**Monocyte Distribution Width, A Novel Indicator of Sepsis-2 and Sepsis-3 in**

**High Risk Emergency Department Patients**

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**Digital Supplement**

**sMethods**

**Monocyte Distribution Width Analysis:**

All blood samples were analyzed on a UniCel DxH 800 analyzer (Beckman Coulter, Inc.) with version 2.0 software within 2 hours of collection. This instrument measures specific cell volume parameters and the distribution of cell volumes within a group of cells (sFig. 1, Supplemental Digital Content 2, ).

**Pilot Study Data to Establish Optimal Monocyte Distribution Width (MDW) Cut-off for Sepsis:**

The optimal MDW cut-off value used to detect sepsis (i.e., >20.0 units) in this study was previously established in an independent pilot study conducted at the same three sites enrolling 505 subjects of which 67 met Sepsis-2 and 54 met Sepsis-3 criteria. Pilot study demographics are provided in sTable 1 (Supplemental Digital Content 3, ), and a breakdown of the study subjects based on Sepsis-2 and Sepsis-3 criteria are provided in sTable 2 (Supplemental Digital Content 4, ) and sTable 3 (Supplemental Digital Content 5, ), respectively. Optimal cut-off values for MDW were based upon sensitivity and specificity and by area under the curve (AUC) analyses for Sepsis-2 (sTable 4, Supplemental Digital Content 6, ; and sFig. 2B, Supplemental Digital Content 8,) and Sepsis-3 (sTable 5, Supplemental Digital Content 7, ; and sFig. 3B, Supplemental Digital Content 9,). The MDW cut-off of 20.0 was optimal for Sepsis-2 detection based upon AUC (0.76; 95% CI: 0.69 to 0.82) and for Sepsis-3 detection based upon AUC (0.78; 95% CI: 0.71-0.86).

**Honest Broker Data De-identification Protocol:**

A schematic of the honest broker system employed for these investigations to obviate the need for informed consent by eliminating all patient identifiers on samples or patient data is shown in sFigure 4 (Supplemental Digital Content 10,).

**sReferences**

1. Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315(8):801-810.
2. Vincent JL, Moreno R, Takala J, et al: Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care* *Med* 1996; 22(7):707-710.

**sFigure Legends**

**sFigure 1.**  **Cell population size distribution changes during sepsis.** The left axis reflects the size of the cells; whereas, color coding conforms to the type of cell, as labeled. Note the changes in monocyte and neutrophil average size (red dotted line) and distribution width (blue dotted line) during sepsis.

**sFigure 2. Monocyte distribution width (MDW) is elevated during Sepsis-2.**  Panel A: Box plot representation of MDW values based upon clinical category. Panel B: Receiver operator characteristic (ROC) curve of MDW >20.0 for detection of Sepsis-2.

**sFigure 3. Monocyte distribution width (MDW) is elevated during Sepsis-3.** Panel A: Box plot representation of MDW values based upon clinical category (note: SIRS does not apply to Sepsis-3). Panel B: Receiver operator characteristic (ROC) curve of MDW >20.0 for detection of Sepsis-3.

**sFigure 4.** **Integration of honest brokers within overall study workflow.** Clinical and research team members were blinded to patient identifiers through the integration of two honest brokers (HBs) at each site. One HB codified patient blood samples, and a second HB extracted clinical data from the electronic medical record 7 days after emergency department admission. (SOC = standard of care; BEC = Beckman Coulter; RBM = risk-based monitoring; TAT = turnaround times; PROService = secure remote service platform providing access for proactive diagnostic and troubleshooting analyses and data acquisition by BEC; CRF = case report form, and SF = screen failure).

**sFigure 5. Performance of monocyte distribution width (MDW) for detection of sepsis based upon gender.** No difference in MDW was observed when comparing the receiver operating characteristic (ROC) curves for sepsis detection (Sepsis-2 criteria) in the emergency department by gender.

**sFigure 6. Added value analysis of monocyte distribution width (MDW) for Sepsis-3 relative to white cell count (WBC) alone based upon receiver operator characteristic (ROC) curves.**