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ORIGINAL RESEARCH

Infectious Disease

Monocyte distribution width as part of a broad pragmatic sepsis screen in the emergency department

Alexandra Malinovska MD[1,2] | Jeremiah S. Hinson MD, PhD[1,3,4] | Oluwakemi Badaki-Makun MD, PhD[3,5] | Benjamin Hernried BA[1] | Aria Smith MS[1,3] | Arnaud Debraine BS[4] | Matthew Toerper BS[1,3,4] | Richard E. Rothman MD, PhD[1] | Thomas Kickler MD[6] | Scott Levin PhD[1,3,4]

[1]Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[2]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

[3]Malone Center for Engineering in Healthcare, Johns Hopkins Whiting School of Engineering, Baltimore, Maryland, USA

[4]StoCastic, Baltimore, Maryland, USA

[5]Division of Pediatric Emergency Medicine, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[6]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Correspondence
Scott Levin, PhD, 5801 Smith Ave, Baltimore, MD 21209, USA.
Email: slevin33@jhmi.edu

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Abstract

Study Objective: Enhancement of a routine complete blood count (CBC) for detection of sepsis in the emergency department (ED) has pragmatic utility for early management. This study evaluated the performance of monocyte distribution width (MDW) alone and in combination with other routine CBC parameters as a screen for sepsis and septic shock in ED patients.

Methods: A prospective cohort analysis of adult patients with a CBC collected at an urban ED from January 2020 through July 2021. The performance of MDW, white blood count (WBC) count, and neutrophil-to-lymphocyte-ratio (NLR) to detect sepsis and septic shock (Sepsis-3 Criteria) was evaluated using diagnostic performance measures.

Results: The cohort included 7952 ED patients, with 180 meeting criteria for sepsis; 43 with septic shock and 137 without shock. MDW was highest for patients with septic shock (median 24.8 U, interquartile range [IQR] 22.0–28.1) and trended downward for patients with sepsis without shock (23.9 U, IQR 20.2–26.8), infection (20.4 U, IQR 18.2–23.3), then controls (18.6 U, IQR 17.1–20.4). In isolation, MDW detected sepsis and septic shock with an area under the receiver operator characteristic curve (AUC) of 0.80 (95% confidence interval [CI] 0.77–0.84) and 0.85 (95% CI 0.80–0 .91), respectively. Optimal performance was achieved in combination with WBC count and NLR for detection of sepsis (AUC 0.86, 95% CI 0.83–0.89) and septic shock (0.86, 95% CI 0.80–0.92).

Conclusion: A CBC differential panel that includes MDW demonstrated strong performance characteristics in a broad ED population suggesting pragmatic value as a rapid screen for sepsis and septic shock.

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KEYWORDS
complete blood count (CBC), emergency medicine, monocyte distribution width (MDW), neutrophil to lymphocyte ratio (NLR), sepsis, septic shock, triage

1 | INTRODUCTION

1.1 | Background and importance

Sepsis is a leading cause of morbidity and mortality worldwide and is responsible for over 1.5 million hospitalizations and 250,000 deaths in the United States each year.[1,2] Early initiation of targeted treatments for sepsis has been associated with improved patient outcomes and lower costs.[2–8] Emergency departments serve a primary role in early detection of sepsis and emergency department (ED) clinicians set care trajectories for the majority of septic patients nationwide.[9,10] However, rapid and reliable identification of sepsis remains challenging in the ED, where a wide variety of acute and undifferentiated diseases are managed with limited information and under intensive time pressure.

Tools for ED-based sepsis screening are limited. Clinical scoring systems that rely on routinely available information are advantageous because of their universal applicability. The original systemic inflammatory response syndrome (SIRS) criteria remain widely used for sepsis screening but lack specificity; patients with acute non-infectious illness often screen positive.[11,12] SIRS criteria were excluded from the third iteration of consensus sepsis definitions (Sepsis-3), which introduced the quick Sequential Organ Failure Assessment score (qSOFA) that has been applied for sepsis screening and prognostication.[13] Unfortunately, qSOFA has proven to lack sensitivity in the ED where patients often present before manifesting overt signs of organ failure.[14] Biomarkers may serve as adjuncts for sepsis screening and diagnosis. However, currently available biomarkers, including lactate, C-reactive protein (CRP), and procalcitonin, perform suboptimally because of limited diagnostic accuracy, detectable signal delay, and/or lack of widespread availability in the clinical setting.[15,16]

Recently, there has been renewed interest in the use of routinely available hematologic parameters for sepsis screening and diagnosis.[17] Unlocking insights from the complete blood count (CBC) with differential could have enormous impacts on ED-based sepsis care. The CBC is the most commonly ordered laboratory panel worldwide.[18] Its differential generates detailed information about blood cell lineages. Leukocytes play a central role in the host response to infection. WBC count was incorporated into original consensus criteria for sepsis but was excluded from more recent sepsis definitions owing to its poor diagnostic accuracy when used in isolation.[12] More nuanced analysis of the leukocyte differential, including measurement of the neutrophil-to-lymphocyte ratio (NLR), has shown more promise for early detection of sepsis.[19,20]

Further, recent advances in laboratory technology have increased capacity for automated assessment of leukocyte morphology generating novel CBC-based parameters.[21] Monocyte distribution width (MDW) is a morphometric parameter that reflects variability in monocyte cell volume. These morphological changes in volume occur early within the monocyte population as a result of pathogen recognition-induced monocyte activation, and thus MDW is altered early in disease trajectory. MDW has demonstrated capability in identification of patients with sepsis in high-risk populations.[22–24]

1.2 | Goals of this investigation

The objective of this study was to evaluate the performance of MDW, alone and in combination with other routinely reported leukocyte parameters, as a rapid and pragmatic screen for sepsis in the ED. The hypothesis was that MDW may play a role in enhancing the utility of a routine CBC for sepsis diagnosis.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This prospective cohort study was conducted between January 21, 2020 and July 14, 2021 at the Johns Hopkins Hospital ED in Baltimore, MD, USA. The study was approved by the institutional review board (IRB) and follows Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.

2.2 | Selection of participants

All adult patients (aged 18 and over) who had a CBC collected within 6 hours of ED arrival, as a part of routine clinical care, were eligible for the study. Patients were enrolled consecutively during time periods when study team members were present. Patients missing a valid MDW (eg, low sample volume or poor sample quality), patients with MDW sample analyses performed more than 2 hours after blood collection, and patients missing other CBC parameters (WBC count, neutrophils, lymphocytes) within 6 hours of arrival were excluded. Repeat ED visits by the same patient during the study period were also excluded.

2.3 | Measurements

Demographics, clinical data (presenting complaints, comorbidities, vital signs, laboratory), and hospital use data were collected from the electronic health record (EHR) system. Presenting complaints

were entered from a picklist at ED triage and comorbidities were mined by grouping diagnostic codes (*International Classification of Diseases, Tenth Revision* [ICD-10]) for active problems available in the EHR at patient presentation.[25–27] The qSOFA score (range, 0–3 points) was estimated at triage using the first measurement of systolic blood pressure (≤ 100 mmHg = 1 point), respiratory rate (≥ 22 breaths/minute = 1 point), and altered mental status (1 point) indicated by a presenting complaint related to altered mental status[26] or a Glasgow Coma Score (GCS) < 15 reported within 6 hours of ED arrival.[28] Mortality was defined as in-hospital mortality or discharge to hospice. Direct admission to an ICU, inpatient hospitalization, and length of stay (ED presentation to physically exiting the hospital) were also reported.

MDW was analyzed on a UniCel DxH900 analyzer (Beckman Coulter, Inc), software version 1.0 in K_2 EDTA tubes. A cutoff value of greater than 20 Units was defined as abnormal.[11–13] MDW measurement was performed by a study team member blind to patient clinical information. MDW was not reported in the EHR; clinicians were blinded to MDW values while providing care to patients enrolled. Other CBC parameters (WBC count and NLR) were measured on a separate hematology analyzer used for routine clinical practice and were available to treating clinicians. An abnormal WBC count was defined as less than 4×10^9/L or greater than 12×10^9/L[12,29] and an abnormal NLR was defined as greater than 10.[17] Lactate (abnormal defined greater than 2.0 mmol/L)[13] and CRP (abnormal defined greater than 10 mg/L)[30] measurements were both performed upon request by the treating team and included in analyses as comparators if performed within 6 hours of ED presentation. The immunosuppressed patient subgroup was defined as those having neutropenia (absolute neutrophil count less than or equal to 1.5×10^9/L measured within 6 hours of ED arrival) or an active problem meeting criteria for an immunocompromised state.[27]

2.4 | Outcomes

The primary outcome was manifestation of sepsis with or without shock within 12 hours of CBC collection. For analyses, patients were assigned to 4 mutually exclusive groups based on previously validated criteria:[13,31] control, infection, sepsis (without shock), or septic shock. Patients met criteria for infection if they either (1) started a new antibiotic over a course of at least 4 days (first to last administration day) and had blood culture ordered within 48 hours of ED arrival, or (2) met ICD-10 code diagnostic criteria for an infection.[31] Patients with a shorter course of antibiotics qualified if death occurred before 4 days from treatment initiation. The Sepsis-3 definition using SOFA[13] was used as reference standard to define the sepsis groups (sepsis without shock and septic shock). Patients were assigned to the sepsis group if they met criteria for infection and met at least 1 of the following SOFA criteria within 12 hours of CBC collection: (1) vasopressor initiation, (2) initiation of mechanical ventilation, (3) doubling in serum creatinine level, (4) decrease by 50 % of estimated glomerular filtration rate relative to baseline, (5) bilirubin level greater than 2.0 mg/dl and doubling from baseline, (6) platelet count less than 100×10^9/L and greater than 50 % decline from baseline (baseline had to be greater than 100×10^9/L), or (7) lactate greater than 2.0 mmol/L. Patients meeting sepsis criteria and for whom vasopressors were initiated and lactate values were greater than 2 mmol/L were assigned to the septic shock group. Patients not meeting infection or sepsis criteria were included in the control group.

Patient outcome classifications were assigned by an automated algorithm applied to EHR data. Two physicians on our study team performed a non-blinded chart review of a subset of 100 patients with sepsis (inclusive of septic shock) and 100 patients without sepsis (infection or control).[32] The review with adjudication was conducted to assess the reliability and accuracy of the algorithm with respect to the stated definitions. The review resulted in confirmation of reliable classification of sepsis with a positive predictive value of 99% and negative predictive value of 100%.

The Bottom Line

Detection of sepsis in the emergency department (ED) is challenging and few lab-based screening tools exist. In a cohort of 7952 ED patients, 180 of whom had sepsis, the authors report that monocyte distribution width, a parameter on the complete blood count, had excellent predictive value for both sepsis and septic shock.

2.5 | Analysis

Continuous variables were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney *U* test. Categorical variables were expressed as numbers and percentages and were compared using the χ^2 test. Correlation coefficients were calculated using the Spearman rank method. Diagnostic performance was evaluated using binary classification measures. The area under the receiver operator characteristic curve (AUC) was calculated using logistic regression models with sepsis (sepsis without shock or septic shock) and septic shock as separate response variables. Leukocyte parameters were modeled in isolation (single predictor) and in combination (multiple predictors) as continuous variables. Comparisons of the AUC and their confidence intervals (CIs) were evaluated using the De Long method.[33] Sensitivity, specificity, positive and negative predictive value, and likelihood ratios were calculated using laboratory cutoffs with definitions for dichotomization as normal or abnormal. Patients with missing lactate or CRP were excluded from respective subgroup analyses. No imputation or interpolation methods were applied to any clinical data used to derive sepsis outcomes. All analysis was performed in Python Version 3.

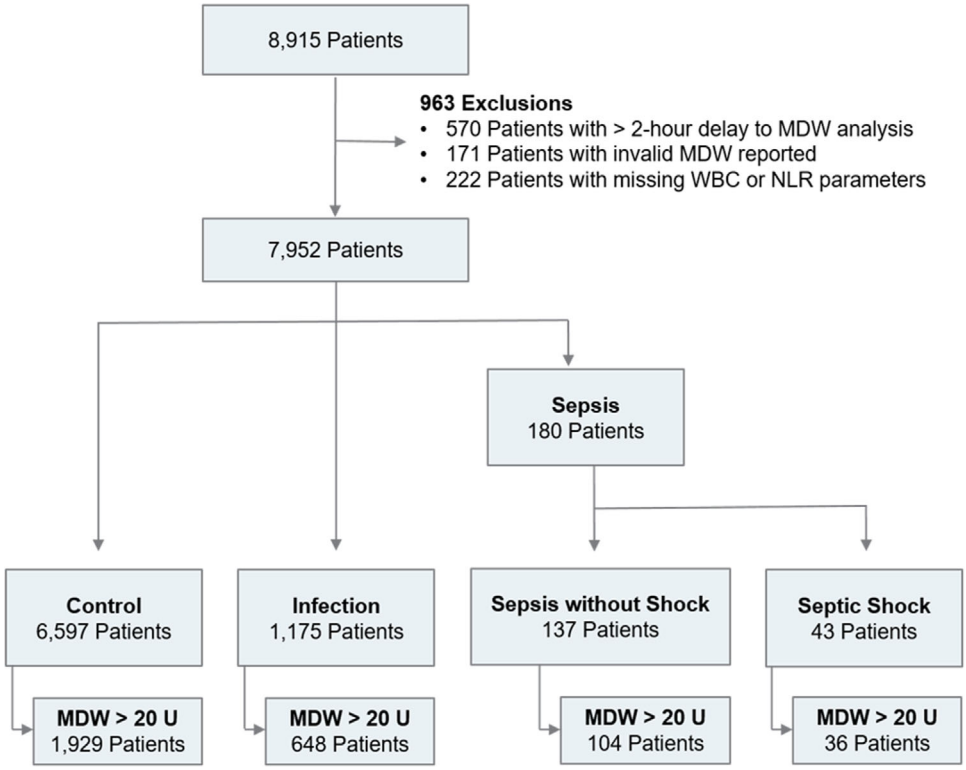

FIGURE 1 Study flow diagram MDW, monocyte distribution width; NLR, neutrophil-to-lymphocyte ratio; U, unit

3 | RESULTS

3.1 | Characteristics of study subjects

A total of 8915 patients with MDW measured within 6 hours of ED arrival were included in the study. Patients were excluded owing to greater than 2-hour delays from blood collection to MDW analysis (570 patients), invalid MDW measurements (171), and missing correlate WBC, neutrophil, or lymphocyte counts (222) as seen in Figure 1. This left a final cohort of 7952 patients comprising 6597 (83.0%) controls, 1175 (14.8%) patients with infection, 137 (1.7%) meeting criteria for sepsis without shock, and 43 patients (0.5%) meeting criteria for septic shock. Patients meeting infectious disease outcome criteria tended to be older and were more likely to suffer from comorbid conditions such as cancer, heart failure, and kidney disease as seen in Table 1. They were also more likely to meet 2 or more qSOFA criteria at presentation, to require hospital or ICU admission, and to experience mortality.

3.2 | Main results

The distribution of MDW, WBC count, and NLR is displayed in Figure 2. MDW was highest for patients with septic shock (median: 24.8 U, IQR 22.0–28.1) and trended downward for sepsis (23.9 U, IQR 20.2–26.8) and infection (20.4 U, IQR 18.2–23.3) with lowest values observed in control patients (18.6 U, IQR 17.1–20.4) as seen in Figure 2. WBC count and NLR distinguished sepsis from non-sepsis (control and infection) groups but showed less discrimination between sepsis (without shock) and septic shock groups compared to MDW ($P = 0.048$). Further MDW demonstrated low positive correlation with WBC count (rho = 0.09, 95% CI [0.07–0.11]) and NLR (rho = 0.19, 95% CI [0.17–0.22]), whereas WBC count and NLR were moderately correlated (rho = 0.52, 95% CI [0.50–0.53]).

The diagnostic performance of qSOFA and leukocyte parameters (MDW, WBC count, NLR) for sepsis groups is displayed in Table 2. MDW detected sepsis with an AUC of 0.80 (95% CI 0.77–0.84) and septic shock with an AUC of 0.85 (95% CI 0.79–0.91). In comparison, WBC count had an AUC of 0.77 (95% CI 0.73–0.81) and 0.79 (95% CI 0.71–0.87) and NLR had an AUC of 0.84 (95% CI 0.81–0.87) and 0.81 (95% CI 0.73–0.88) for sepsis and septic shock, respectively. Using a cutoff of 20 U or greater for MDW as a test for sepsis shows a sensitivity of 77.8% (95% CI 71.1–83.9) and specificity of 66.8% (95% CI 65.8–67.9%). Overall diagnostic performance (AUC) of MDW and NLR in isolation was superior to qSOFA for sepsis ($P < 0.05$). Combining MDW, WBC count, and NLR increased overall diagnostic performance to an AUC of 0.86 (95% CI 0.83–0.89) for sepsis and 0.86 (95% CI 0.80–0.92) for septic shock as seen in Table 2.

3.3 | Subgroup analyses

During routine care in the ED, lactate was measured for a subgroup of 2712 patients (34.1% of total cohort) and CRP was measured for a

TABLE 1 study patient characteristics

	Total	Control	Infection	Sepsis	Septic shock
Patients, no.	7952	6597	1175	137	43
Sex female, no. (%)	4196 (52.8%)	3494 (53.0%)	621 (52.9%)	54 (39.4%)	27 (62.8%)
Age, median (IQR) [years]	50.0 (34.0–63.0)	49.0 (33.0–62.0)	53.0 (36.0–65.0)	62.0 (49.0–69.0)	66.0 (53.5–73.5)
Race, no. (%)					
Black	4567 (57.4%)	3843 (58.3%)	635 (54.0%)	64 (46.7%)	25 (58.1%)
White	2499 (31.4%)	1999 (30.3%)	423 (36.0%)	60 (43.8%)	17 (39.5%)
Other	886 (11.1%)	755 (11.4%)	117 (10.0%)	13 (9.5%)	1 (2.3%)
Presenting complaints, no. (%)					
Abdominal pain	802 (10.1%)	653 (9.9%)	136 (11.6%)	10 (7.3%)	3 (7.0%)
Altered mental status	130 (1.6%)	100 (1.5%)	19 (1.6%)	7 (5.1%)	4 (9.3%)
Chest pain	749 (9.4%)	698 (10.6%)	50 (4.3%)	1 (0.7%)	0 (0.0%)
Dizziness	166 (2.1%)	150 (2.3%)	14 (1.2%)	0 (0.0%)	2 (4.7%)
Fever	162 (2.0%)	89 (1.3%)	57 (4.9%)	13 (9.5%)	3 (7.0%)
Generalized weakness	97 (1.2%)	72 (1.1%)	17 (1.4%)	6 (4.4%)	2 (4.7%)
Hypotension	46 (0.6%)	15 (0.2%)	24 (2.0%)	4 (2.9%)	3 (7.0%)
Shortness of breath	632 (7.9%)	489 (7.4%)	118 (10.0%)	20 (14.6%)	5 (11.6%)
Comorbidities, No. (%)					
Coronary artery disease	614.0 (7.7%)	486.0 (7.4%)	110.0 (9.4%)	17.0 (12.4%)	1.0 (2.3%)
Cancer	1157.0 (14.5%)	889.0 (13.5%)	216.0 (18.4%)	38.0 (27.7%)	14.0 (32.6%)
Cerebrovascular disease	389.0 (4.9%)	315.0 (4.8%)	60.0 (5.1%)	11.0 (8.0%)	3.0 (7.0%)
Diabetes	1057.0 (13.3%)	819.0 (12.4%)	200.0 (17.0%)	31.0 (22.6%)	7.0 (16.3%)
Heart failure	475.0 (6.0%)	368.0 (5.6%)	82.0 (7.0%)	18.0 (13.1%)	7.0 (16.3%)
Hypertension	2030.0 (25.5%)	1611.0 (24.4%)	358.0 (30.5%)	47.0 (34.3%)	14.0 (32.6%)
Immunosuppression	850.0 (10.7%)	614.0 (9.3%)	189.0 (16.1%)	38.0 (27.7%)	9.0 (20.9%)
Kidney disease	831.0 (10.5%)	593.0 (9.0%)	204.0 (17.4%)	26.0 (19.0%)	8.0 (18.6%)
Liver disease	897.0 (11.3%)	719.0 (10.9%)	154.0 (13.1%)	18.0 (13.1%)	6.0 (14.0%)
Prior respiratory failure	43.0 (0.5%)	30.0 (0.5%)	11.0 (0.9%)	2.0 (1.5%)	0.0 (0.0%)
qSOFA ≥ 2, No. %	94 (1.2%)	54 (0.8%)	19 (1.6%)	11 (8.0%)	10 (23.3%)
Secondary outcomes					
Mortality, no. (%)	132 (1.7%)	67 (1.0%)	37 (3.1%)	19 (13.9%)	9 (20.9%)
Intensive care, no. (%)	239 (3.0%)	121 (1.8%)	53 (4.5%)	36 (26.3%)	29 (67.4%)
Hospitalization, no. (%)	2717 (34.2%)	1864 (28.3%)	673 (57.3%)	137 (100.0%)	43 (100.0%)
Hospital duration, median (IQR) [hours]	18.3 (8.1–80.3)	14.6 (7.6–56.8)	72.9 (13.5–167.5)	219.4 (149.0–392.3)	273.6 (156.3–387.9)
Lab results, median (IQR) [Units]					
Monocyte distribution width [U]	18.8 (17.3–21.0)	18.6 (17.1–20.4)	20.4 (18.2–23.3)	23.9 (20.2–26.8)	24.8 (22.0–28.1)
WBC count [G/L]	7.4 (5.6–9.8)	7.1 (5.6–9.3)	8.7 (6.2–11.7)	13.0 (8.9–18.6)	14.8 (8.7–17.8)
Neutrophil-lymphycyte ratio	3.0 (1.9–5.4)	2.8 (1.8–4.7)	4.4 (2.4–8.5)	11.2 (6.6–19.6)	9.6 (5.4–18.8)

Abbreviations: IQR, interquartile range; No, number; qSOFA, quick sequential organ failure assessment; U, unit.

subgroup 542 patients (6.8%). Figure 3 displays the distribution of lactate (Panel A) and CRP (Panel B) in comparison to leukocyte parameters (MDW, WBC, NLR) for these respective subgroups. Lactate demonstrated reliable differences between sepsis and non-sepsis (control and infection) groups with limited differentiation between sepsis (without shock) and septic shock groups as seen in Figure 3 (Panel A). CRP in a smaller sample showed similar trends, with no clear differentiation between sepsis (without shock) and septic shock groups (Figure 3 Panel B). MDW maintained its upward trend between control, infection, sepsis, and septic shock in both of these subgroups where additional laboratory workup was performed. This trend was also maintained for a group of 965 (12.2%) patients

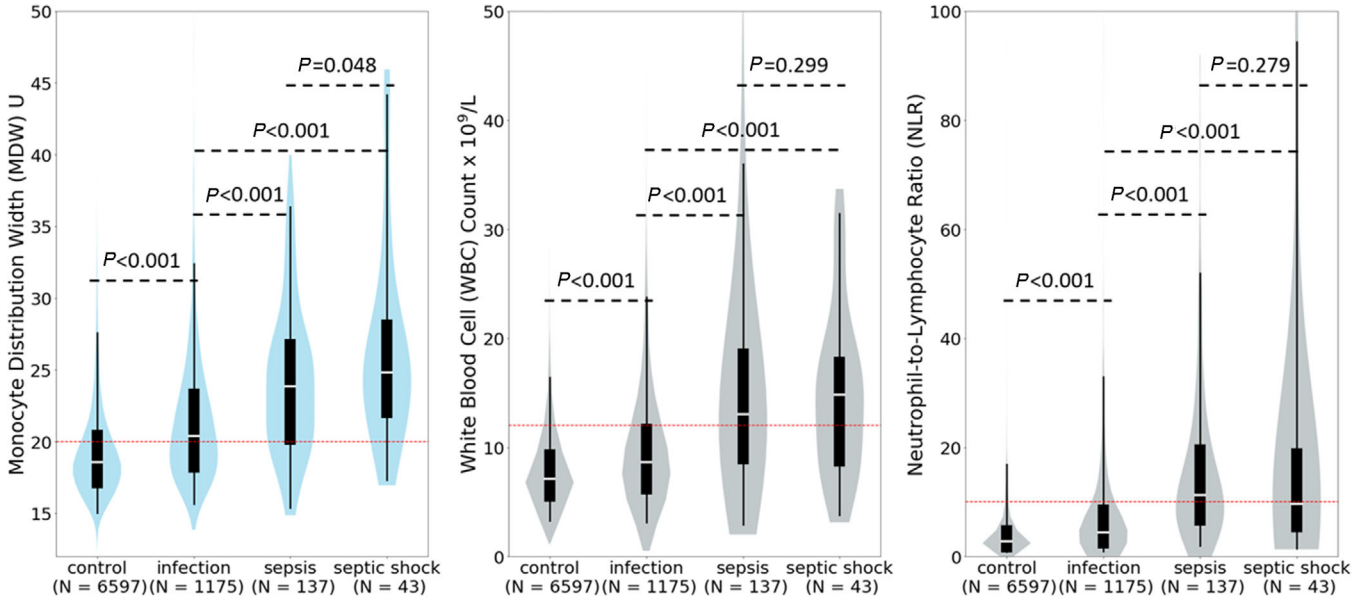

FIGURE 2 Monocyte distribution width, WBC count, and neutrophil-to-lymphocyte ratio comparisons by group. The red dashed line represents cutoff value of respective test. MDW, monocyte distribution width; NLR, neutrophil-to-lymphocyte ratio; U, unit

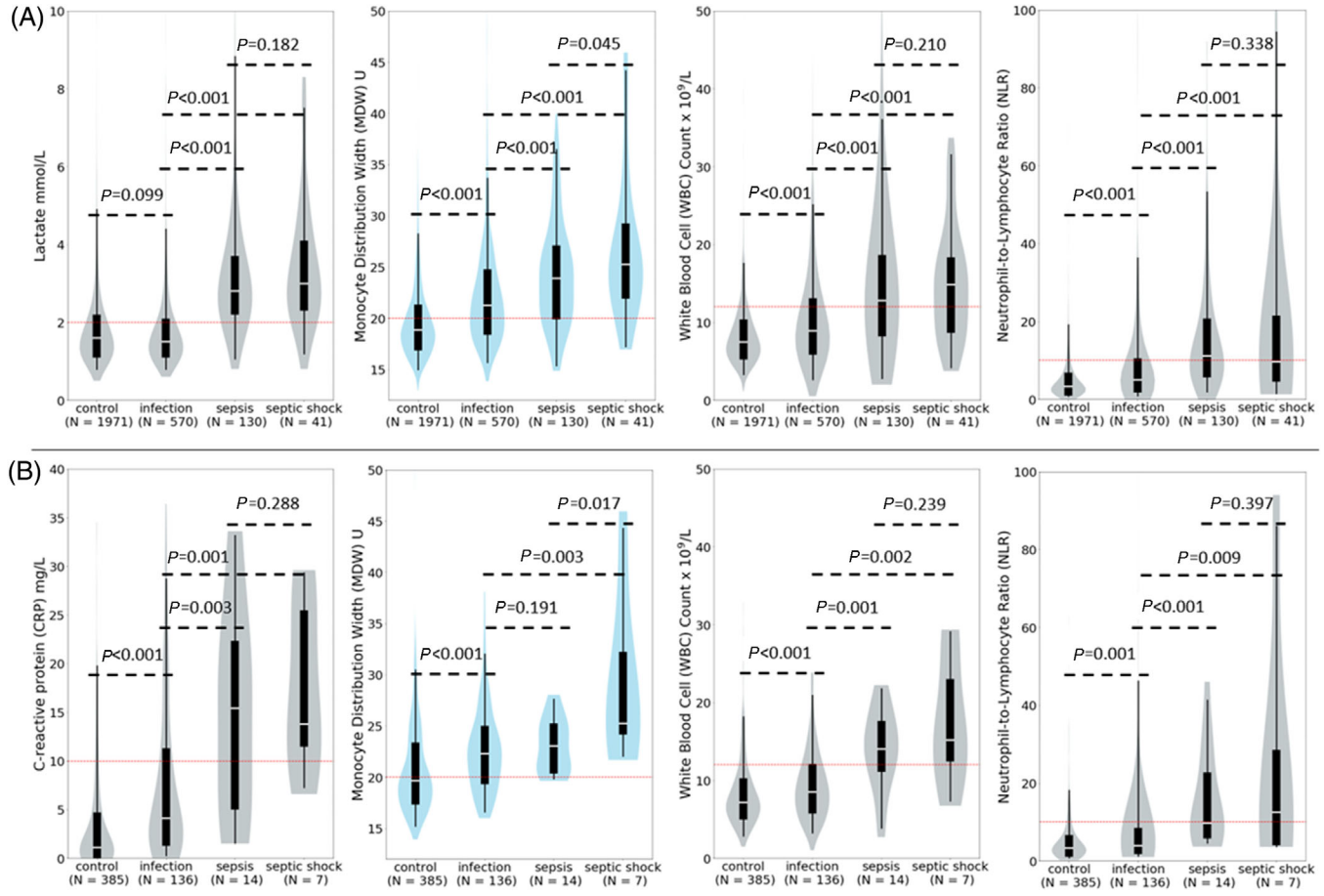

FIGURE 3 Lactate (row A) and C-reactive protein (Row B) by group compared to leukocyte measures for the same sub-populations. The red dashed line represents cutoff value of respective test. Sepsis and septic shock are defined according to Sepsis-3 consensus definition. CRP, C-reactive protein; MDW, monocyte distribution width; NLR, neutrophil-to-lymphocyte ratio; U, unit, N, number

TABLE 2 Diagnostic performance of monocyte distribution width, WBC, and neutrophil-to-lymphocyte ratio in isolation and in combination for sepsis (with or without shock) and septic shock

	AUC (95% CI)	Definition for positive Test	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)	NPV% (95% CI)	LR+	LR−
Sepsis (without shock or septic shock)								
qSOFA	0.71 (0.67–0.75)	≥2	52.2 (44.9–59.5)	88.6 (87.9–89.4)	9.6 (7.8–11.5)	98.8 (98.5–99.0)	4.60	0.54
MDW	0.80 (0.77–0.84)	> 20	77.8 (71.7–83.9)	66.8 (65.8–67.9)	5.2 (4.3–6.0)	99.2 (99.0–99.5)	2.35	0.33
WBC	0.77 (0.73– 0.81)	> 12 or < 4	60.6 (53.4–67.7)	81.3 (80.5–82.2)	7.0 (5.7–8.3)	98.9 (98.6-99.1)	3.25	0.48
NLR	0.84 (0.81–0.87)	> 10	53.3 (46.0–60.6)	90.8 (90.2–91.5)	11.9 (9.6–14.1)	98.8 (98.6–99.1)	5.81	0.51
MDW and WBC	0.83 (0.80–0.86)	Both tests positive	52.2 (44.9–59.5)	91.1 (90.4–91.7)	11.9 (9.7–14.2)	98.8 (98.5–99.1)	5.85	0.52
MDW or WBC		Either test positive	86.1 (81.1–91.2)	57.1 (56.0–58.2)	4.4 (3.8–5.1)	99.4 (99.2–99.7)	2.01	0.24
MDW and NLR	0.85 (0.82–0.88)	Both tests positive	43.3 (36.1–50.6)	94.6 (94.1–95.1)	15.7 (12.5–18.9)	98.6 (98.4–98.9)	8.06	0.60
MDW or NLR		Either test positive	87.8 (83.0–92.6)	63.0 (62.0–64.1)	5.2 (4.4–6.0)	99.6 (99.4–99.7)	2.38	0.19
WBC and NLR	0.85 (0.82–0.88)	Both tests positive	36.7 (29.6–43.7)	95.7 (95.2–96.1)	16.5 (12.8–20.1)	98.5 (98.2–98.8)	8.51	0.66
WBC or NLR		Either test positive	77.2 (71.1–83.3)	76.5 (75.5–77.4)	7.1 (5.9–8.2)	99.3 (99.1–99.5)	3.28	0.30
MDW and WBC and NLR	0.86 (0.83–0.89)	All tests positive	32.8 (25.9–39.6)	97.3 (96.9–97.6)	21.9 (16.9–26.8)	98.4 (98.1–98.7)	12.07	0.69
MDW or WBC or NLR		Any test positive	92.2 (88.3–96.1)	54.9 (53.8–56.0)	4.5 (3.9–5.2)	99.7 (99.5–99.8)	2.05	0.14
Septic shock								
qSOFA	0.82 (0.75–0.89)	≥2	74.4 (61.4–87.4)	88.1 (87.3–88.8)	3.3 (2.2–4.4)	99.8 (99.7–99.9)	6.23	0.20
MDW	0.85 (0.79–0.91)	>20	83.7 (72.7–94.8)	66.1 (65.1–67.1)	1.3 (0.9–1.8)	99.9 (99.8–100.0)	2.47	0.25
WBC	0.79 (0.71–0.87)	>12 or < 4	65.1 (50.9–79.4)	80.6 (79.8–81.5)	1.8 (1.1–2.5)	99.8 (99.6–99.9)	3.36	0.43
NLR	0.81 (0.73–0.88)	>10	46.5 (31.6–61.4)	90.0 (89.4–90.7)	2.5 (1.4–3.5)	99.7 (99.5–99.8)	4.66	0.59
MDW or WBC	0.84 (0.77–0.90)	Noth tests positive	55.8 (41.0–70.7)	90.3 (89.7–91.0)	3.0 (1.8–4.2)	99.7 (99.6–99.9)	5.78	0.49
MDW and WBC		Either test positive	93.0 (85.4–100.0)	56.4 (55.3–57.5)	1.1 (0.8–1.5)	99.9 (99.9–100.0)	2.13	0.12
MDW or NLR	0.87 (0.82–0.92)	Both tests positive	39.5 (24.9–54.1)	93.9 (93.4–94.5)	3.4 (1.8–5.0)	99.7 (99.5–99.8)	6.53	0.64
MDW and NLR		Either test positive	90.7 (82.0–99.4)	62.2 (61.1–63.3)	1.3 (0.9–1.7)	99.9 (99.8–100.0)	2.40	0.15
WBC or NLR	0.85 (0.78–0.91)	Both tests positive	32.6 (18.6–46.6)	95.1 (94.6–95.6)	3.5 (1.7–5.3)	99.6 (99.5–99.8)	6.65	0.71
WBC and NLR		Either test positive	79.1 (66.9–91.2)	75.6 (74.6–76.5)	1.7 (1.2–2.3)	99.8 (99.8–99.9)	3.24	0.28
MDW or WBC or NLR	0.86 (0.80–0.92)	All tests positive	30.2 (16.5–44.0)	96.8 (96.4–97.1)	4.8 (2.3–7.4)	99.6 (99.5–99.7)	9.30	0.72
MDW and WBC and NLR		Any test positive	97.7 (93.2–100.0)	54.1 (53.0–55.2)	1.1 (0.8–1.5)	100.0 (99.9–100.0)	2.13	0.04

Abbreviations: AUC, area under curve; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MDW, monocyte distribution width; NLR, neutrophil-to-lymphocyte ratio; NPP, negative predictive value; PPV, positive predictive value; qSOFA, quick sequential organ failure assessment; U, unit.

meeting criteria for immunosuppression as seen in supplemental Figure S1.

4 | LIMITATIONS

There are several limitations to this study. First, it was conducted at a single ED site, which could limit generalizability of findings. Second, qSOFA was measured early in the patients' stay to facilitate comparisons to MDW and other biomarkers as an early sepsis screen. Our assessment of altered mental status, a key component of qSOFA, was limited by retrospective analysis. Patients who had GCS <15 documented within 6 hours of ED arrival were captured, but GCS was not measured and recorded for all patients. To increase sensitivity, we incorporated ED chief complaints into our definition of altered mental status but it is likely that some patients with altered mental status were still not captured. Third, mortality was defined as in-hospital mortality or expectation of imminent death due to discharge to hospice. A definitive confirmation of death was not obtainable for all patients discharged to hospice. However, manual chart review did confirm the reliability of this definition. Last, we used EHR-based criteria to define sepsis and septic shock and individual cases. However, criteria used were robust and have been previously validated in ED populations.[31,35,36] These criteria are also highly objective and routinely used as a comparator in evaluating performance of new diagnostic assays, as they rely on structured laboratory, vital sign, and medication administration data to define organ dysfunction and clinician-initiated therapies to define infection and shock. Use of such endpoint criteria derived from EHR data increases the feasibility of large studies like this and reduces opportunity for bias and misclassification associated with post hoc clinical adjudication.[37,38] Finally, we reported on the isolated performance of selected hematologic parameters in early identification of sepsis, yet these data are a small subset of the information available to ED clinicians in real-time. It is likely that rapid simultaneous interpretation of WBC count, NLR, and MDW would be challenging in a fast-paced ED environment; it is equally likely that the information gained from such interpretation would be more valuable when considered in the broader context of the patient encounter (eg, presenting complaint, medical history and vital signs trends). Development of algorithms with capacity to assist clinicians in separating signal from noise (ie, unused clinical information reported in the EHR) in busy environments and facilitating actionable insights from novel diagnostics are important future aims of our work.

5 | DISCUSSION

Despite widespread recognition that early initiation of targeted therapy for sepsis is critical to outcome improvement, rapid identification of patients with the condition remains a major challenge.[39] Sepsis diagnosis is complicated by vague presentations and a lack of biomarkers or other ancillary tests that reliably rule in or rule out the disease.[15,16,40] Sepsis screening is particularly challenging in the ED, where SIRS and organ failure are often driven by non-infectious pathology and patients with occult infection may present before manifesting the telltale signs of sepsis (eg, tachycardia, hypotension, and altered mental status) detected by tools like qSOFA that have been applied for screening.[13,14,41]

In this pragmatic study we found that MDW may have concurrent utility as an ED-based sepsis screen and for severity of illness stratification. In isolation, MDW was the most sensitive marker tested for both sepsis and septic shock, outperforming qSOFA, WBC count, and NLR (Table 2). It also demonstrated an NPV of 99.2% for sepsis and 99.9% for septic shock. This makes MDW a strong candidate for broad-based screening where the aim is to identify unsuspected cases of sepsis. In addition, MDW was unique in distinguishing severity of illness (eg, septic shock from sepsis) compared to WBC count, NLR, lactaten and CRP. For example, NLR, which reported the highest discriminatory power for sepsis in our cohort (AUC = 0.84), showed limited capability in differentiating sepsis without shock from septic shock; this is consistent with prior findings in higher-risk populations (eg, ICU).[17] Thus, complementary clinical attributes of different leukocyte parameters (eg, utility for screening vs risk-stratification) suggests that they are most useful in combination.

When applied together, MDW, WBC, and NLR increased the AUC to 0.86 for both sepsis and septic shock (Table 2); a sensitivity of 92.2% for sepsis and 97.7% for septic shock was achieved. These sensitivities translate to negative likelihood ratios of 0.14 and 0.04, respectively. For a patient who presented to the ED with low pretest probability (eg, 20%), sepsis and septic shock would be effectively ruled out (posttest probabilities 3% and 1%, respectively) by not meeting threshold criteria for any of these 3 parameters. Further, it is likely that additional precision could be achieved through algorithms that incorporate other clinical data such as patient demographics, medical history, presenting complaints, and vital signs, all available before CBC results.[26]

Although work to leverage automated algorithms to support sepsis care in EDs is growing, a single simple biomarker that could enable early identification in an undifferentiated population would be highly valuable. To date, none has been discovered. Lactate, CRP, and procalcitonin are commonly employed for sepsis risk-stratification, but none exhibits optimal diagnostic performance when used in isolation.[42] Lactate, the only biomarker whose use is recommended by consensus guidelines, is a non-specific marker of cellular dysfunction and its elevation does not occur until late in the disease course; its use is recommended for prognostication and monitoring response to therapy rather than case identification.[43,44] CRP has been shown to lack sensitivity and specificity for sepsis in undifferentiated populations and to be particularly unreliable in the ED setting.[45,46] Procalcitonin may have a role in the differentiation of bacterial from viral infections, but recent data suggest its sensitivity for invasive infection is unacceptably low to warrant its use as a screening tool.[47,48] Utility of these biomarkers for early sepsis screening is further undermined by availability that depends on clinical suspicion and is subject to practice variability.

Lactate and CRP were measured in only 34.1% and 6.8% of our study population, respectively, and procalcitonin is not used clinically at our study site ED.

Thus, the importance of our focus on the CBC, and the availability of MDW as part of the CBC differential, should not be underestimated. The identification of disease-specific patterns within such a routinely used laboratory panel allows for recognition of a clinically time-sensitive disease (sepsis) when it is not suspected and has potential value in directing interventions to those most at risk of missed or delayed diagnosis and adverse outcome. In this study MDW was comparable to lactate and CRP in the highly selected group of patients for whom these tests were ordered by treating clinicians (Figure 3), yet MDW was available for the entire study cohort. WBC count, NLR, and MDW in isolation exhibited predictive value and unique diagnostic performance characteristics (Figure 2 and Table 2). However, lack of correlation between MDW and the other CBC parameters indicate that MDW has an important additive role[23] and could help optimize the use of CBC results.[17]

This is the largest clinically focused study of MDW to date. Our findings support those of several smaller studies that showed MDW in isolation has fair to good accuracy for detection of sepsis in an undifferentiated ED population.[22–24,49–51] Our study extends their findings by evaluating the performance of MDW alone and in combination with multiple routinely reported components of the CBC to optimize sensitivity and specificity. This is also the first study to show the performance of MDW relative to both lactate and CRP and to evaluate its performance in a subpopulation of patients with immunosuppression. Although this subanalysis was limited by its small sample size, MDW was effective in differentiating patients with infection and sepsis from those without infection, and similar trends in MDW signal were seen in this sample as in the larger population (Figure S1). These data strengthen the evidence supporting use of MDW for broad-based sepsis screening and argue for its incorporation into comprehensive algorithms for sepsis diagnosis and illness severity estimation.[51]

In this study, we evaluated the diagnostic accuracy of MDW for sepsis and septic shock, alone and in combination with other routinely reported hematologic parameters. Using this pragmatic approach, we found that MDW has utility for early identification of sepsis and severity of illness stratification. However, optimal diagnostic performance can be achieved through combination with other routinely available CBC parameters.

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CONFLICT OF INTERESTS

Stocastic (Jeremiah S. Hinson, Arnaud Debraine, Matthew Toerper, and Scott Levin) is collaborating with Beckman Coulter on integrating data-driven clinical decision support (CDS) with biomarkers measured by Beckman Coulter devices, including MDW. Jeremiah S. Hinson, Matthew Toerper, and Scott Levin and Johns Hopkins University have equity ownership in Stocastic. Although no CDS was directly studied, this research could underpin development of CDS in the future. These authors and the university are entitled to royalty distributions related to CDS technology that may be created. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with conflict of interest policies.

AUTHOR CONTRIBUTIONS

Alexandra Malinovska, Jeremiah S. Hinson, Oluwakemi Badaki-Makun, and Scott Levin were responsible for the study design and concept. Benjamin Hernried, Aria Smith, Matthew Toerper, and Scott Levin contributed to the data acquisition. Aria Smith, Matthew Toerper, Arnaud Debraine, and Scott Levin performed both data normalization and statistical analyses. All authors contributed to the interpretation of the data. Alexandra Malinovska, Jeremiah S. Hinson, Oluwakemi Badaki-Makun, Benjamin Hernried, and Thomas Kickler performed critical revisions of the manuscript for important intellectual content.

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AUTHOR BIOGRAPHY

Alexandra Malinovska, MD, is a physician trained in Switzerland and master of science (ScM) candidate at Bloomberg School of Public Health at Johns Hopkins University in Baltimore, Maryland.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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