An Objective Measure of The Host Response Suggests Social Determinants, Rather than Pathobiology, as a Factor in Disparate Sepsis Outcomes Among Races

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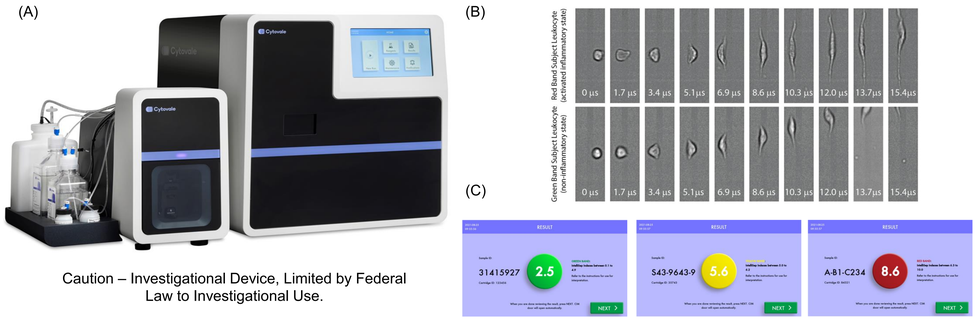
Introduction

Sepsis, a dysregulated host immune response to infection leading to life-threatening organ dysfunction[1], is a common and fast-moving condition, and leading cause of in-hospital death. The majority of cases develop in the community and present to Emergency Departments (ED)[2], where urgent action is required to prevent resultant morbidity and mortality[3]. Studies have shown that the incidence of sepsis and risk of sepsis morbidity and mortality increases with age[4-5]. With increased efforts on early detection and process of care, in-hospital sepsis deaths have declined; however, racial disparities have been observed in sepsis-related outcomes[6-7].

Initial investigations demonstrated that immune cell activation is accompanied by changes in biomechanical properties[8], and Follow-up studies demonstrated the potential for clinically actionable performance characteristics of an investigational test[9]. The objective of this study was to assess demographic, severity, and outcome differences among septic patients presenting to the ED self-reporting as White vs. Black and evaluate the potential of the IntelliSep test in risk stratifying these subpopulations for risk of poor outcomes.

Methods



Caution – Investigational Device, Limited by Federal Law to Investigational Use.

Figure 1: (A) Photograph of the Cytovale system, a benchtop instrument on which the IntelliSep Test is performed; (B) Graphical rendering of blood cell movement through the microfluidic deformation junction, and time series of cell deformation for a representative leukocyte of a septic Red Band patient (top) and a not-septic Green Band patient (bottom); (C) Representative images of the ISI result.

The IntelliSep test

The IntelliSep test, performed on the Cytovale system benchtop instrument (Fig. 1-A) is an investigational in-vitro diagnostic that quantifies the state of immune activation by measuring the biophysical properties of leukocytes from a routine blood specimen. These properties have been shown to differ in the septic patient when compared to those in the quiescent state, enabling rapid assessment of immune activation signatures and the sepsis risk stratification[8] (Fig. 1-B).

By leveraging microfluidic cell handling techniques in combination with technological advances in high-speed imaging and machine learning, biophysical properties of thousands of leukocytes are analyzed and distilled into the IntelliSep Index (ISI), a single score between 0.1-10.0. The score is stratified into three discrete interpretation bands of increasing probability of disease: Green, Yellow, and Red, developed in prior studies[9, 10] (Fig. 1-C).

Analysis Design & Setting

- Multiple large academic medical centers in Baton Rouge, LA, and Milwaukee, WI,USA.
- Adults presenting to the ED with signs or suspicion of infection prospectively enrolled (Apr. 2019 – Feb. 2020).
  - Exclusions consisted of hematologic malignancies, receiving a cytotoxic chemotherapeutic agent in the past 3 months, hematopoietic stem cell or any solid organ transplants, transfers from other acute care facilities.
- EDTA-anticoagulated blood was assayed with the IntelliSep test within 4 hours of draw, and patients were followed by retrospective chart review for outcome information. Treating clinicians did not have access to assay results.

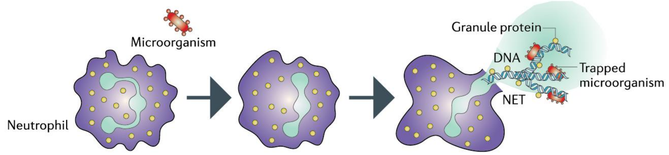


Figure 2: Neutrophil extracellular traps (NETs) formation is a rapid active process mediated by NETosis, involving chromatin decondensation and nuclear membrane disintegration[12].

Scientific Theory of Operation

Neutrophil and monocyte structure and biophysical properties such as deformability, density, and size are thought to shift with degranulation, NET formation[11], or maturity that occurs during the dysregulated immune activation associated with sepsis[13, 14].

Results & Discussion

- Of the 150 patients included in the analysis, 92 (53%) self-reported as White and 58 (42%) Black.
- Black subjects were significantly younger (mean difference 8.3 years; $p < 0.01$) compared to White subjects (Fig. 3) .
- No significant differences across race were observed in biological sex or severity of illness (Fig. 4, Fig. 5).
- Independent of race, the ISI correlated with increasing likelihood of adverse sepsis-related outcomes (Fig. 5).

Figure 3: Age distributions of Black and White subjects. Black subjects were on average 8.3 years younger than white subjects ($p < 10^{-6}$). (Bold colored lines following histograms represent kernel distribution estimations (KDE). Dashed vertical lines display median of each group).

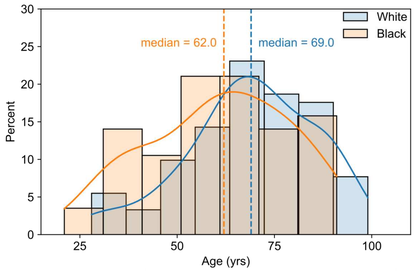
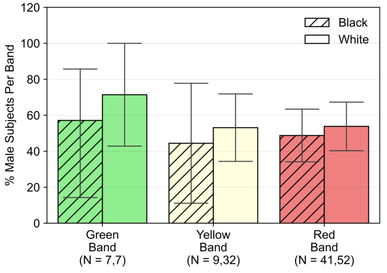


Figure 4: Biological sex of subjects across IntelliSep interpretation band and race. No significant difference was observed across race or interpretation band.



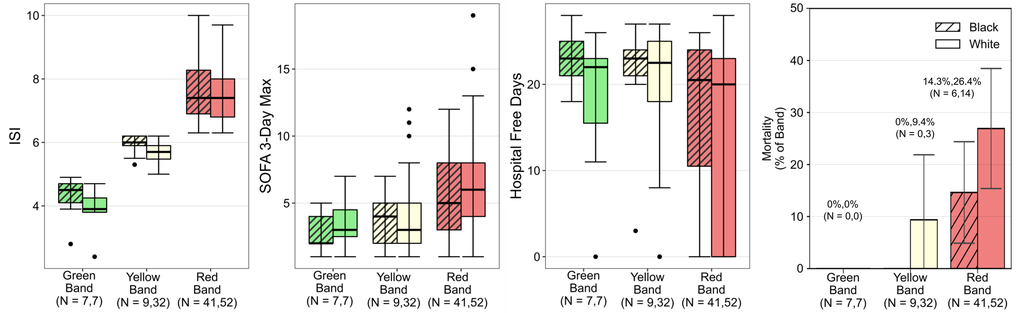


Figure 5: Measurements of immune dysregulation (ISI), organ dysfunction (SOFA, maximum of 3-days following presentation, baseline subtracted), all-cause-in-hospital mortality, and hospital free days across IntelliSep interpretation band and race. No significant difference in any of these measurements was observed across race.
Note: Hospital Free Days is defined as 28 days minus Hospital Length of Stay, where deceased subjects (in-hospital mortality) are allocated a zero value.

Conclusions

- Black subjects enrolled in our study were on average 8.3 years younger than white subjects; yet no significant differences in immune dysregulation or organ dysfunction we observed.
- Age discrepancy of subjects despite similar biological measurements trends with a number studies [6, 7, 15] showing discrepancies in healthcare outcomes from social determinants.
- The IntelliSep Test, an objective measurement of immune dysregulation, that may have the potential to aid in risk-stratification patients with sepsis for adverse outcomes, independent of race.

Acknowledgements

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