarker being abnormal or elevated if: PCT: ≥0.50ng/mL, CRP: >10mg/L, Lactate: ≥1mmol/L, WBC: <4 OR >12x10^{3}cells/mm^3.

RESULTS

Mean AUCs for models only using SeptiScore®, PCT, CRP, WBC Min & Max & and lactate alone were 0.85, 0.75, 0.60, 0.60, 0.57, 0.54, respectively, for distinguishing sepsis from SIRS (Fig. 1). Use of all five other biomarkers in combination with SeptiScore® had an AUC of 0.85 (95% CI: 0.85-0.86). A model with CRP, PCT, Lactate, and WBC (Min & Max) had a mean AUC (0.74, 95%CI: 0.69-0.81) compared to models with SeptiScore® (mean AUC=0.85). There were seven patients retrospectively diagnosed with sepsis that had a composite score of 0, i.e., none of the other biomarkers commonly tested were found to be elevated in these cases, showing an atypical/early presentation of sepsis. The median SeptiScore® of these patients indicated an elevated likelihood of sepsis in Band 3. SeptiScore® AUCs were 0.83, 0.82, and 0.85 for patients with composite scores of 1, 2, or 3, respectively (Fig. 2) when distinguishing sepsis from SIRS cases with those biomarkers elevated. The median SeptiScore® of all sepsis patients with at least 2, 3, or 4 of the other elevated biomarkers was in Band 4, indicating the highest probability of sepsis. In contrast, patients that received an RPD of SIRS despite 2, 3, or 4 of the other biomarkers being elevated consistently had median SeptiScore® in Band 2, indicating a lower probability of sepsis than Bands 3 and 4. The mean SeptiScore® for sepsis patients with a composite score of 4 (n=8) was 8.8 (range 0-15). There weren't any SIRS patients in this cohort, with all other biomarkers elevated.

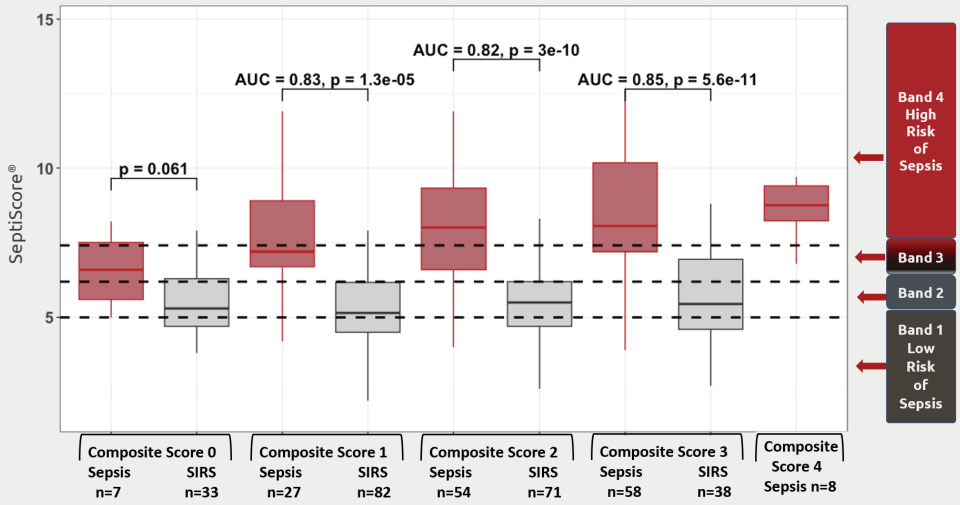
Figure 1: Combining SeptiCyte® RAPID With Other Clinical Variables: CRP, Lactate, PCT, WBC. Min & Max



Distinguishing Sepsis From SIRS								
Markers	**SeptiScore®**	Lactate	WBC Min	WBC Max	CRP	PCT	**SeptiScore®+ 5 Biomarkers**	5 Biomarkers combined without SeptiScore®
Mean AUC	**0.85**	0.54	0.57	0.60	0.60	0.75	**0.85 (0.85-0.87)**	0.68 (0.51-0.84)

Multivariable analysis to evaluate the combinatorial performance of logistic regression models either using SeptiScore® by itself or in combination with other commonly used biomarkers for triaging sepsis patients to include PCT, CRP, Lactate, WBC Min and Max. Missing data was imputed in 100 copies of the dataset using Amelia [3]. The vertical lines show mean AUC of models of each clinical parameter by itself. Models in red have SeptiScore® in them, those in blue have PCT (but no SeptiScore®) and models colored in black don't have PCT or SeptiScore® in them, but are combinations of the remaining variables to include lactate, CRP, WBC Min and Max. The X-axis shows the AUC from these models when stratifying sepsis from SIRS.

Figure 2: Concordance of SeptiCyte® RAPID with Routine Clinical Parameters Elevated in Sepsis



Y-axis showing SeptiScores® for sepsis (n=154) & SIRS (n=224) per Consensus RPD stratifying on the X-axis using a 4-point composite scoring. 1 point was given to each biomarker being abnormal/elevated: PCT (>0.50 ng/ml), CRP (>10mg/L), Lactate (>1 mmol/L), and if WBC count was low (<4 x 10^3 cells/mm^3) or elevated (>12 x 10^3 cells/mm^3) per SIRS criteria. The median SeptiScore® of all SIRS cases are in Band 2, which is the lower probability of sepsis Band for SeptiCyte® RAPID. The median SeptiScore® of sepsis cases with 2, 3, or 4 clinical parameters abnormal are in Band 4, which is the highest probability of sepsis Band for SeptiCyte® RAPID.

CONCLUSIONS

No combination of biomarkers outperformed SeptiScore® alone, or models including SeptiScore®, at identifying sepsis.

SeptiCyte® RAPID is not intended to be used as a standalone test; in this study, adding other biomarkers to SeptiScore® did not appreciably increase the diagnostic certainty of differentiating sepsis from SIRS.

References

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[2]Miller III RRM, Lopansri BK, Burke JP, et al. Validation of a Host Response Assay, SeptiCyte® LAB, for Discriminating Sepsis from Systemic Inflammatory Response Syndrome in the ICU. Am J Resp Crit Care. 2018;198(7):903-913.

[3]Honaker, J., King, G., & Blackwell, M. (2011). Amelia II: A Program for Missing Data. Journal of Statistical Software, 45(7), 1–47. https://doi.org/10.18637/jss.v045.i07

SeptiCyte® RAPID

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SeptiCyte® RAPID is a CE-marked IVD within the EU and and has 510(k) clearance in the US. Immunexpress is using the Idylla trademark under license from Biocartis.