JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
Open Access
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
American College of Emergency Physicians®
ADVANCING EMERGENCY CARE

SYSTEMATIC REVIEW

Infectious Disease

Check for updates

Diagnostic Performance of Monocyte Distribution Width for the Detection of Sepsis: A Systematic Review and Meta-Analysis

Gregory J. Eisinger MD, MSSW[1,2], Quinn Hosler MD[3], Elliott D. Crouser MD[1], Derrick D. Herman MD[1]

[1]*Division of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA*
[2]*Department of Emergency Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA*
[3]*Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Internal Medicine, University of Illinois, Chicago, Illinois, USA*

Correspondence

Gregory J. Eisinger, MD, MSSW, Division of Pulmonary/Critical Care and Sleep Medicine, Department of Emergency Medicine, The Ohio State University Wexner Medical Center, 241 W. 11th Ave Suite 5055E Columbus, OH 43210, USA. Email: Gregory.Eisinger@osumc.edu

An earlier version of our data was presented the annual meeting of the American Thoracic Society in May of 2023 (Washington, DC) and several departmental conferences at The Ohio State University (4/2023; 5/2023), it has never been published in manuscript form and has not been presented with the current updated search.

Received: September 27, 2024
Revised: January 14, 2025
Accepted: January 17, 2025
https://doi.org/10.1016/j.acepjo.2025.100073

Abstract

Objectives: To aggregate literature on the diagnostic performance of monocyte distribution width (MDW) for sepsis detection among adults in the emergency department and inpatient settings.

Methods: We searched the MEDLINE, EMBASE, SCOPUS, and Cochrane databases for studies evaluating MDW for sepsis diagnosis in adults in the hospital setting through October 19, 2024. Two authors (G.E. and Q.H.) independently performed eligibility assessment, data extraction, and risk of bias assessment. We evaluated performance for sepsis-2 and sepsis-3 separately and applied separate diagnostic thresholds depending on the anticoagulant used in blood collection. Data were pooled using a random-effects model. We performed multiple sensitivity analyses to evaluate the stability of our findings.

Results: Twenty-five observational studies comprising 39,041 patients were included. The area under the summary receiver operating curve (AUC) was 0.82 (95% CI, 0.78-0.85) for both sepsis-2 and sepsis-3. Sensitivity and specificity were 0.79 (95% CI, 0.74-0.83) and 0.7 (95% CI, 0.61-0.78) for sepsis-2 and 0.83 (95% CI, 0.78-0.88) and 0.64 (95% CI, 0.55-0.71) for sepsis-3. The threshold-independent weighted-average AUC was 0.76 (SD, 0.1) for sepsis-2 and 0.77 (SD, 0.07) for sepsis-3. The aggregate negative predictive value was 94% for sepsis-2 and 96% for sepsis-3. We observed similar performance across all sensitivity analyses. We assessed the overall quality of evidence to be low.

abstract continues

Supervising Editor: Faheem Guirgis, MD

JACEP OPEN

Abstract (continued)

Conclusions: MDW performs similarly to other biomarkers such as procalcitonin for the diagnosis of sepsis, with the unique advantage of rapid availability as part of routine testing.

Keywords: *sepsis, monocytes, biomarkers, diagnostic tests, blood cell count*

1 INTRODUCTION

1.1 Background

The complete blood count (CBC) is one of the oldest and most widely used blood tests in the evaluation of sepsis. Volume, conductivity, and scatter (VCS) technology performed by some hematology analyzers adds unique cell morphology data to the routine CBC without additional time or cost. In 2005, Chaves et al[1] reported the first evaluation of VCS for sepsis detection. Subsequent studies identified monocyte distribution width (MDW), a measure of variation in monocyte volume, as the best-performing VCS parameter, with negative predictive value (NPV) as high as 97%.[2] Other devices generate similar data using flow cytometry.[3]

1.2 Importance

Sepsis is a life-threatening syndrome characterized by dysregulated host response to infection. It is the leading cause of death in hospitals[4] and causes 20% of deaths worldwide.[5] Early recognition is challenging, and delayed treatment leads to measurably increased mortality.[6,7] Better biomarkers could save lives by enhancing clinicians' ability to detect the deadly syndrome before the onset of organ dysfunction.

1.3 Goals of This Investigation

Amid a growing body of literature on the use of MDW for sepsis detection, we conducted a systematic review and meta-analysis to summarize its diagnostic performance in the hospital setting with the hypothesis that it would be similar to that of procalcitonin (PCT).

2 METHODS

We designed this study using the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[8] The protocol was prespecified and registered in the PROSPERO database (CRD42021253088). The report follows the Meta-analysis Of Observational Studies in Epidemiology checklist.[9]

2.1 Search Strategy and Study Selection

In consultation with a research librarian, we performed a comprehensive search of the MEDLINE, EMBASE, SCOPUS, and Cochrane databases on October 19, 2024. The full search strategy is shown in Supplementary Appendix 1. We reviewed the bibliographies of the screened studies to identify additional references.

Two authors (G.E. and Q.H.) independently performed eligibility assessment using the COVIDENCE bibliographic database. The senior author (D.H.) resolved any disagreements. We included studies evaluating MDW for sepsis detection among adults in a hospital setting (emergency department [ED], wards, or intensive care unit [ICU]). We excluded studies if the data were previously published in another included manuscript, accepted sepsis definitions were not used, data to construct 2 × 2 contingency tables were not available, or if non-VCS technology was used. We did not apply any language filters. Unpublished conference abstracts were excluded. When needed, we contacted study authors to solicit further information.

2.2 Measures of Diagnostic Accuracy

The primary measure of interest was the area under the summary receiver operator characteristic (ROC) curve (sAUC) of MDW for sepsis-2[10] and sepsis-3,[11] which we analyzed as separate reference standards. Other measures assessed included sensitivity, specificity, and positive/negative predictive value (PPV/NPV). To pool diagnostic accuracy data, contingency tables of true/false positive/negative rates were constructed using prevalence and sensitivity/specificity at a given diagnostic threshold. The thresholds reported in studies vary dramatically and depend on the anticoagulant used in blood collection.[12–14] To avoid bias, when multiple cutpoints were reported, we used the one closest to a *common threshold*, rather than the best-performing cutpoint. The common threshold for dipotassium (K2) EDTA was defined by the manufacturer-recommended cutpoint of 20 and for tripotassium (K3) EDTA by the median best cutpoint of 22. If the anticoagulant could not be determined, it was inferred from the range of MDW values obtained and deemed ambiguous.

Because the AUC for each individual study applies across the full range of cutpoints, we also calculated a weighted-average AUC (wAUC), which provides an additional threshold-independent method of pooling data for the AUC.

2.3 Data Extraction, Risk of Bias Assessment, and Quality of Evidence Assessment

Two trained investigators (G.E. and Q.H.) who were not blinded to the study purpose independently performed data extraction and risk of bias (ROB) assessment using a standardized process. Any disputes were settled by the senior author. We evaluated ROB using an adapted version of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) instrument.[15] We assessed the overall quality of

evidence using the Grading of Recommendations, Assessment, Development, and Evaluate (GRADE) system.[16] The GRADE method rates the level of confidence in the findings of the analysis as high, moderate, low, or very low based on ROB, inconsistency, imprecision, indirectness, and publication bias. Application of GRADE to studies of diagnostic test accuracy has been previously described.[17]

2.4 Statistical Analysis

The authors performed data analysis in consultation with a biostatistics team using the MIDAS (Meta-analytical Integration of Diagnostic test Accuracy Studies) program in STATA (v.17, StataCorp).[18] Data were pooled using a random-effects model. We performed prespecified sensitivity analyses for studies conducted in the ED setting, those enrolling undifferentiated patients (ie, without required clinical suspicion of sepsis), and those at low ROB. Additional post-hoc sensitivity analyses are described in the Results section.

We assessed heterogeneity using the I^2 statistic. We evaluated sources of heterogeneity using meta-regression and publication bias using the Deeks' funnel plot and rank-correlation test.[19]

3 RESULTS

3.1 Results of the Search

Figure 1 shows the study selection diagram. The initial search yielded 8061 articles. After removing duplicates, 2494 studies underwent title and abstract screening, of which 2066 were irrelevant and 402 did not meet inclusion criteria. Bibliography review of the 29 articles selected for full-text review identified 3 additional studies. Two of these were unpublished conference abstracts with insufficient data for inclusion.[20,21] The third was an unpublished derivation cohort for the 2019 study by Crouser et al[22] and was included. Ultimately, we included 25 studies comprising 39,041 patients.[2,12,13,22–41]

3.2 Features of Included Studies

Supplementary Appendix 2 summarizes salient features of the included studies. All were observational and published between 2017 and 2024. Most (n = 19) were conducted in the ED setting, whereas 3 were performed in the ICU,[24,29,42] 2 in an inpatient ward,[12,41] and 1 in multiple settings.[36] Fourteen studies included undifferentiated patients, 10 only enrolled patients with suspected infection,[12,28,29,32–38] and 1 included only patients with suspected complications of cirrhosis.[23] Eight studies used sepsis-2 criteria, 11 used sepsis-3, and 6 reported both sepsis-2 and sepsis-3, though 1 of these 6 did not include sufficient data to be included in our sepsis-2 analysis.[25]

Thirteen studies were analyzed with the common threshold for K2EDTA and 12 for K3. For 2 studies[23,32] that did not report the anticoagulant, the authors did not respond to our request for clarification. K2EDTA was inferred from the range of MDW values and they were deemed ambiguous. For

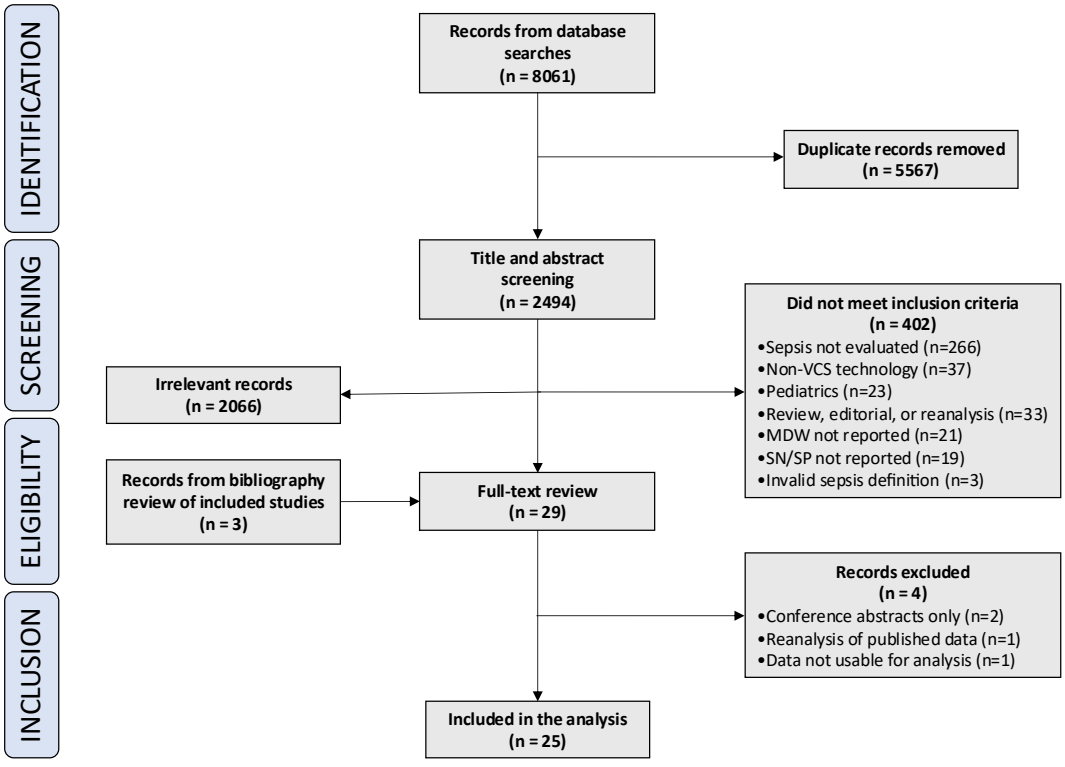

FIGURE 1. Study selection diagram. MDW, monocyte distribution width; SN, sensitivity; SP, specificity; VCS, volume, conductivity, scatter.

2 others,[24,28] the authors confirmed the anticoagulant but their response was discordant with the reported MDW values, so they were also treated as ambiguous. Excluding ambiguous studies, the median (IQR) best cutpoint was 20 (0.3) for K2EDTA and 22 (1.5) for K3EDTA.

Many studies compared the performance of MDW with other biomarkers or combinations of biomarkers. For this analysis, we only considered the performance of MDW in isolation.

3.3 ROB of Included Studies

Figure 2 depicts the QUADAS-2 assessment. Five studies[2,13,26,31,35] were deemed at low ROB, 5 were of unclear risk,[22,25,27,30] and the remaining 15 were at high risk. The most common sources of bias were (1) poorly described sepsis adjudication methods; (2) no blinding of adjudicators to the MDW result; and (3) lack of a prespecified diagnostic cutpoint. Concern regarding applicability to our research question was high for 12 studies,[12,23,28,29,32–38,41] all due to enrollment of limited patient populations such as those with suspected infection.

3.4 Summary of Diagnostic Performance

3.4.1 Overall analysis

Figure 3 depicts the sample-size weighted-average MDW for each patient group stratified by the anticoagulant used. Median MDW was higher for K3 EDTA vs K2, though less so in control patients. Median MDW increased linearly with progression from control patients, to localized infection (ie, infection without sepsis), to sepsis, and to septic shock. Median MDWs for noninfectious systemic inflammatory response syndrome (SIRS) were below sepsis thresholds.

Figure 4 shows the summary ROCs and forest plots for sepsis-2 and sepsis-3. The sAUC was 0.82 (95% CI, 0.78-0.85) both for the 13 studies evaluating sepsis-2 and the 17 studies of sepsis-3. The threshold-independent wAUC was 0.76 (SD, 0.1) for sepsis-2 and 0.77 (SD, 0.07) for sepsis-3. Summary sensitivity and specificity were 0.79 (95% CI, 0.74-0.83) and 0.7 (95% CI 0.61-0.78) for sepsis-2 and 0.83 (0.78-0.88) and 0.64 (0.55-0.71) for sepsis-3. Using the sample-size-weighted aggregate disease prevalence (17.2% for sepsis-2 and 13.9% for sepsis-3) and the summary sensitivity and specificity yields a NPV of 0.94 and PPV of 0.35 for sepsis-2 and NPV of 0.96 and PPV of 0.27 for sepsis-3. Supplementary Appendix 3 shows conditional probability plots for estimating the likelihood of sepsis based on pretest probability.

3.4.2 Sensitivity analyses

Table summarizes the results of the sensitivity analyses. Too few sepsis-3 studies were at low ROB to permit a full meta-analysis so we used the meta-regression function to calculate sensitivity and specificity for that subgroup. All studies evaluating sepsis-2 were performed in the ED so no sensitivity analysis was required. We conducted additional post-hoc sensitivity analyses with exclusion of studies with ambiguous anticoagulant, outlier studies[13,24] (see Supplementary Appendix 4 for outlier impact analysis), studies with <500 patients, and separated by anticoagulant used.

With the exception of some minor variation in specificity (<10% in all cases), the results of all sensitivity analyses were very similar to the main analysis.

Given the likely greatest utility of MDW as a rule-out test for sepsis in the ED, we conducted an additional analysis of the NPV in studies conducted in the ED. The sample-size-weighted NPV among ED studies was lower than in the overall analysis at 0.89 for sepsis-2 (n = 13) and 0.95 for sepsis-3 (n = 11).Because this appeared to be driven by several studies with very high sepsis prevalence due to enrollment of only patients with suspected infection, we conducted a further analysis of only ED studies of undifferentiated patients and found a NPV of 0.96 for sepsis-2 (n = 8) and 0.99 for sepsis-3 (n = 6).

3.5 Heterogeneity and Publication Bias

Heterogeneity was severe for both sepsis-2 (I^2 = 99; 95% CI, 98-99) and sepsis-3 (I^2 = 100; 95% CI, 100-100) with 6% and 18% respectively attributed to the threshold effect. Other significant sources of heterogeneity ($P < .1$) identified in the meta-regression model (Supplementary Appendix 5) included study setting (ED vs other), enrollment of undifferentiated patients, outlier status, anticoagulant and cutpoint used, sepsis prevalence, and study design (prospective vs retrospective). Severe heterogeneity persisted in all sensitivity analyses was conducted.

Supplementary Appendix 6 shows Deeks' funnel plots. There was evidence of significant publication bias ($P < .1$) for both sepsis-2 and sepsis-3.

3.6 Quality of Evidence

We rated the overall quality of evidence as *low* both for sepsis-2 and sepsis-3. This assessment was based on all studies being observational, severe heterogeneity, and evidence of significant publication bias. Although many studies were assessed to be at high or unclear ROB, the presence of 5 large well-conducted studies at low ROB was felt sufficient to assess the impact of bias as "not serious." Additionally, although no studies assessed the impact of MDW on patient outcomes, we did not downgrade the quality rating for indirectness because the scope of this review was to assess diagnostic accuracy rather than clinical utility.

4 DISCUSSION

4.1 Summary of Results

Despite severe heterogeneity and high ROB in many studies, our analysis suggests moderate performance of MDW for

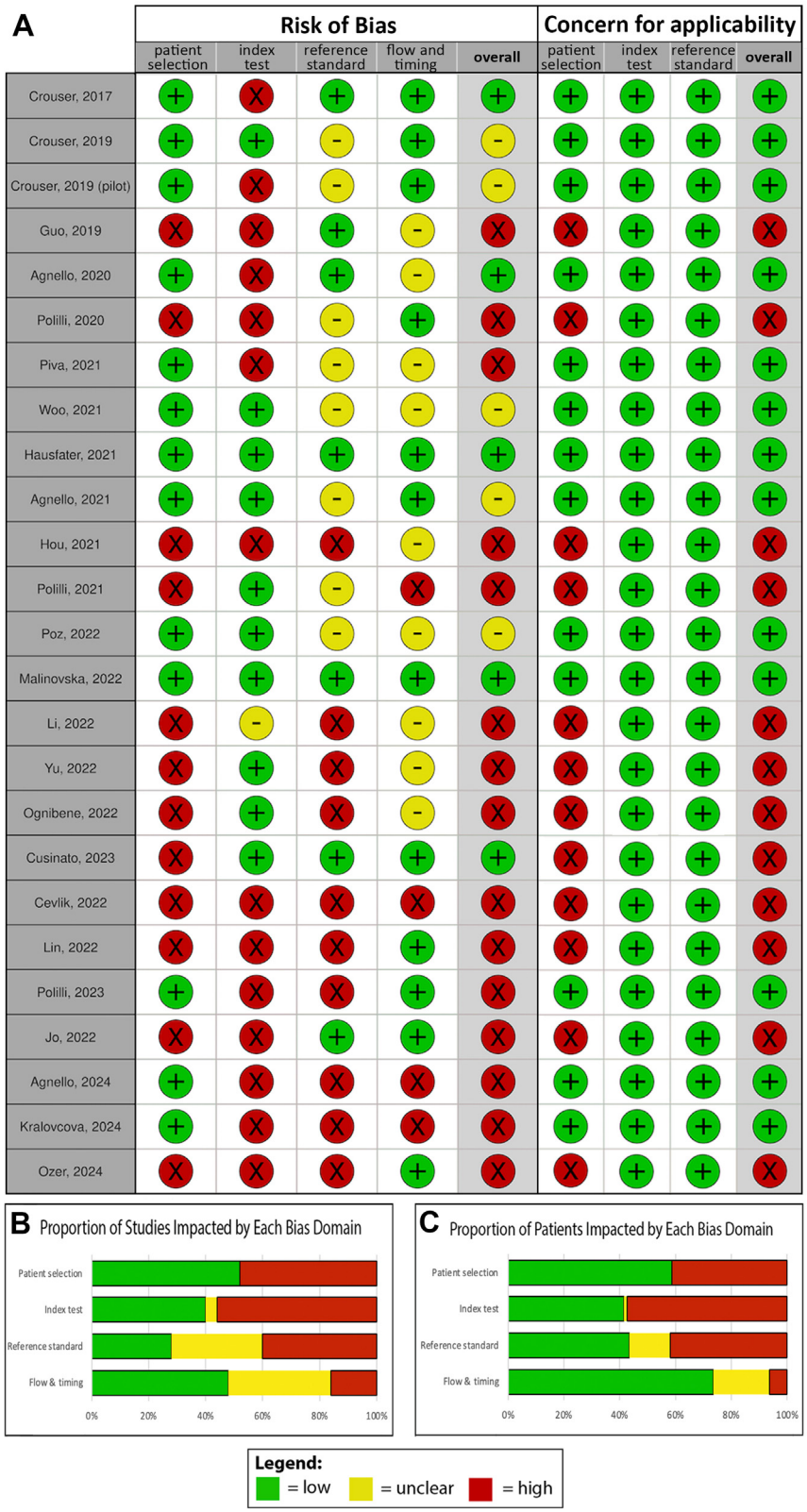

FIGURE 2. Risk of bias assessment. A, The risk of bias and concerns for applicability to the research question according to the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for each included study. B, The distribution of domains of bias across the included studies. C, The distribution across the included patients.

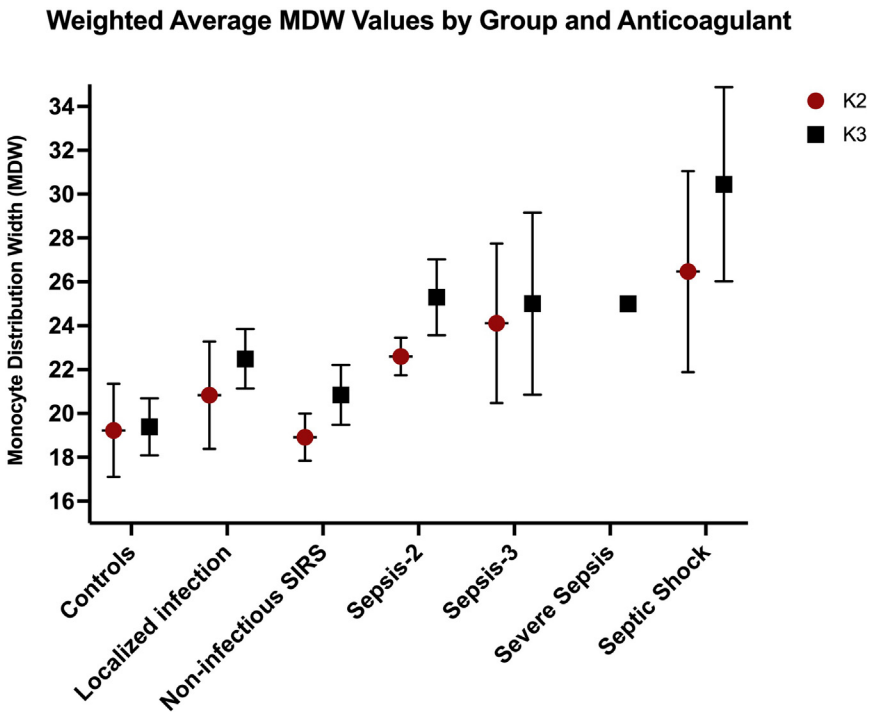

FIGURE 3. Points indicate the weighted average and error bars indicate the weighted SD monocyte distribution width (MDW) across the included studies. The *n* below each patient group indicates the number of studies that reported a median MDW for that group. Note that for the severe sepsis group, only a single study using K3EDTA and no studies using K2EDTA reported a value. K2, dipotassium; K3, tripotassium; SIRS, systemic inflammatory response syndrome.

sepsis detection, which was robust to multiple sensitivity analyses. The greatest utility of MDW lies in its high NPV for both sepsis 2 and 3, though given the more modest sensitivity, this is highly dependent on disease prevalence. Additionally, low PPV creates potential for many false positives if interpreted in isolation.

4.2 Comparison With Other Meta-Analyses

Several previous meta-analyses have examined MDW for sepsis diagnosis.[43–46] The study by Motawea et al[46] reviewed only 5 studies, focused on correlation between MDW and PCT, and is difficult to compare with our own. The other analyses all have important differences in scope/objective, methodology, and included studies compared to our own (see Supplementary Appendix 7), but have generally similar findings. Pooled estimates for AUC ranged from 0.75 to 0.93 and for sensitivity and specificity ranged from 0.73 to 0.81 and 0.65 to 0.85 respectively for sepsis-2 and from 0.81 to 0.93 and 0.56 to 0.73 for sepsis-3. Despite slight differences driven primarily by methodology, these studies all conclude that MDW sensitivity is greater than its specificity and that sensitivity is higher and specificity lower for sepsis-3 than sepsis-2. In our own study and the others that compared performance in K3 vs K2EDTA,[44,45] performance was slightly better in K3, largely driven by greater specificity, likely due to higher cutpoints used in K3 studies. Notably only 2 of the other meta-analyses[44,45] systematically evaluated the ROB in the included studies and neither commented on the overall ROB for each study. In Huang et al[45] no studies were assessed to be at high ROB in any domain and in Malinovska et al[44] much fewer high-risk assessments were made than in our study. These differences are likely due to the more stringent criteria we applied related to prespecified cutpoints, descriptions of sepsis adjudication methods, and blinding to the results of the index test by adjudicators.

Although each of these other meta-analyses has its own advantages and limitations, our study adds valuable new data to the existing literature. First, it is the largest meta-analysis to date. Compared with the next largest,[45] we included 8 additional studies and >16,000 additional patients (22,459 vs 39,041). Secondly, our approach to handling the complexity of studies reporting multiple different cutpoints and using different anticoagulants and sepsis definitions was unique. As there is no perfect way to handle these issues, additional studies using different approaches help to bolster confidence in the findings. This is also the first study to employ the GRADE system for assessing quality of evidence. Additional strengths of our study include use of rigorous methodology, best practices for systematic review and meta-analysis, a preregistered protocol, a validated reporting checklist, execution of multiple sensitivity analyses and investigations into sources of heterogeneity, a conservative approach to evaluating ROB and quality of evidence, and reporting of aggregate median MDW

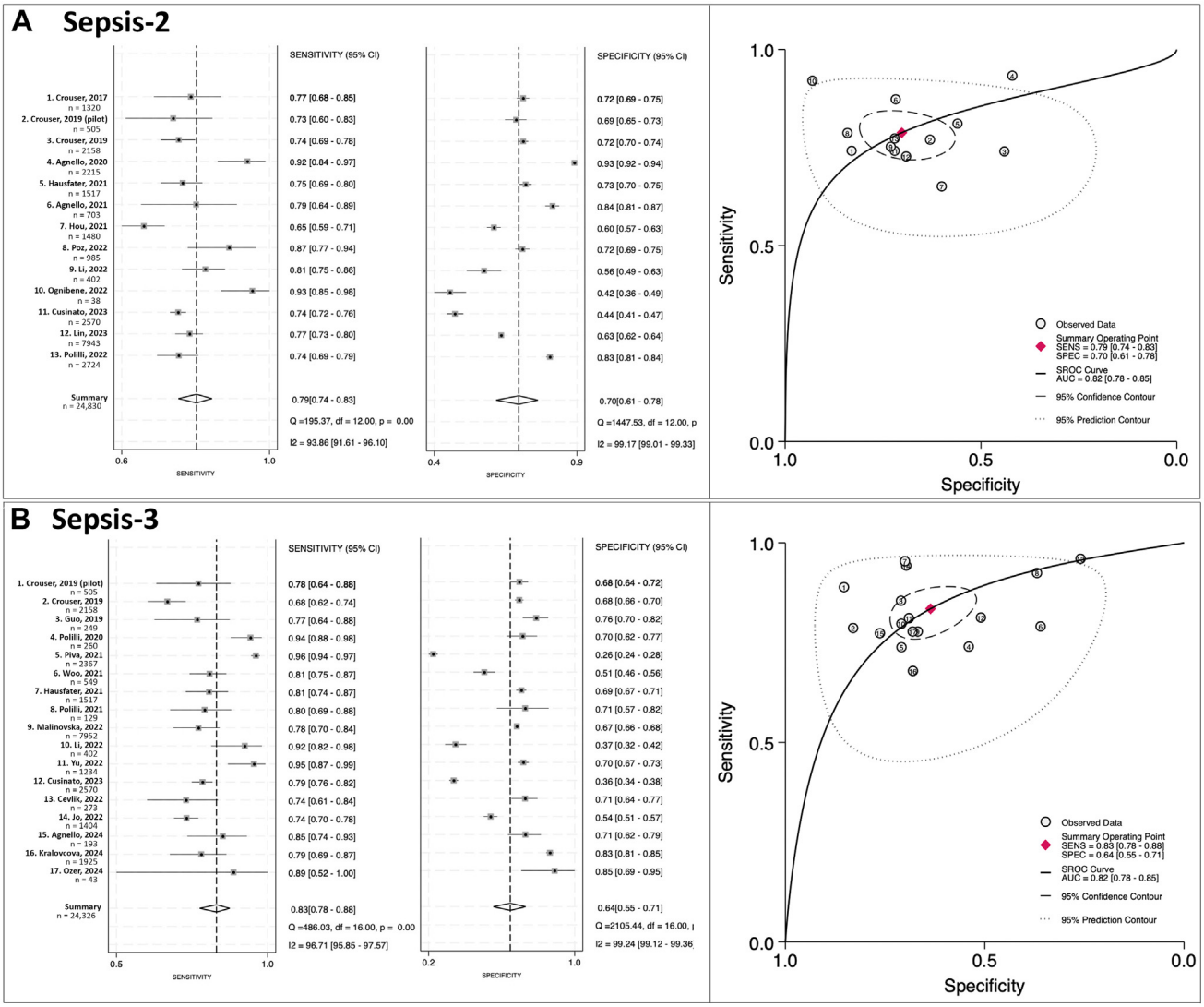

FIGURE 4. Primary analysis. A, The forest plots for sensitivity and specificity and the summary receiver operating characteristic curve for sepsis-2. B The same outputs for the sepsis-3 outcome. AUC, area under the curve; SENS, sensitivity; SPEC, specificity; SROC, summary receiver operating characteristic.

values by group and PPV/NPV, which, to our knowledge, was not done in prior studies.

4.3 Comparison With Other Biomarkers

A 2013 meta-analysis[47] evaluated PCT for sepsis-2 detection in 30 studies and found a sAUC of 0.85 with sensitivity and specificity of 0.77 and 0.79, respectively. Fewer studies have evaluated PCT using the sepsis-3 criteria. A 2019 retrospective study[48] found a sensitivity of 0.748 and specificity of 0.638 for sepsis-3 among 866 patients, mirroring the lower specificity of MDW for sepsis-3 in our study. The meta-analysis by Motawea et al[46] found a high degree of correlation between MDW and PCT, with slightly higher AUC for MDW. The meta-analysis by Huang et al[45] found that MDW had a similar AUC to PCT but with higher sensitivity and lower specificity, and very similar performance to C-reactive protein (CRP). A 2018 meta-analysis found poorer performance for CRP vs PCT for sepsis-2 driven by lower specificity with CRP.[49]

Compared with PCT and CRP, MDW has the advantage of inclusion within the routine CBC without additional cost, processing time, or need for suspicion of sepsis to prompt ordering. Other traditional CBC parameters have also been studied for sepsis. Evaluation of white blood cell (WBC) and band neutrophil count for sepsis-2 is confounded by incorporation bias because the index test is contained within the reference standard SIRS criteria. Several of our included studies[25,26,31,37] compared WBC with MDW for sepsis-3 diagnosis and found lower AUC for WBC. The neutrophil-to-lymphocyte ratio (NLR) has more support as a prognostic than diagnostic biomarker.[50] A recent meta-analysis including 14 studies of NLR found

TABLE. Sensitivity analyses.

	AUROC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Main analysis			
Sepsis-2 (n = 13)	0.82 (0.78-0.85)	0.79 (0.74-0.83)	0.7 (0.61-0.78)
Sepsis-3 (n = 17)	0.82 (0.78-0.85)	0.83 (0.78-0.88)	0.64 (0.55-0.71)
Weighted average			
Sepsis-2 (n = 13)	0.76 (SD 0.1)	n/a	n/a
Sepsis-3 (n = 17)	0.77 (SD 0.07)	n/a	n/a
Prespecified sensitivity analyses			
Low risk of bias			
Sepsis-2 (n = 4)	0.83 (0.79-0.86)	0.8 (0.74-0.85)	0.75 (0.52-0.89)
Sepsis-3 (n = 3)[a]	n/a	0.79 (0.67-0.91)	0.58 (0.38- 0.77)
ED setting			
Sepsis-2 (n = 13)	n/a	n/a	n/a
Sepsis-3 (n = 11)	0.80 (0.77-0.84)	0.8 (0.75-0.84)	0.63 (0.53-0.71)
Undifferentiated patients			
Sepsis-2 (n = 8)	0.85 (0.81-0.88)	0.78 (0.73-0.83)	0.79 (0.71-0.85)
Sepsis-3 (n = 9)	0.82 (0.78-0.85)	0.82 (0.74-0.88)	0.66 (0.54-0.76)
Post-hoc sensitivity analyses			
K2-EDTA			
Sepsis-2 (n = 7)	0.79 (0.75-0.82)	0.8 (0.73-0.85)	0.62 (0.52-0.71)
Sepsis-3 (n = 10)	0.8 (0.77-0.84)	0.84 (0.77-0.9)	0.59 (0.46-0.7)
K3-EDTA			
Sepsis-2 (n = 6)	0.85 (0.81-0.87)	0.78 (0.7-0.84)	0.78 (0.67-0.87)
Sepsis-3 (n = 7)	0.83 (0.8-0.86)	0.82 (0.76-0.87)	0.7 (0.63-0.77)
Excluding outlier studies			
Sepsis-2 (n = 12)	0.79 (0.76-0.83)	0.77 (0.73-0.81)	0.67 (0.59-0.74)
Sepsis-3 (n = 16)	0.82 (0.79-0.85)	0.82 (0.77-0.86)	0.66 (0.59-0.72)
Excluding studies with ambiguous anticoagulant used			
Sepsis-2 (n = 12)	0.83 (0.79-0.86)	0.80 (0.75-0.83)	0.71 (0.61-0.79)
Sepsis-3 (n = 14)	0.82 (0.78-0.85)	0.82 (0.77-0.87)	0.65 (0.57-0.72)
Excluding studies with sample size <500			
Sepsis-2 (n = 11)	0.82 (0.78-0.85)	0.77 (0.73-0.81)	0.73 (0.65-0.81)
Sepsis-3 (n = 10)	0.79 (0.76-0.83)	0.82 (0.75-0.88)	0.6 (0.49-0.7)

AUROC, area under the receiver operating curve; ED, emergency department; K2, dipotassium; K3, tripotassium. The "main analysis" group contains all included studies. The "weighted average" group depicts the threshold-independent weighted-average AUROC for comparison. "Low risk of bias," "ED setting," and "undifferentiated patients" are the prespecified sensitivity analyses with the latter referring to studies of all-comer patients without a required suspicion for infection. No sensitivity analysis is reported for sepsis-2 studies in the ED setting because all included studies of sepsis-2 were conducted in the ED. Additional analyses with studies separated by anticoagulant used (K2 vs K3EDTA), excluding outlier studies, excluding studies with ambiguous anticoagulant, and excluding small studies were conducted post-hoc based on the findings of our initial analysis.

[a] Because too few studies of sepsis-3 were assessed to be at low risk of bias to permit a full meta-analysis, this sensitivity and specificity data were generated using the meta-regression function with low risk of bias as a subgroup analysis.

an AUC of 0.87, sensitivity of 0.77, and specificity of 0.88 for neonatal sepsis.[51] A large retrospective study of NLR for sepsis-2 diagnosis in adults found a more modest AUC of 0.68, though this was identical PCT in that study.[52]

Several other monocyte and neutrophil VCS parameters have also been evaluated for sepsis detection with MDW showing the best performance.[2] Numerous other biomarkers have been studied, though few have gained widespread adoption into clinical practice.[53]

4.4 Role of MDW in Sepsis Detection

Sepsis diagnosis is challenging due to variable clinical presentations and delayed availability of gold standard testing.

Sepsis criteria are intended to render complex, diverse, and inaccessible cellular physiology recognizable as a syndrome at the bedside, but do so imperfectly.[54] The sepsis-3 definition prioritizes specificity, with focus on organ dysfunction while potentially missing patients with earlier manifestations who may benefit from intervention.

Increased MDW appears to signify activation of cellular inflammatory machinery. In an in vitro sepsis model, our group showed that increased MDW reflects cellular swelling associated with pyroptosis.[55] Another study demonstrated that monocyte subset switching also plays a role.[56] As a reflection of these early events in the translation of an infectious stimulus to a systemic response, MDW may identify septic patients before they experience severe clinical manifestations.[22]

However, given its modest sensitivity, MDW cannot be relied on to rule-out sepsis in a population with high pretest probability. For example, in one study with a sepsis-2 prevalence of 67%, NPV was found to be as low as 45%.[35] Additionally, due to poor PPV indiscriminate use in a low prevalence population may lead to overtreatment. Interpretation in the context of other biomarkers and vital signs may improve performance. Adding MDW to WBC[2] or SIRS/quick sequential organ failure assessment (qSOFA) criteria has been shown to improve performance.[57] More complex composite variables have also been studied. The "sepsis index" improved specificity with minimal impact on sensitivity.[27] The "simple scoring system" for sepsis incorporating MDW and other clinical variables[28] and the "FANS score"[34] also improved performance. Given the complexity of applying such scoring systems at the bedside, artificial intelligence programs may be useful.[58] Future studies incorporating MDW into machine learning algorithms are of great interest (ClinicalTrials.gov identifier: NCT05304728).

As with all diagnostic tests, dichotomization into positive vs negative results relative to a given cutpoint is necessary in the evaluation of diagnostic performance, and common in implementation in clinical laboratories. Although selection of the cutpoint with the best balance of sensitivity and specificity (ie, highest AUC) is required in the research setting, in clinical practice it may be advantageous to treat the biomarker as a continuous variable and adjust one's own threshold based on pretest probability and whether sensitivity vs specificity is of greater value for an individual patient. As is often done with PCT, laboratories may consider providing multiple MDW cutpoints to help clinicians to interpret the results (ie, sepsis unlikely, sepsis possible, sepsis likely).

4.5 Limitations of This Review

The high degree of heterogeneity and ROB in the included studies limits the certainty of our performance estimates. Also, the transition to sepsis-3 resulted in 2 distinct reference standards, making it impossible to pool data across all studies. Additionally, the impact of anticoagulant on MDW reference range precludes use of a single threshold value to derive performance measures. Our strategy of using the common threshold was felt to be the fairest approach, though all approaches have limitations. Ambiguity regarding the anticoagulant used in several studies further complicates interpretation of the data. Lastly, statistical measures of interrater agreement in study selection and ROB assessment were not initially calculated and were unable to be reconstructed retrospectively due to having completed the search in several waves as new studies were published.

4.6 Future Directions

Randomized trials are needed to assess whether use of MDW vs usual practice influences clinician behavior, such as disposition to home vs admission or wards vs ICU level of care, antibiotic prescribing, and fluid resuscitation. More importantly, studies evaluating the impact of MDW use on patient-oriented outcomes such as mortality, length of stay, and development of organ failures will provide the ultimate test of utility. Use of machine learning algorithms integrating MDW with other clinical, laboratory, imaging, and microbiologic data to create more robust diagnostic models requires further investigation. The significance of changes in an individual patient's baseline MDW or in response to treatment should also be investigated. Further study of MDW as a predictor of developing sepsis in patients presenting with localized infection or being admitted for noninfectious reasons is also warranted.

In conclusion, this large meta-analysis demonstrated high NPV of MDW for sepsis in the hospital setting. Performance was comparable to other biomarkers such as PCT, though with higher sensitivity and lower specificity. Low cost, short processing time, and inclusion in routine testing are unique advantages to MDW as a sepsis screening tool.

ACKNOWLEDGMENTS

The authors wish to acknowledge the biostatistics team including Guy Brock, Jing Peng, and Jiang Ma for their consultation, as well as our research librarian Stephanie Schulte for her assistance in developing our search strategy.

AUTHOR CONTRIBUTIONS

G.J.E.: study design, literature search, eligibility assessment, data extraction, risk of bias assessment, statistical analysis (in consultation with biostatistics team), manuscript preparation, submission. Q.H.: literature search, eligibility assessment, data extraction, risk of bias assessment, and manuscript review and editing. D.D.H.: study design, settling disagreements on study inclusion and risk of bias assessment, methodology supervision, statistical analysis (in consultation with biostatistics team), and manuscript review and editing. E.D.C.: study design, scientific/content consultation, eligibility assessment, supervision of study execution and analysis, and manuscript review and editing.

FUNDING AND SUPPORT

By *JACEP Open* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

CONFLICT OF INTEREST

EDC is the clinical lead on a project jointly funded by the Department of Defense (BARDA) and Beckman-Coulter regarding the incorporation of MDW into a machine learning algorithm for early sepsis detection. Beckman-Coulter had no role in the design or conduct of this analysis, nor the preparation of the manuscript, and did not review the data or manuscript prior to submission. He also receives funding from the National Institutes of Health for unrelated work on sarcoidosis and COVID-19, as well funding from several private companies for unrelated work on sarcoidosis. The remaining authors have no pertinent conflicts of interest to disclose, financial or otherwise.

DATA SHARING STATEMENT

The entire master dataset and analytic code for this study are available on request, from the date of article publication by contacting the corresponding author.

ORCID

Gregory J. Eisinger MD, MSSW https://orcid.org/0000-0003-2748-9603

REFERENCES

1. Chaves F, Tierno B, Xu D. Quantitative determination of neutrophil VCS parameters by the coulter automated hematology analyzer: new and reliable indicators for acute bacterial infection. *Am J Clin Pathol*. 2005;124(3):440-444. http://doi.org/10.1309/LLF7-5W0F-WQQ8-TCC5
2. Crouser ED, Parrillo JE, Seymour C, et al. Improved early detection of sepsis in the ED with a novel monocyte distribution width biomarker. *Chest*. 2017;152(3):518-526. http://doi.org/10.1016/j.chest.2017.05.039
3. Urrechaga E. Reviewing the value of leukocytes cell population data (CPD) in the management of sepsis. *Ann Transl Med*. 2020;8(15). http://doi.org/10.21037/atm-19-3173; 953-953.
4. Liu V, Escobar GJ, Greene JD, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA*. 2014;312(1):90-92. http://doi.org/10.1001/jama.2014.5804
5. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet*. 2020;395(10219):200-211. http://doi.org/10.1016/S0140-6736(19)32989-7
6. Peltan ID, Brown SM, Bledsoe JR, et al. ED door-to-antibiotic time and long-term mortality in sepsis. *Chest*. 2019;155(5):938-946. http://doi.org/10.1016/j.chest.2019.02.008
7. Seymour CW, Kahn JM, Martin-Gill C, et al. Delays from first medical contact to antibiotic administration for sepsis. *Crit Care Med*. 2017;45(5):759-765. http://doi.org/10.1097/CCM.0000000000002264
8. Macaskill P, Gatsonis C, Deeks JJ, Harbord RM, Takwoingi Y. Chapter 10: analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0*. The Cochrane Collaboration; 2023:1-61.
9. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. http://doi.org/10.1001/jama.283.15.2008
10. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31:1250-1256. http://doi.org/10.1097/01.CCM.0000050454.01978.3B
11. Singer M, Deutschman CS, Seymour C, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810. http://doi.org/10.1001/jama.2016.0287
12. Polilli E, Sozio F, Frattari A, et al. Comparison of monocyte distribution width (MDW) and procalcitonin for early recognition of sepsis. *PLoS One*. 2020;15(1):e0227300. http://doi.org/10.1371/journal.pone.0227300
13. Agnello L, Bivona G, Vidali M, et al. Monocyte distribution width (MDW) as a screening tool for sepsis in the emergency department. *Clin Chem Lab Med*. 2020;58(11):1951-1957. http://doi.org/10.1515/cclm-2020-0417
14. Lopez-Molina M, Ganduxé XT, Iribarren AM, et al. Influence of K2-EDTA and K3-EDTA tubes for monocyte distribution width measurement. *Clin Chim Acta*. 2019;493:S384. http://doi.org/10.1016/j.cca.2019.03.819
15. Whiting PF, Rutjes AWS, Westwood ME, et al. Quadas-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536. http://doi.org/10.7326/0003-4819-155-8-201110180-00009
16. Schünemann HJ, Jaeschke R, Cook DJ, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *Am J Respir Crit Care Med*. 2006;174(5):605-614. http://doi.org/10.1164/rccm.200602-197ST
17. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. *GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. The GRADE Working Group; 2013.
18. Dwamena B. MIDAS: Stata module for meta-analytical integration of diagnostic test accuracy studies. Statistical Software Components, Boston College Department of Economics. 2009. Accessed March 10, 2023. https://EconPapers.repec.org/RePEc:boc:bocode:s456880
19. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*. 2005;58(9):882-893. http://doi.org/10.1016/J.JCLINEPI.2005.01.016
20. Cortegiani A, DiBenedetto A, Marino L, et al. Evaluation of automated hematologic VCS parameters in severe sepsis and septic shock: a case-control study. *Crit Care*. 2010;14(suppl 1):31.
21. Dilmoula A, Kassengera Z, Turkan H, et al. Volume, conductivity and scatter properties of leukocytes (VCS technology) in detecting sepsis in critically ill adult patients. *Blood*. 2011;118(21):4729-4729. http://doi.org/10.1182/blood.V118.21.4729.4729
22. Crouser ED, Parrillo JE, Seymour CW, et al. Monocyte distribution width: a novel indicator of sepsis-2 and sepsis-3 in high-risk emergency department patients. *Crit Care Med*. 2019;47(8):1018-1025.
23. Guo F, Feng YC, Zhao G, et al. The leukocyte VCS parameters compared with procalcitonin, interleukin-6, and soluble hemoglobin scavenger receptor sCD163 for prediction of sepsis in patients with cirrhosis. *Dis Markers*. 2019;2019:1369798. http://doi.org/10.1155/2019/1369798
24. Piva E, Zuin J, Pelloso M, Tosato F, Fogar P, Plebani M. Monocyte distribution width (MDW) parameter as a sepsis indicator in intensive care units. *Clin Chem Lab Med*. 2021;59(7):1307-1314. http://doi.org/10.1515/cclm-2021-0192

25. Woo A, Oh DK, Park CJ, Hong SB. Monocyte distribution width compared with C-reactive protein and procalcitonin for early sepsis detection in the emergency department. *PLoS One*. 2021;16(4):e0250101. http://doi.org/10.1371/JOURNAL.PONE.0250101
26. Hausfater P, Boter NR, Indiano CM, et al. Monocyte distribution width (MDW) performance as an early sepsis indicator in the emergency department: comparison with CRP and procalcitonin in a multicenter international European prospective study. *Crit Care*. 2021;25(1):1-12. http://doi.org/10.1186/S13054-021-03622-5
27. Agnello L, Iacona A, Maestri S, et al. Independent validation of sepsis index for sepsis screening in the emergency department. *Diagnostics (Basel)*. 2021;11(7):1292. http://doi.org/10.3390/DIAGNOSTICS11071292
28. Hou SK, Lin HA, Chen SC, Lin CF, Lin SF. Monocyte distribution width, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio improves early prediction for sepsis at the emergency. *J Pers Med*. 2021;11(8):732. http://doi.org/10.3390/JPM11080732
29. Polilli E, Frattari A, Esposito JE, et al. Monocyte distribution width (MDW) as a new tool for the prediction of sepsis in critically ill patients: a preliminary investigation in an intensive care unit. *BMC Emerg Med*. 2021;21(1):1-11. http://doi.org/10.1186/S12873-021-00521-4/TABLES/5
30. Poz D, Crobu D, Sukhacheva E, Rocchi MBL, Anelli MC, Curcio F. Monocyte distribution width (MDW): a useful biomarker to improve sepsis management in emergency department. *Clin Chem Lab Med*. 2022;60(3):433-440. http://doi.org/10.1515/CCLM-2021-0875
31. Malinovska A, Hinson JS, Badaki-Makun O, et al. Monocyte distribution width as part of a broad pragmatic sepsis screen in the emergency department. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12679. http://doi.org/10.1002/EMP2.12679
32. Li CH, Seak CJ, Chaou CH, et al. Comparison of the diagnostic accuracy of monocyte distribution width and procalcitonin in sepsis cases in the emergency department: a prospective cohort study. *BMC Infect Dis*. 2022;22(1):26. http://doi.org/10.1186/S12879-021-06999-4
33. Yu S, Song SA, Jun KR, Park HY, Lee JN. Clinical performance of monocyte distribution width for early detection of sepsis in emergency department patients: a prospective study. *Ann Lab Med*. 2022;42(2):286-289. http://doi.org/10.3343/ALM.2022.42.2.286
34. Ognibene A, Lorubbio M, Montemerani S, et al. Monocyte distribution width and the fighting action to neutralize sepsis (FANS) score for sepsis prediction in emergency department. *Clin Chim Acta*. 2022;534:65-70. http://doi.org/10.1016/J.CCA.2022.07.007
35. Cusinato M, Sivayoham N, Planche T. Sensitivity and specificity of monocyte distribution width (MDW) in detecting patients with infection and sepsis in patients on sepsis pathway in the emergency department. *Infection*. 2023;51(3):715-727. http://doi.org/10.1007/S15010-022-01956-Y
36. Çevlik T, Kaya Ö, Gül F, et al. Evaluation of the diagnostic value of cell population data in sepsis in comparison to localized infection, chronic inflammation, and noninfectious inflammation cases. *J Intensive Care Med*. 2023;38(4):382-390. http://doi.org/10.1177/08850666221127185
37. Lin SF, Lin HA, Pan YH, Hou SK. A novel scoring system combining Modified Early Warning Score with biomarkers of monocyte distribution width, white blood cell counts, and neutrophil-to-lymphocyte ratio to improve early sepsis prediction in older adults. *Clin Chem Lab Med*. 2022;61(1):162-172. http://doi.org/10.1515/CCLM-2022-0656
38. Jo SJ, Kim SW, Choi JH, Choi SP, Lee J, Lim J. Monocyte distribution width (MDW) as a useful indicator for early screening of sepsis and discriminating false positive blood cultures. *PLoS One*. 2022;17(12):e0279374. http://doi.org/10.1371/JOURNAL.PONE.0279374
39. Polilli E, Di Iorio G, Silveri C, et al. Monocyte distribution width as a predictor of community acquired sepsis in patients prospectively enrolled at the emergency department. *BMC Infect Dis*. 2022;22(1):849. http://doi.org/10.1186/S12879-022-07803-7
40. Kralovcova M, Müller J, Hajsmanova Z, et al. Understanding the value of monocyte distribution width (MDW) in acutely ill medical patients presenting to the emergency department: a prospective single center evaluation. *Sci Rep*. 2024;14(1):15255. http://doi.org/10.1038/s41598-024-65883-8
41. Özer A, Tak S, Demirtaş H, et al. The role of monocyte distribution width in the early prediction of sepsis in patients undergoing cardiovascular surgery: a cross-sectional study. *Medicina (Kaunas)*. 2024;60(9):1558. http://doi.org/10.3390/MEDICINA60091558
42. Agnello L, Ciaccio AM, Del Ben F, et al. Monocyte distribution width (MDW) kinetic for monitoring sepsis in intensive care unit. *Diagnosis (Berl)*. 2024;11(4):422-429. http://doi.org/10.1515/DX-2024-0019
43. Agnello L, Vidali M, Lo Sasso B, et al. Monocyte distribution width (MDW) as a screening tool for early detecting sepsis: a systematic review and meta-analysis. *Clin Chem Lab Med*. 2022;60(5):786-792. http://doi.org/10.1515/CCLM-2021-1331
44. Malinovska A, Hernried B, Lin A, et al. Monocyte distribution width as a diagnostic marker for infection: a systematic review and meta-analysis. *Chest*. 2023;164(1):101-113. http://doi.org/10.1016/j.chest.2022.12.049
45. Huang YH, Chen CJ, Shao SC, et al. Comparison of the diagnostic accuracies of monocyte distribution width, procalcitonin, and C-reactive protein for sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2023;51(5):e106-e114. http://doi.org/10.1097/CCM.0000000000005820
46. Motawea KR, S Rozan S, Elsayed Talat N, et al. Comparison of monocyte distribution width and procalcitonin as diagnostic markers for sepsis: meta-analysis of diagnostic test accuracy studies. *PLoS One*. 2023;18(8):e0288203. http://doi.org/10.1371/JOURNAL.PONE.0288203
47. Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13(5):426-435. http://doi.org/10.1016/S1473-3099(12)70323-7
48. Kim SJ, Hwang SO, Kim YW, Lee JH, Cha KC. Procalcitonin as a diagnostic marker for sepsis/septic shock in the emergency department; a study based on Sepsis-3 definition. *Am J Emerg Med*. 2019;37(2):272-276. http://doi.org/10.1016/J.AJEM.2018.05.047
49. Tan M, Lu Y, Jiang H, Zhang L. The diagnostic accuracy of procalcitonin and C-reactive protein for sepsis: a systematic review and meta-analysis. *J Cell Biochem*. 2019;120(4):5852-5859. http://doi.org/10.1002/JCB.27870
50. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med*. 2020;38(3):641-647. http://doi.org/10.1016/J.AJEM.2019.10.023
51. Xin Y, Shao Y, Mu W, Li H, Zhou Y, Wang C. Accuracy of the neutrophil-to-lymphocyte ratio for the diagnosis of neonatal sepsis: a systematic review and meta-analysis. *BMJ Open*. 2022;12(12):e060391. http://doi.org/10.1136/BMJOPEN-2021-060391
52. Ljungström L, Pernestig AK, Jacobsson G, Andersson R, Usener B, Tilevik D. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. *PLoS One*. 2017;12(7):e0181704. http://doi.org/10.1371/JOURNAL.PONE.0181704
53. Kim MH, Choi JH. An update on sepsis biomarkers. *Infect Chemother*. 2020;52(1):1-18. http://doi.org/10.3947/ic.2020.52.1.1
54. Gordon AC, Alipanah-Lechner N, Bos LD, et al. From ICU syndromes to ICU subphenotypes consensus report and recommendations for developing precision medicine in the ICU. *Am J Respir Crit Care Med*. 2024;210(2):155-166. http://doi.org/10.1164/rccm.202311-2086SO
55. Eisinger GJ, Osman W, Prather ER, et al. Inflammasome activation in an in vitro sepsis model recapitulates increased monocyte distribution width seen in patients with sepsis. *Crit Care Explor*. 2022;4(2):e0631. http://doi.org/10.1097/CCE.0000000000000631
56. Cusinato M, Hadcocks L, Yona S, Planche T, Macallan D. Increased monocyte distribution width in COVID-19 and sepsis arises from a complex interplay of altered monocyte cellular size and subset frequency. *Int J Lab Hematol*. 2022;44(6):1029-1039. http://doi.org/10.1111/IJLH.13941
57. Crouser ED, Parrillo JE, Martin GS, et al. Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. *J Intensive Care*. 2020;8(1):33. http://doi.org/10.1186/s40560-020-00446-3

58. Giacobbe DR, Signori A, Del Puente F, et al. Early detection of sepsis with machine learning techniques: a brief clinical perspective. *Front Med (Lausanne)*. 2021;8:617486. http://doi.org/10.3389/fmed.2021.617486

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.acepjo.2025.100073

How to cite this article: Eisinger GJ, Hosler Q, Crouser ED, et al. Diagnostic Performance of Monocyte Distribution Width for the Detection of Sepsis: A Systematic Review and Meta-Analysis. JACEP Open. 2025;6:100073.

https://doi.org/10.1016/j.acepjo.2025.100073