MONOCYTE DISTRIBUTION WIDTH (MDW) FOR SEVERE INFECTION AND RISK OF SEPSIS ASSESSMENT

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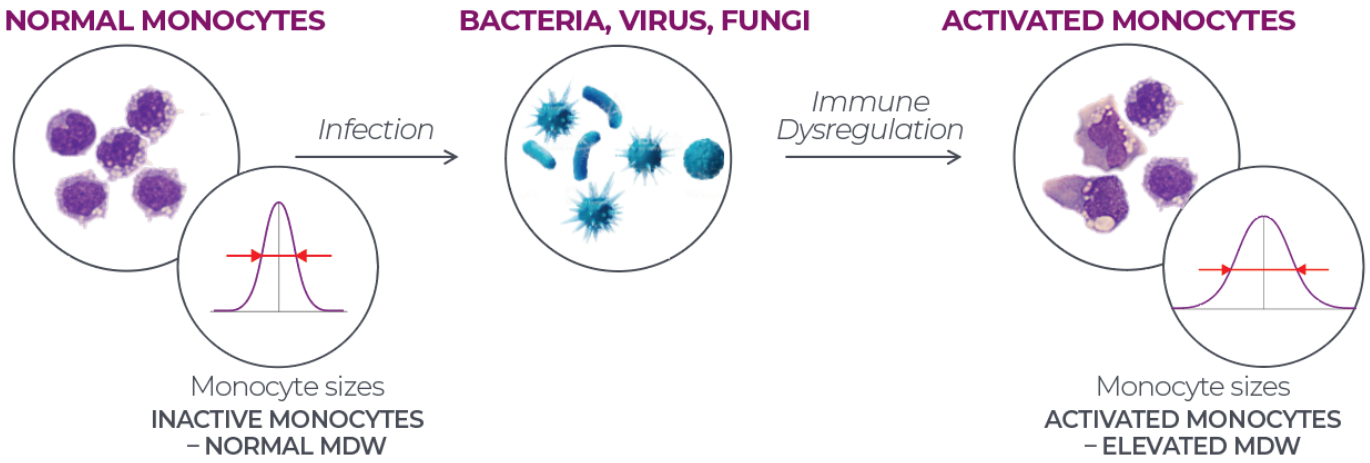
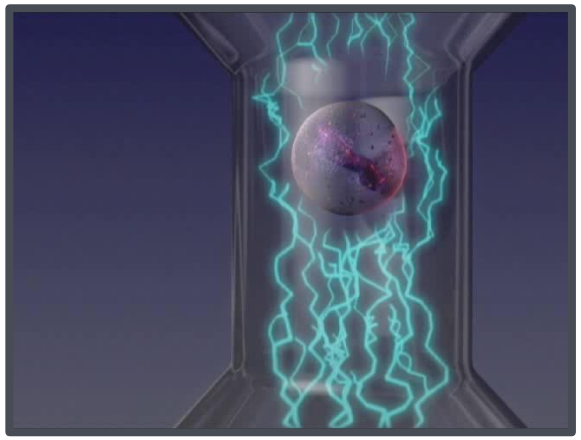
AGENDA

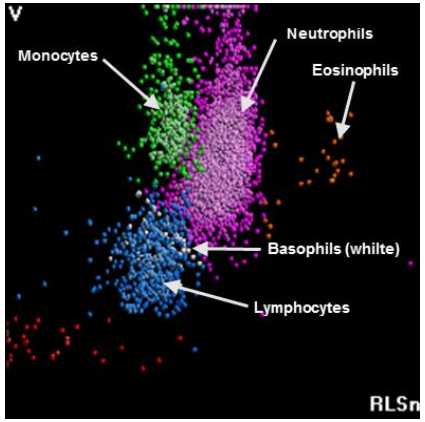
- Introduction to MDW, technology, Intended use
- MDW clinical trial results in Emergency Department
- MDW in ICU
- MDW and COVID-19
- Summary

Introduction to MDW, Technology, Intended use

MONOCYTE DISTRIBUTION WIDTH (MDW)





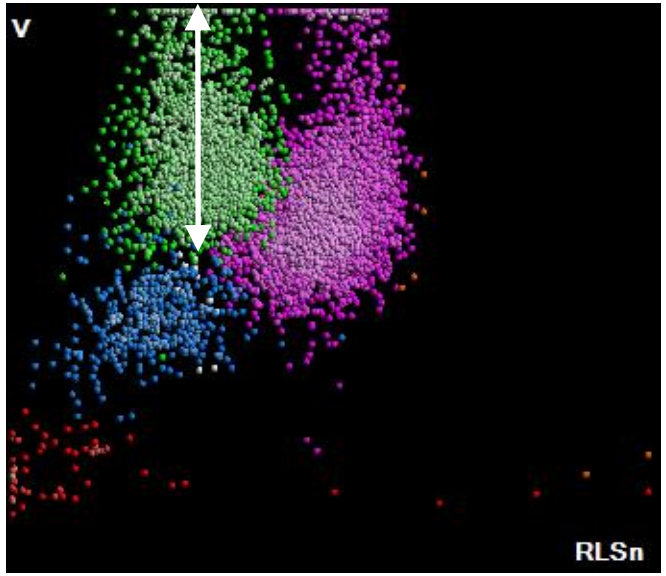


Full Blood Count (FBC) Analyzer: Beckman Coulter DxH 900

WHY DO MONOCYTES MATTER?

Immunosuppression
- Sepsis-related immunosuppression

Pro-inflammatory State
- Cytokine Storm
- Overwhelming Inflammation
- Organ failure



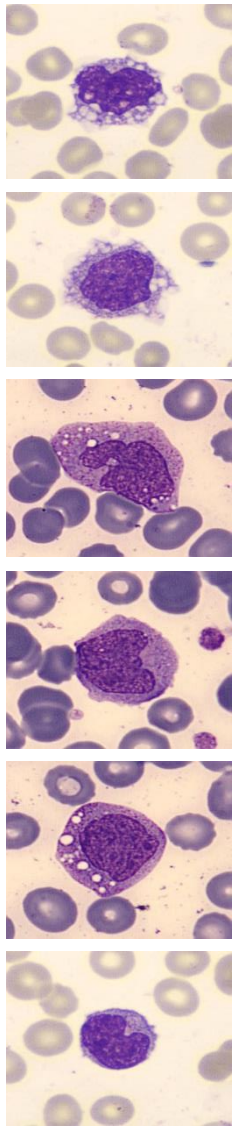
Increased functional heterogeneity (diversity) of monocytes in sepsis

↓

Morphological variability

↓

Increased MDW



MDW – INTENDED USE

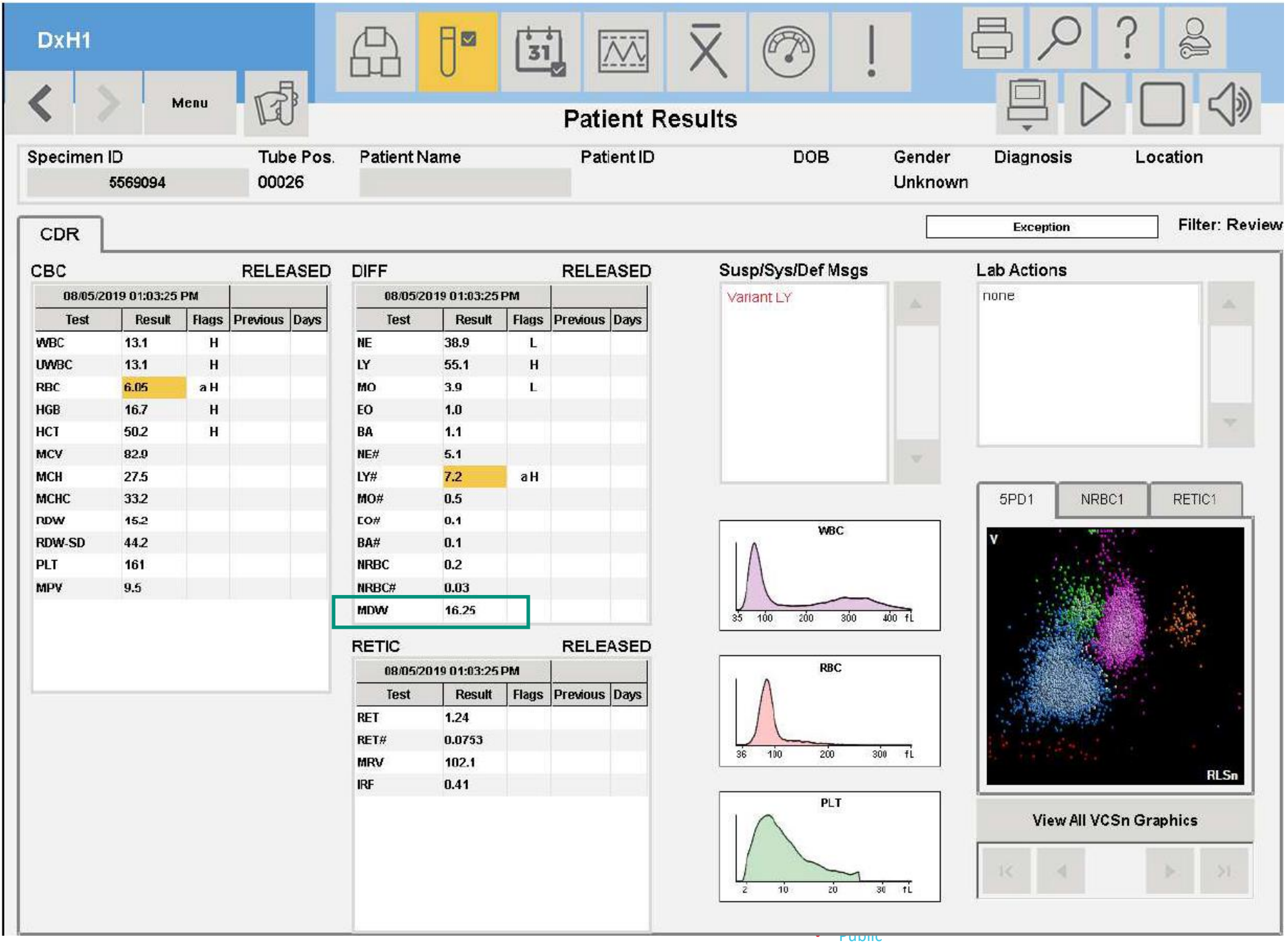
Intended Use

The Unicel DxH 900 Series with System Manager Software Coulter Cellular Analysis System with Early Sepsis Indicator (ESId) application is the quantitative measurement of Monocyte Distribution Width (MDW). The ESId is intended for use with adult patients presenting to the emergency department, on whom a white blood cell differential test has been ordered.

MDW is tested from a (K_2EDTA or K_3EDTA) whole-blood venous sample within two hours of collection. MDW results greater than 20.0 for K_2EDTA OR greater than 21.5 for K_3EDTA together with other laboratory findings and clinical information, aids in identifying patients with sepsis or at increased risk of developing sepsis within the first 12 hours of hospital admission.

CE IVD

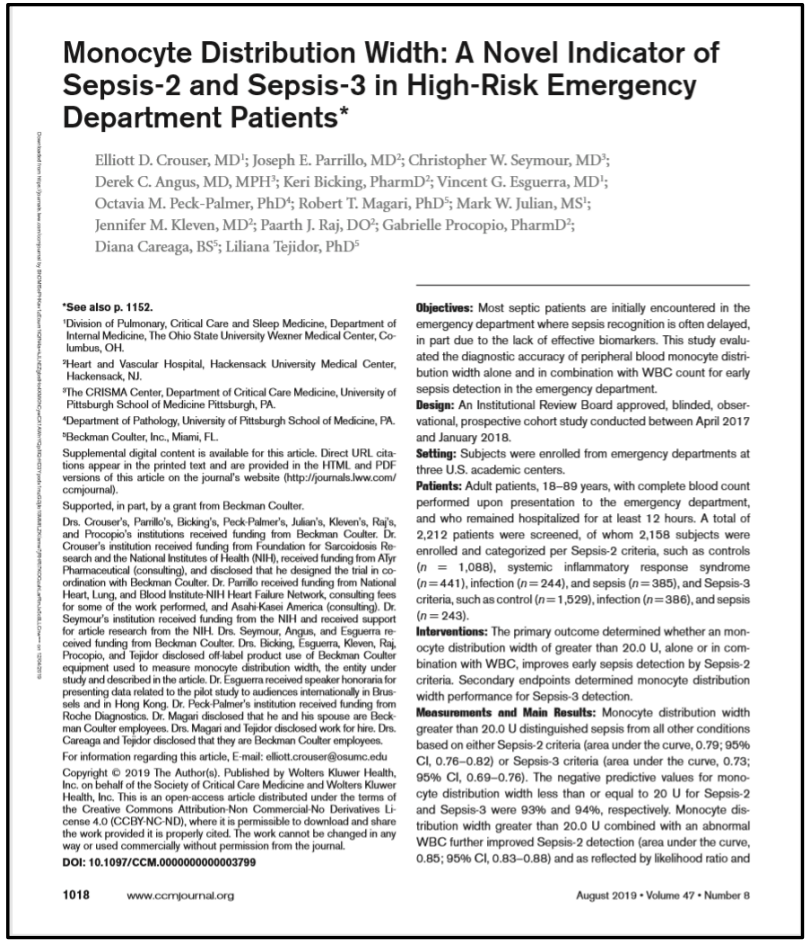
FDA CLEARED



MDW is Reported Automatically as Part of a Full Blood Count (or FBC) with differential

MDW clinical trial results: US and EU

CLINICAL TRIALS PUBLICATIONS



Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients*

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*See also p. 1152.

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Objectives: Most septic patients are initially encountered in the emergency department where sepsis recognition is often delayed, in part due to the lack of effective biomarkers. This study evaluated the diagnostic accuracy of peripheral blood monocyte distribution width alone and in combination with WBC count for early sepsis detection in the emergency department.

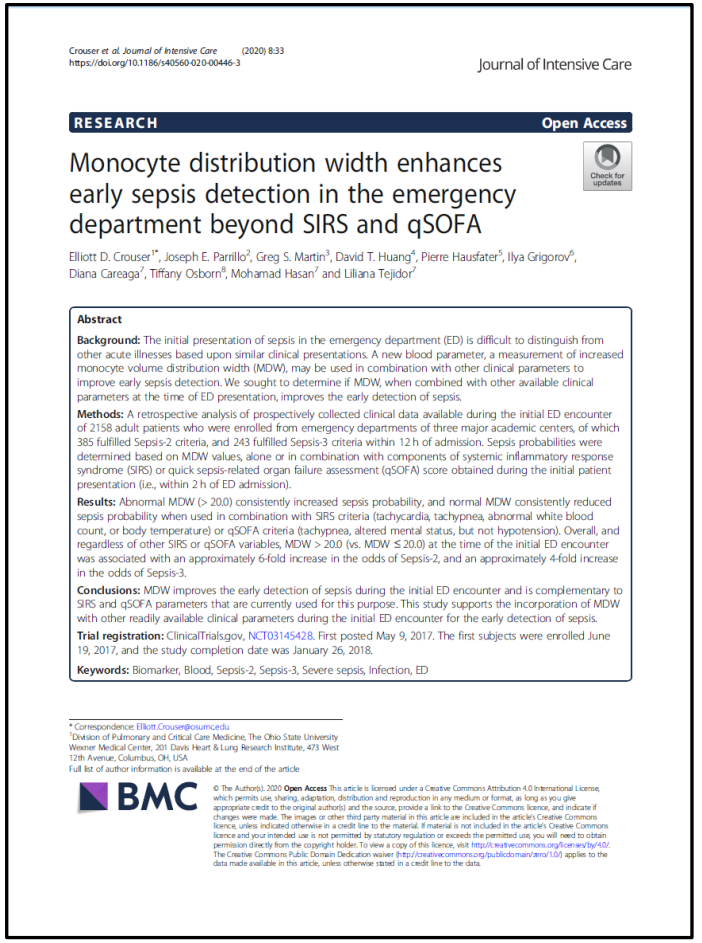
Design: An Institutional Review Board approved, blinded, observational, prospective cohort study conducted between April 2017 and January 2018.

Setting: Subjects were enrolled from emergency departments at three U.S. academic centers.

Patients: Adult patients, 18–89 years, with complete blood count performed upon presentation to the emergency department, and who remained hospitalized for at least 12 hours. A total of 2,212 patients were screened, of whom 2,158 subjects were enrolled and categorized per Sepsis-2 criteria, such as controls (n = 1,088), systemic inflammatory response syndrome (n = 441), infection (n = 244), and sepsis (n = 385), and Sepsis-3 criteria, such as control (n = 1,529), infection (n = 386), and sepsis (n = 243).

Interventions: The primary outcome determined whether an monocyte distribution width of greater than 20.0 U, alone or in combination with WBC, improves early sepsis detection by Sepsis-2 criteria. Secondary endpoints determined monocyte distribution width performance for Sepsis-3 detection.

Measurements and Main Results: Monocyte distribution width greater than 20.0 U distinguished sepsis from all other conditions based on either Sepsis-2 criteria (area under the curve, 0.79; 95% CI, 0.76–0.82) or Sepsis-3 criteria (area under the curve, 0.73; 95% CI, 0.69–0.76). The negative predictive values for monocyte distribution width less than or equal to 20 U for Sepsis-2 and Sepsis-3 were 93% and 94%, respectively. Monocyte distribution width greater than 20.0 U combined with an abnormal WBC further improved Sepsis-2 detection (area under the curve, 0.85; 95% CI, 0.83–0.88) and as reflected by likelihood ratio and



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Journal of Intensive Care

RESEARCH Open Access

Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA

Elliott D. Crouser[1*], Joseph E. Parrillo[2], Greg S. Martin[3], David T. Huang[4], Pierre Hausfater[5], Ilya Grigorov[6], Diana Careaga[7], Tiffany Osborn[8], Mohamad Hasan[7] and Liliana Tejidor[7]

Abstract

Background: The initial presentation of sepsis in the emergency department (ED) is difficult to distinguish from other acute illnesses based upon similar clinical presentations. A new blood parameter, a measurement of increased monocyte volume distribution width (MDW), may be used in combination with other clinical parameters to improve early sepsis detection. We sought to determine if MDW, when combined with other available clinical parameters at the time of ED presentation, improves the early detection of sepsis.

Methods: A retrospective analysis of prospectively collected clinical data available during the initial ED encounter of 2158 adult patients who were enrolled from emergency departments of three major academic centers, of which 385 fulfilled Sepsis-2 criteria, and 243 fulfilled Sepsis-3 criteria within 12 h of admission. Sepsis probabilities were determined based on MDW values, alone or in combination with components of systemic inflammatory response syndrome (SIRS) or quick sepsis-related organ failure assessment (qSOFA) score obtained during the initial patient presentation (i.e., within 2 h of ED admission).

Results: Abnormal MDW (> 20.0) consistently increased sepsis probability, and normal MDW consistently reduced sepsis probability when used in combination with SIRS criteria (tachycardia, tachypnea, abnormal white blood count, or body temperature) or qSOFA criteria (tachypnea, altered mental status, but not hypotension). Overall, and regardless of other SIRS or qSOFA variables, MDW > 20.0 (vs. MDW ≤ 20.0) at the time of the initial ED encounter was associated with an approximately 6-fold increase in the odds of Sepsis-2, and an approximately 4-fold increase in the odds of Sepsis-3.

Conclusions: MDW improves the early detection of sepsis during the initial ED encounter and is complementary to SIRS and qSOFA parameters that are currently used for this purpose. This study supports the incorporation of MDW with other readily available clinical parameters during the initial ED encounter for the early detection of sepsis.

Trial registration: ClinicalTrials.gov, NCT03145428. First posted May 9, 2017. The first subjects were enrolled June 19, 2017, and the study completion date was January 26, 2018.

Keywords: Biomarker, Blood, Sepsis-2, Sepsis-3, Severe sepsis, Infection, ED

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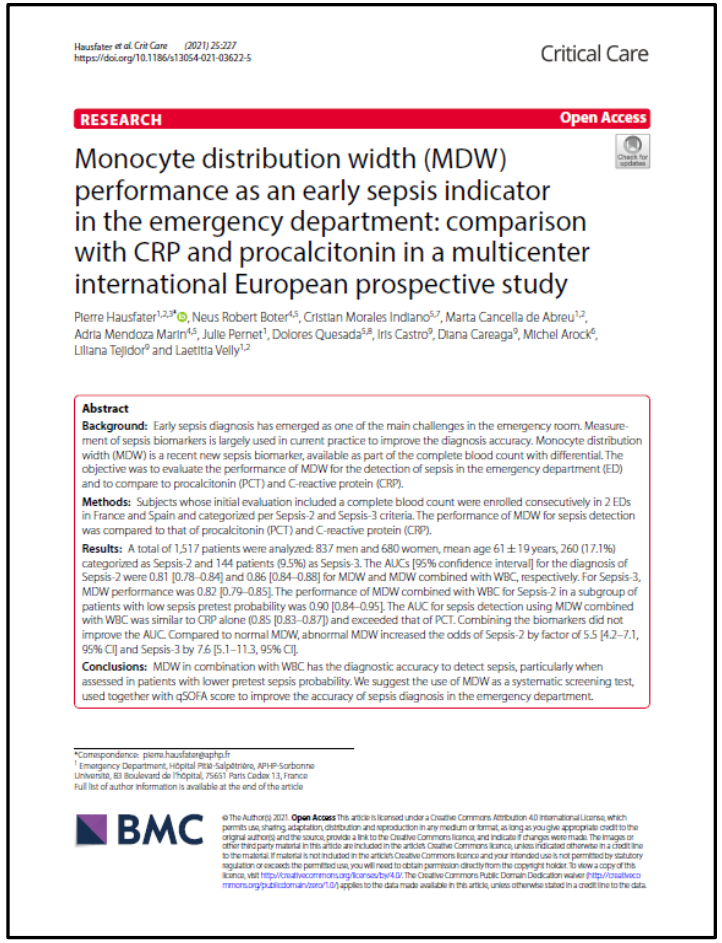

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Critical Care

RESEARCH Open Access

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

Pierre Hausfater[1,2,3*], Neus Robert Boter[4,5], Cristian Morales Indiano[5,7], Marta Cancella de Abreu[1,2], Adria Mendoza Marin[4,5], Julie Pernet[1], Dolores Quesada[5,8], Iris Castro[9], Diana Careaga[9], Michel Arock[6], Liliana Tejidor[9] and Laetitia Velly[1,2]

Abstract

Background: Early sepsis diagnosis has emerged as one of the main challenges in the emergency room. Measurement of sepsis biomarkers is largely used in current practice to improve the diagnosis accuracy. Monocyte distribution width (MDW) is a recent new sepsis biomarker, available as part of the complete blood count with differential. The objective was to evaluate the performance of MDW for the detection of sepsis in the emergency department (ED) and to compare to procalcitonin (PCT) and C-reactive protein (CRP).

Methods: Subjects whose initial evaluation included a complete blood count were enrolled consecutively in 2 EDs in France and Spain and categorized per Sepsis-2 and Sepsis-3 criteria. The performance of MDW for sepsis detection was compared to that of procalcitonin (PCT) and C-reactive protein (CRP).

Results: A total of 1,517 patients were analyzed: 837 men and 680 women, mean age 61 ± 19 years, 260 (17.1%) categorized as Sepsis-2 and 144 patients (9.5%) as Sepsis-3. The AUCs [95% confidence interval] for the diagnosis of Sepsis-2 were 0.81 [0.78–0.84] and 0.86 [0.84–0.88] for MDW and MDW combined with WBC, respectively. For Sepsis-3, MDW performance was 0.82 [0.79–0.85]. The performance of MDW combined with WBC for Sepsis-2 in a subgroup of patients with low sepsis pretest probability was 0.90 [0.84–0.95]. The AUC for sepsis detection using MDW combined with WBC was similar to CRP alone (0.85 [0.83–0.87]) and exceeded that of PCT. Combining the biomarkers did not improve the AUC. Compared to normal MDW, abnormal MDW increased the odds of Sepsis-2 by factor of 5.5 [4.2–7.1, 95% CI] and Sepsis-3 by 7.6 [5.1–11.3, 95% CI].

Conclusions: MDW in combination with WBC has the diagnostic accuracy to detect sepsis, particularly when assessed in patients with lower pretest sepsis probability. We suggest the use of MDW as a systematic screening test, used together with qSOFA score to improve the accuracy of sepsis diagnosis in the emergency department.

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CLINICAL TRIAL RESULTS: MDW PERFORMANCE

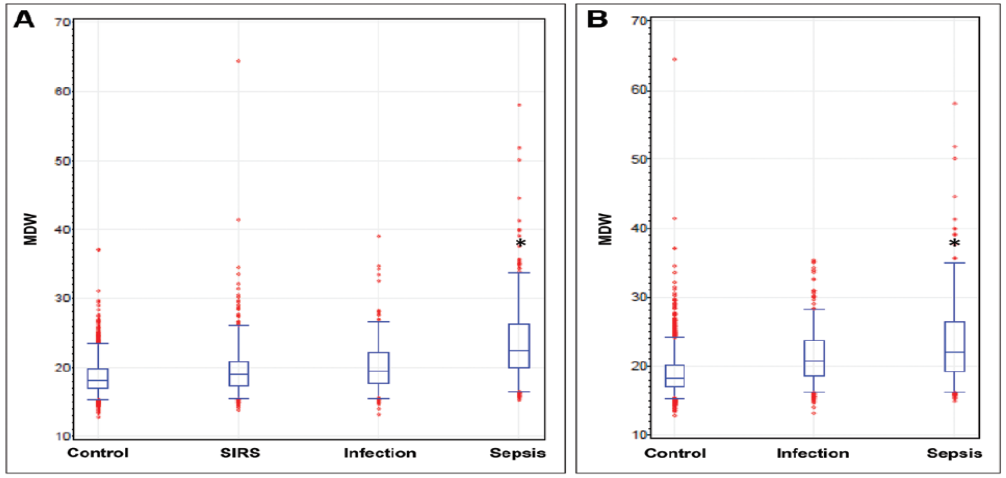
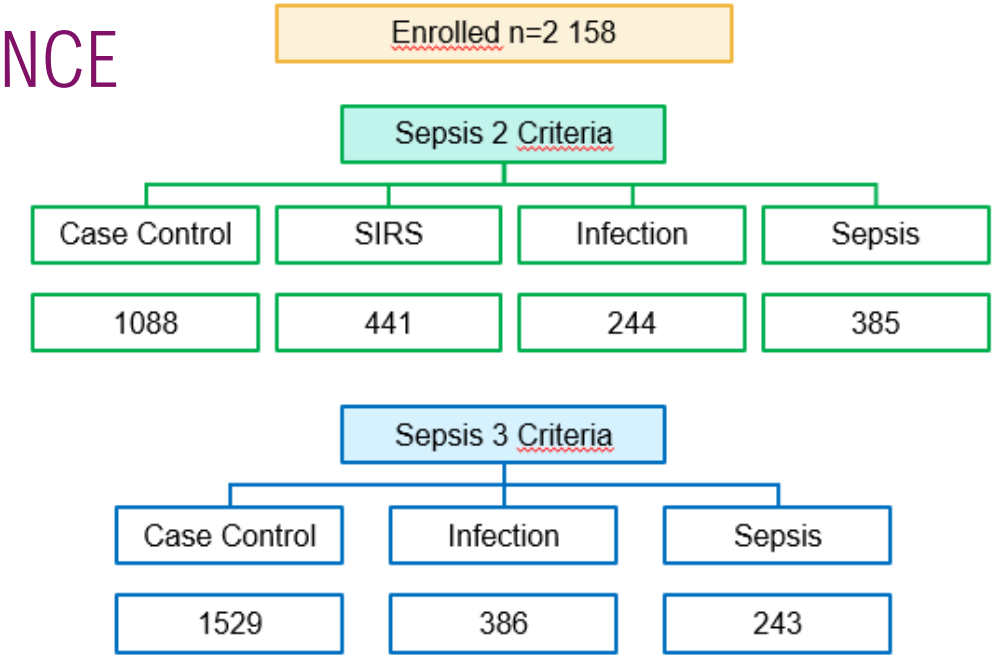
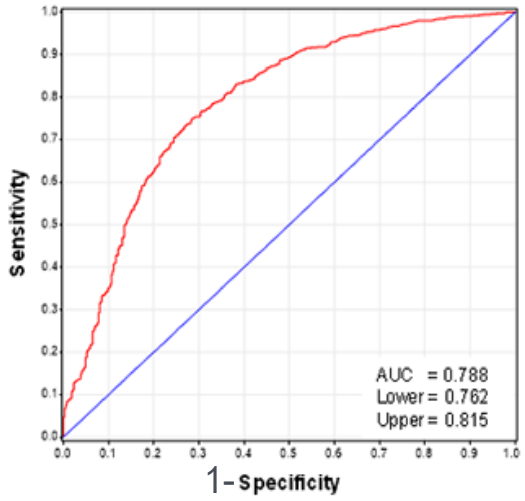
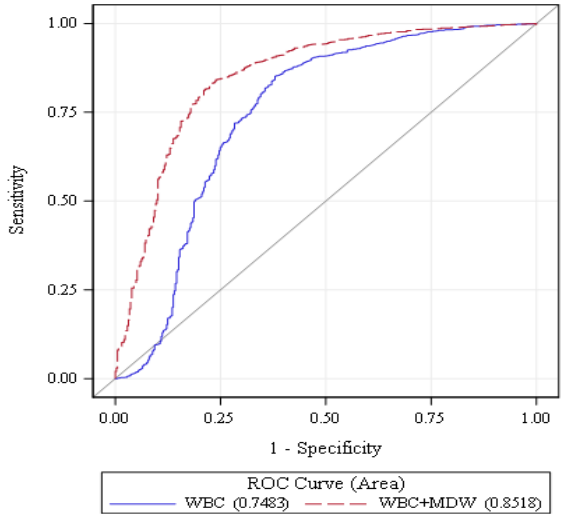


Figure 2. *Box plots* for monocyte distribution width (MDW) conforming to Sepsis-2 and Sepsis-3 criteria. **A**, *Box plot* representation of MDW values showing significantly higher values for patients meeting Sepsis-2 criteria compared with all other emergency department (ED) patient populations. **B**, MDW was statistically higher than those fulfilling Sepsis-3 criteria compared with other ED patient populations (*$p < 0.05$ compared with each of the other groups). SIRS = systemic inflammatory response syndrome.



MDW





AUC MDW 0.79
WBC 0.75
MDW+WBC 0.85

MDW at cut-off 20:
sensitivity 74%, specificity 72%

Crouser et al. Crit Care Med. 2019 Aug;47(8):1018-1025

ADDED VALUE OF MDW

Crouser *et al. Journal of Intensive Care* (2020) 8:33
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Journal of Intensive Care

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Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA

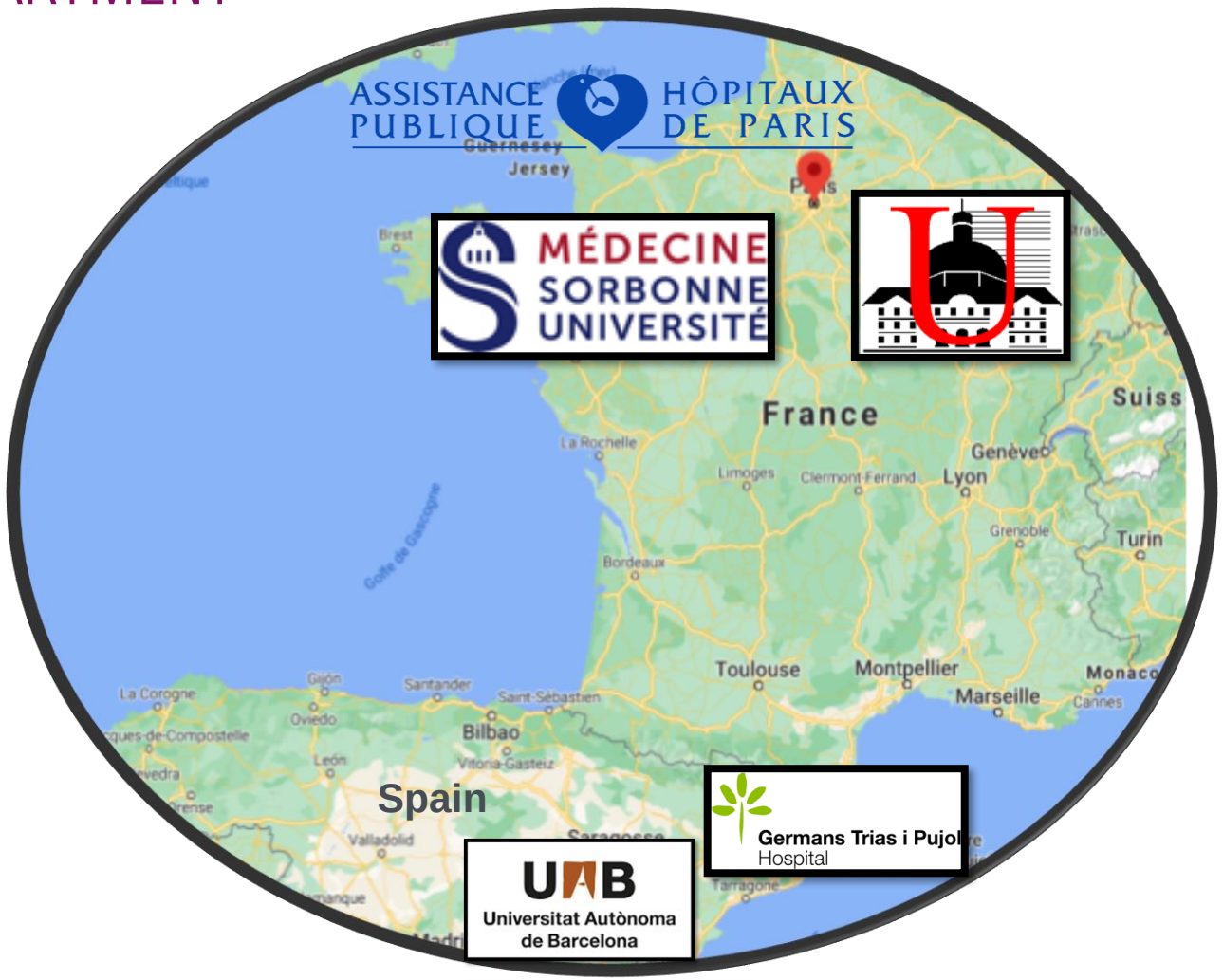
Elliott D. Crouser[1*], Joseph E. Parrillo[2], Greg S. Martin[3], David T. Huang[4], Pierre Hausfater[5], Ilya Grigorov[6], Diana Careaga[7], Tiffany Osborn[8], Mohamad Hasan[7] and Liliana Tejidor[7]

The researchers propose a clinical role of MDW to supplement current clinical parameters used to screen for sepsis, in essence, potentially serving as a fifth SIRS criteria or a fourth qSOFA criteria, to aid in the early detection of sepsis in the ED.

COMPARISON OF MDW TO PROCALCITONIN AND CRP IN DETECTION OF SEPSIS-2 OR SEPSIS-3 IN THE EMERGENCY DEPARTMENT

STUDY DESIGN:
Pan-European Prospective Observational Study

N=1517 adult patients presenting to the ED who had a FBC performed



MDW VALUES AND PERFORMANCE FOR SEPSIS DETECTION

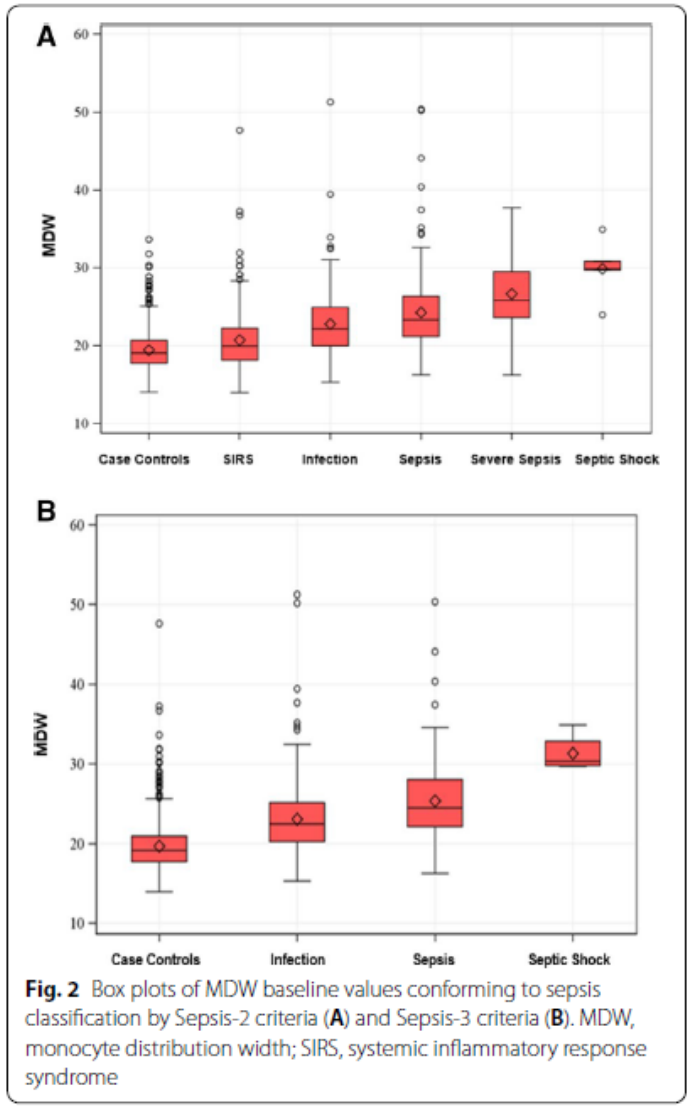


Fig. 2 Box plots of MDW baseline values conforming to sepsis classification by Sepsis-2 criteria (**A**) and Sepsis-3 criteria (**B**). MDW, monocyte distribution width; SIRS, systemic inflammatory response syndrome

MDW	SEPSIS-2		
	Median	ST	N
Sepsis	23.30	4.79	217
Severe Sepsis	25.83	4.41	38
Septic Shock	29.87	3.91	5
All	23.92	4.84	260
Infection	22.14	4.21	241
SIRS≥2 SIRS	19.93	4.22	197
Controls	19.04	2.54	819
Total	**20.15**	**4.1**	**1517**

MDW	SEPSIS-3		
	Median	ST	N
Sepsis	24.49	5.02	140
Septic Shock	30.34	2.44	4
All	24.61	5.06	144
Infection	22.46	4.27	357
Controls	19.15	2.98	1016
Total	**20.15**	**4.1**	**1517**

MDW AUC = 0,81

MDW	Estimate	CI 95%
Sensitivity	75%	[69%-80%]
Specificity	73%	[70%-75%]
PPV	36%	[32%-40%]
NPV	93%	[92%-95%]

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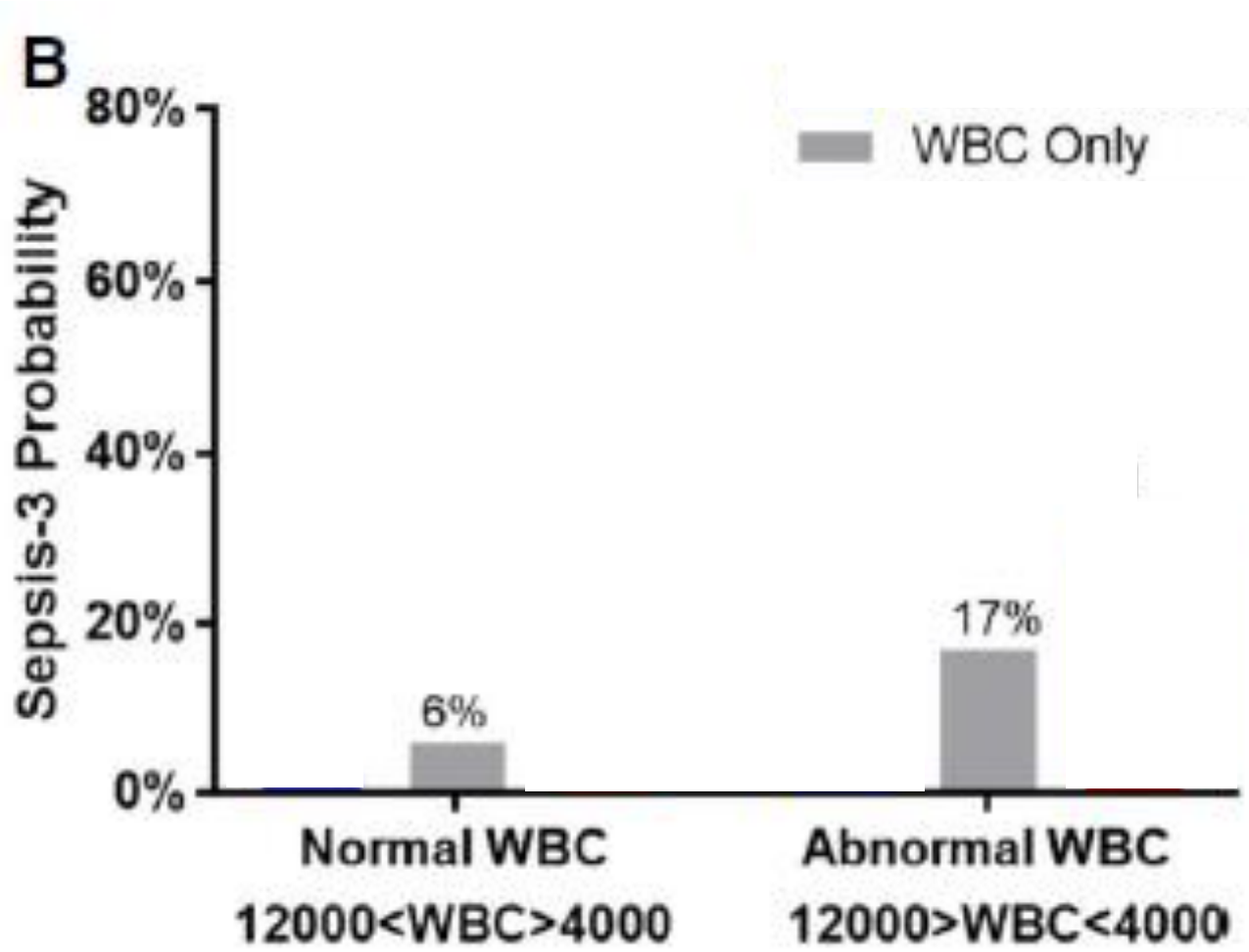
MDW: ADDED VALUE to WBC



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MDW PERFORMANCE COMPARED TO PCT AND CRP

Parameters	SEPSIS-2		SEPSIS-3	
	AUC	CI 95%	AUC	CI 95%
MDW	**0.81**	**[0.78-0.84]**	**0.82**	**[0.79-0.85]**
WBC	0.76	[0.72-0.79]	0.65	[0.60-0.70]
MDW+WBC	**0.86**	**[0.84-0.88]**	**0.83**	**[0.79-0.86]**
PCT	0.78	[0.75-0.81]	0.84	[0.81-0.87]
CRP	0.85	[0.83-0.87]	0.85	[0.82-0.87]

- MDW and WBC: **available as a part of CBC-DIFF** unlike PCT or CRP which are usually ordered only in patients with high index of suspicion for infection/sepsis
- Abnormal MDW and WBC at the time of ED admission may alert for potential severe infection/sepsis **even in situations of low clinical suspicion**

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CASE STUDY: 85 Y.O. FEMALE

Presented to ED: Fall in an elderly women. Confusion, no infectious focus, normal auscultation. Hypernatremia 166 mmol/l

CLINICAL HISTORY

Cardio Vascular	HTA
Metabolic	Dyslip.
Genito Urinary	No
Respiratory	No
Hemato Oncology	No
CNS	No
Gastro Intestinal	No
Auto Immune	No
Renal	No
Hepatic	No
Other	No

OTHER LABORATORY

BUN	38.9
CREA	181

HEMATOLOGY DATA

WBC	**8.76**
HgB, g/dL	15.3
PL x 10^9	148
NL x 10^9	7.9

NL %	90.2
LYMPH%	2.9
MONO%	6.8
ESN%	

PRESENTING SYMPTOMS

TEMP	36.4
HR	74
RR	16
SBP	128
AMS	No

SEPSIS BIOMARKERS

MDW	22.7
CRP	308
PCT	0.67

SYMPTOMS @ 12H

TEMP	36.4
HR	86
RR	16
SBP	104
AMS	16

RESP	0
COAG	1
LIVER	0
CARDIO	0
CNS	0
RENAL	2
SCORE	**3**

ADJUDICATE DIAGNOSIS @ 12H AND HOSPITAL COURSE

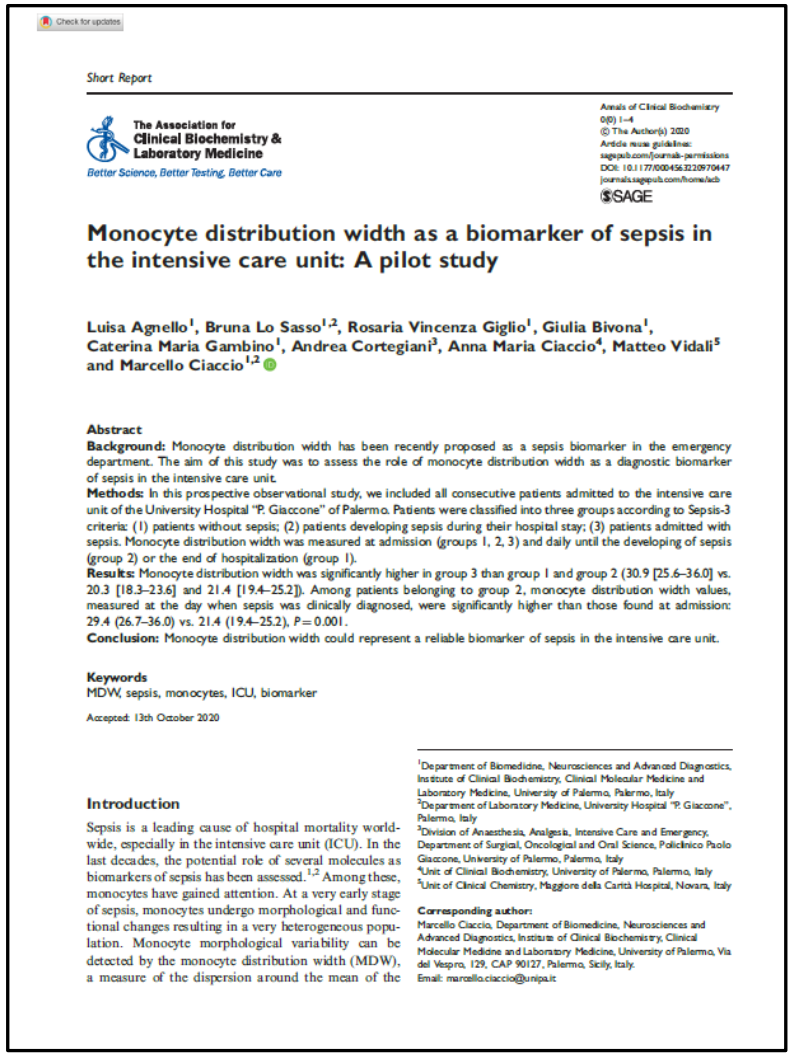
Sepsis 2	Sepsis 3	Hospital LOS	ICU LOS	Death
Infection	SEPSIS	Admitted	N/A	N/A

- 12h after ED admission: desaturation 88%, non conclusive Chest X-Ray
- 24h after ED admission: hypotension+ acute respiratory failure →CT-scan → pneumonia -→ ICU

MDW* in ICU

* MDW is not intended for patients in ICU

MDW IN ICU*



Short Report

The Association for Clinical Biochemistry & Laboratory Medicine
Better Science, Better Testing, Better Care

Annals of Clinical Biochemistry
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Monocyte distribution width as a biomarker of sepsis in the intensive care unit: A pilot study

Luisa Agnello[1], Bruna Lo Sasso[1,2], Rosaria Vincenza Giglio[1], Giulia Bivona[1], Caterina Maria Gambino[1], Andrea Cortegiani[3], Anna Maria Ciaccio[4], Matteo Vidali[5] and Marcello Ciaccio[1,2]

Abstract

Background: Monocyte distribution width has been recently proposed as a sepsis biomarker in the emergency department. The aim of this study was to assess the role of monocyte distribution width as a diagnostic biomarker of sepsis in the intensive care unit.

Methods: In this prospective observational study, we included all consecutive patients admitted to the intensive care unit of the University Hospital "P. Giaccone" of Palermo. Patients were classified into three groups according to Sepsis-3 criteria: (1) patients without sepsis; (2) patients developing sepsis during their hospital stay; (3) patients admitted with sepsis. Monocyte distribution width was measured at admission (groups 1, 2, 3) and daily until the developing of sepsis (group 2) or the end of hospitalization (group 1).

Results: Monocyte distribution width was significantly higher in group 3 than group 1 and group 2 (30.9 [25.6–36.0] vs. 20.3 [18.3–23.6] and 21.4 [19.4–25.2]). Among patients belonging to group 2, monocyte distribution width values, measured at the day when sepsis was clinically diagnosed, were significantly higher than those found at admission: 29.4 (26.7–36.0) vs. 21.4 (19.4–25.2), $P = 0.001$.

Conclusion: Monocyte distribution width could represent a reliable biomarker of sepsis in the intensive care unit.

Keywords
MDW, sepsis, monocytes, ICU, biomarker

Accepted: 13th October 2020

Introduction

Sepsis is a leading cause of hospital mortality worldwide, especially in the intensive care unit (ICU). In the last decades, the potential role of several molecules as biomarkers of sepsis has been assessed.[1,2] Among these, monocytes have gained attention. At a very early stage of sepsis, monocytes undergo morphological and functional changes resulting in a very heterogeneous population. Monocyte morphological variability can be detected by the monocyte distribution width (MDW), a measure of the dispersion around the mean of the

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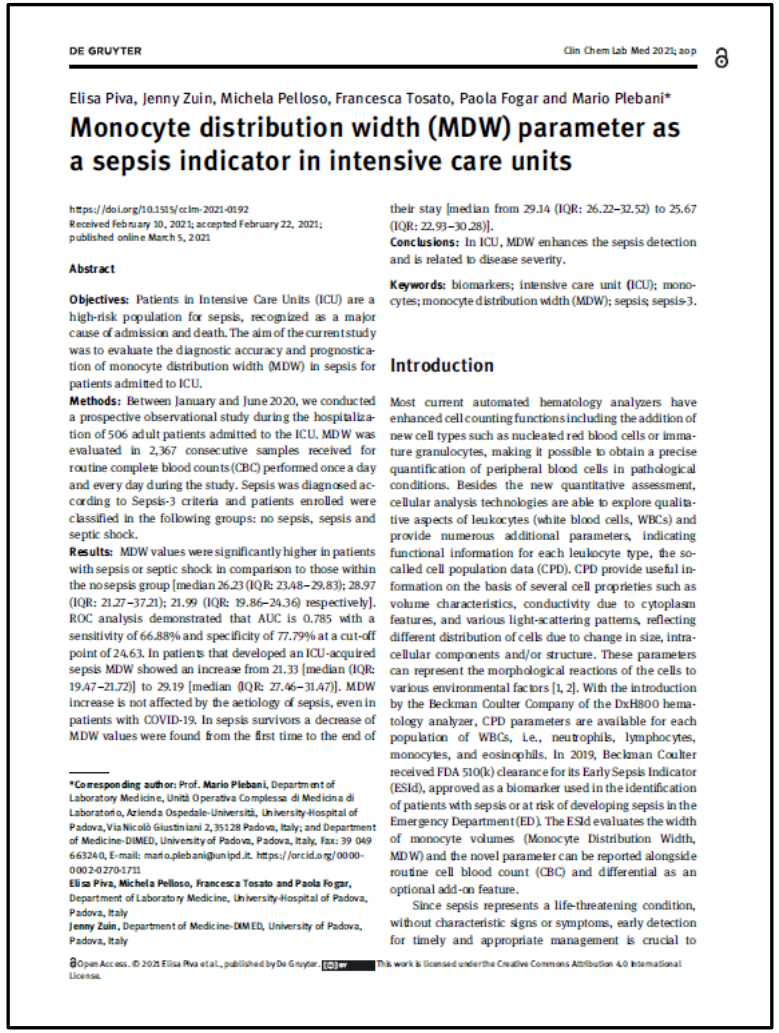

Elisa Piva, Jenny Zuin, Michela Pelloso, Francesca Tosato, Paola Fogar and Mario Plebani*

Monocyte distribution width (MDW) parameter as a sepsis indicator in intensive care units

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Abstract

Objectives: Patients in Intensive Care Units (ICU) are a high-risk population for sepsis, recognized as a major cause of admission and death. The aim of the current study was to evaluate the diagnostic accuracy and prognostication of monocyte distribution width (MDW) in sepsis for patients admitted to ICU.

Methods: Between January and June 2020, we conducted a prospective observational study during the hospitalization of 506 adult patients admitted to the ICU. MDW was evaluated in 2,367 consecutive samples received for routine complete blood counts (CBC) performed once a day and every day during the study. Sepsis was diagnosed according to Sepsis-3 criteria and patients enrolled were classified in the following groups: no sepsis, sepsis and septic shock.

Results: MDW values were significantly higher in patients with sepsis or septic shock in comparison to those within the no sepsis group [median 26.23 (IQR: 23.48–29.83); 28.97 (IQR: 21.27–37.21); 21.99 (IQR: 19.86–24.36) respectively]. ROC analysis demonstrated that AUC is 0.785 with a sensitivity of 66.88% and specificity of 77.79% at a cut-off point of 24.63. In patients that developed an ICU-acquired sepsis MDW showed an increase from 21.33 [median (IQR: 19.47–21.72)] to 29.19 [median (IQR: 27.46–31.47)]. MDW increase is not affected by the aetiology of sepsis, even in patients with COVID-19. In sepsis survivors a decrease of MDW values were found from the first time to the end of their stay [median from 29.14 (IQR: 26.22–32.52) to 25.67 (IQR: 22.93–30.28)].

Conclusions: In ICU, MDW enhances the sepsis detection and is related to disease severity.

Keywords: biomarkers; intensive care unit (ICU); monocytes; monocyte distribution width (MDW); sepsis; sepsis-3.

Introduction

Most current automated hematology analyzers have enhanced cell counting functions including the addition of new cell types such as nucleated red blood cells or immature granulocytes, making it possible to obtain a precise quantification of peripheral blood cells in pathological conditions. Besides the new quantitative assessment, cellular analysis technologies are able to explore qualitative aspects of leukocytes (white blood cells, WBCs) and provide numerous additional parameters, indicating functional information for each leukocyte type, the so-called cell population data (CPD). CPD provide useful information on the basis of several cell proprieties such as volume characteristics, conductivity due to cytoplasm features, and various light-scattering patterns, reflecting different distribution of cells due to change in size, intracellular components and/or structure. These parameters can represent the morphological reactions of the cells to various environmental factors [1, 2]. With the introduction by the Beckman Coulter Company of the DxH800 hematology analyzer, CPD parameters are available for each population of WBCs, i.e., neutrophils, lymphocytes, monocytes, and eosinophils. In 2019, Beckman Coulter received FDA 510(k) clearance for its Early Sepsis Indicator (ESId), approved as a biomarker used in the identification of patients with sepsis or at risk of developing sepsis in the Emergency Department (ED). The ESId evaluates the width of monocyte volumes (Monocyte Distribution Width, MDW) and the novel parameter can be reported alongside routine cell blood count (CBC) and differential as an optional add-on feature.

Since sepsis represents a life-threatening condition, without characteristic signs or symptoms, early detection for timely and appropriate management is crucial to

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Intensive Care Medicine Experimental 2020, **8**(Suppl 2):73

000647

Monocyte distribution width: new biomarker of sepsis

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Intensive Care Medicine Experimental 2020, **8(2)**: 000647

Introduction: Sepsis is a major healthcare problem which affects millions of people around the world each year. Despite significant advances in diagnostic tools and the increasing use of biomarkers, the early recognition of sepsis in critically ill patients could be challenging. Recently, it has been described that morphological changes in leukocyte populations, especially the morphology and size of monocytes, could be used as a new biomarker for the early detection of sepsis.
Objectives: The main purpose is to determine if the monocyte distribution width (MDW) could be used as a new biomarker of sepsis. The secondary objective is to assess if MDW could be a prognostic factor of mortality in septic patients.
Methods: Prospective, observational study carried out during 2019 in the Intensive Care Unit (ICU). Critically ill patients with all kind of pathologies were included. It has been collected demographic variables, severity scores and ICU mortality. According to Sepsis-3 criteria, patients were divided into 3 groups on admission: non-infected (NI), sepsis (S) and septic shock (SS). MDW and traditional biomarkers were analyzed on admission. Statistical analysis includes qualitative variables, presented as proportions, and quantitative variables, presented as medians and minimum-maximum (Min-Max). Kolmogorov-Smirnov test was used for the assessment of normality. Kruskal-Wallis test was used to compare biomarkers among groups. The association between

* MDW is not intended for patients in ICU

MDW in ICU*

- 506 patients (346 men and 160 women)
- Age 18-89 years (median 68, IQR: 57–76 years)
- Patient groups:
  - 394 - sepsis negative;
  - 108 - Sepsis
  - 4 - septic shock
- Sepsis-3 diagnosis with SOFA score
- K3 EDTA blood collection tubes used

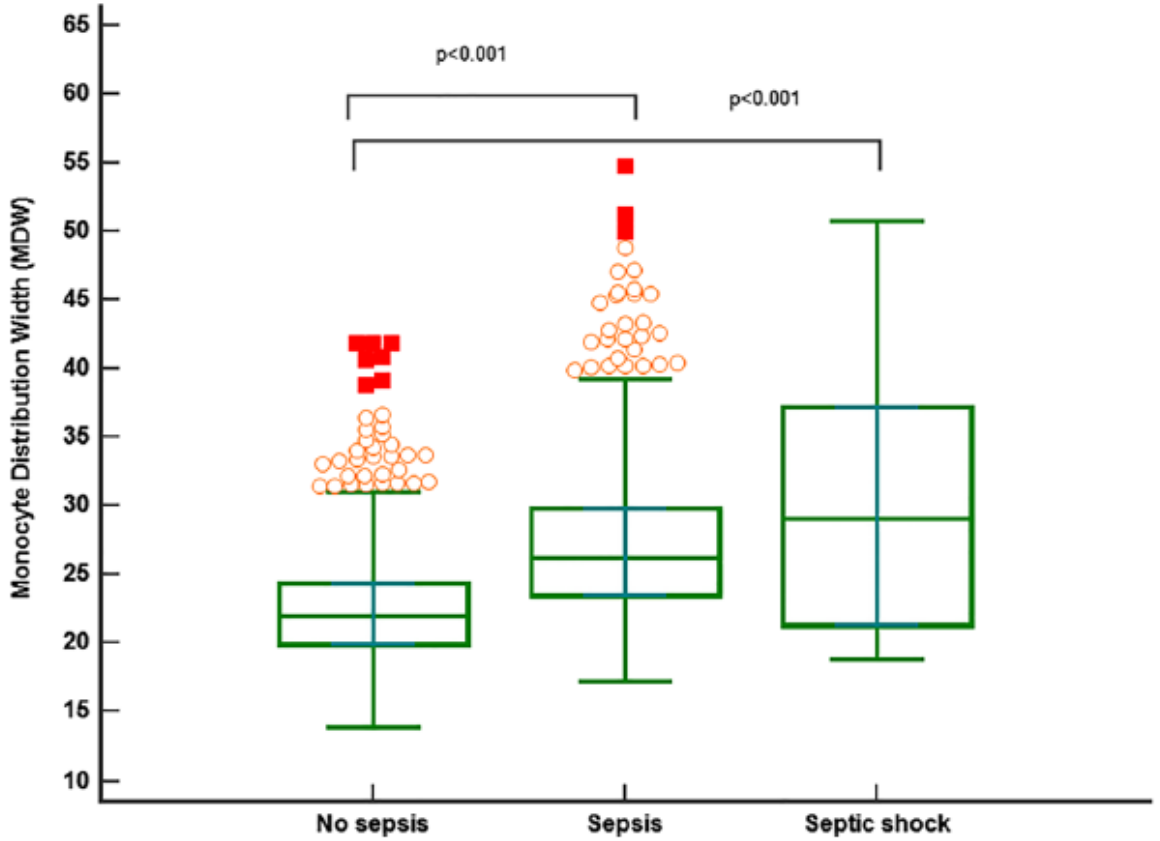


Figure 1: Distribution of MDW values for patient groups; MDW was statistically higher in those with sepsis or septic shock than those without sepsis.

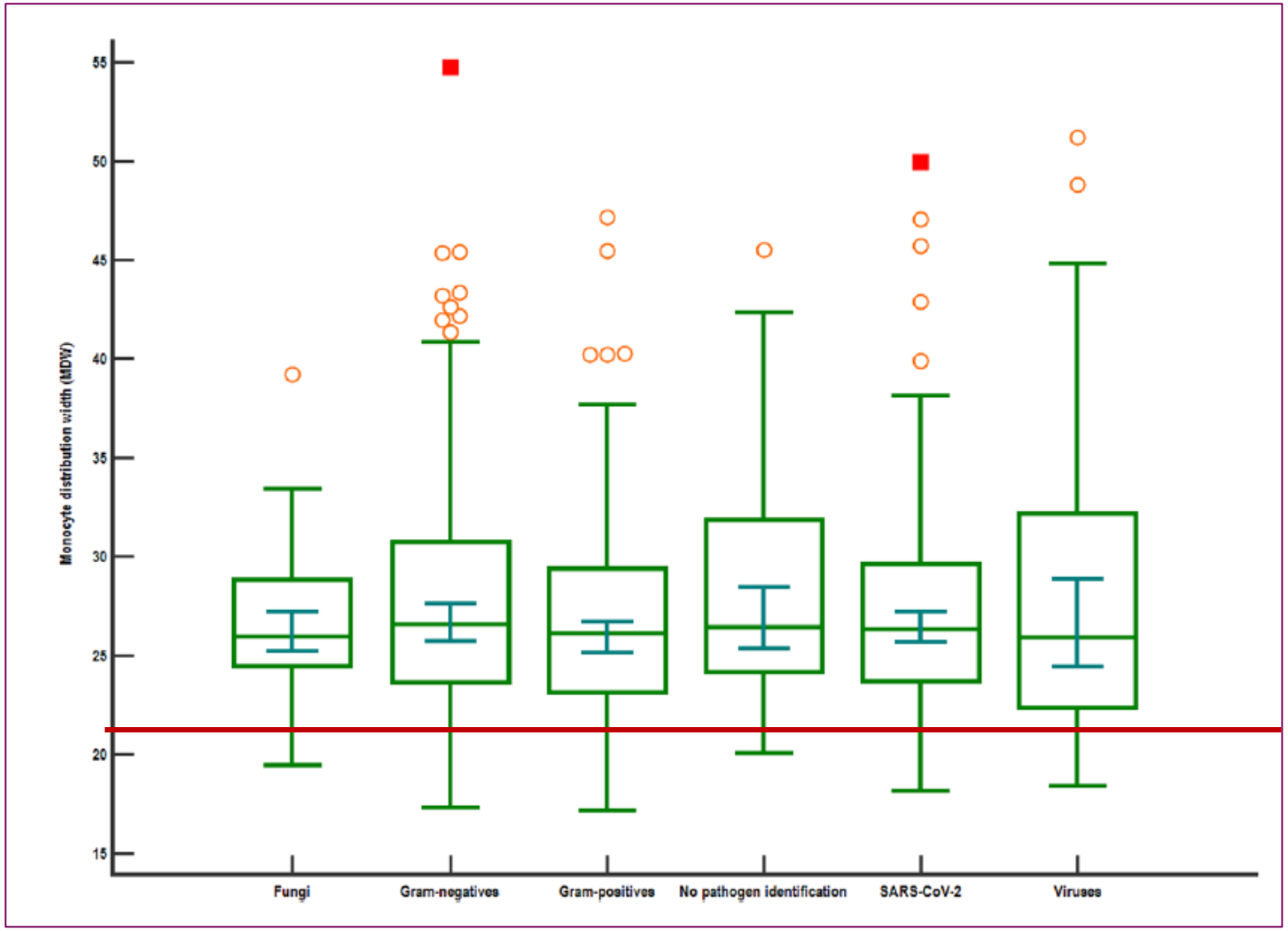
Clin Chem Lab Med 2021; https://doi.org/10.1515/cclm-2021-0192

* MDW is not intended for patients in ICU

MDW in ICU*

MDW values shown considering the causative organism type according to bacterial, fungal or viral infection attributed as the cause of sepsis.

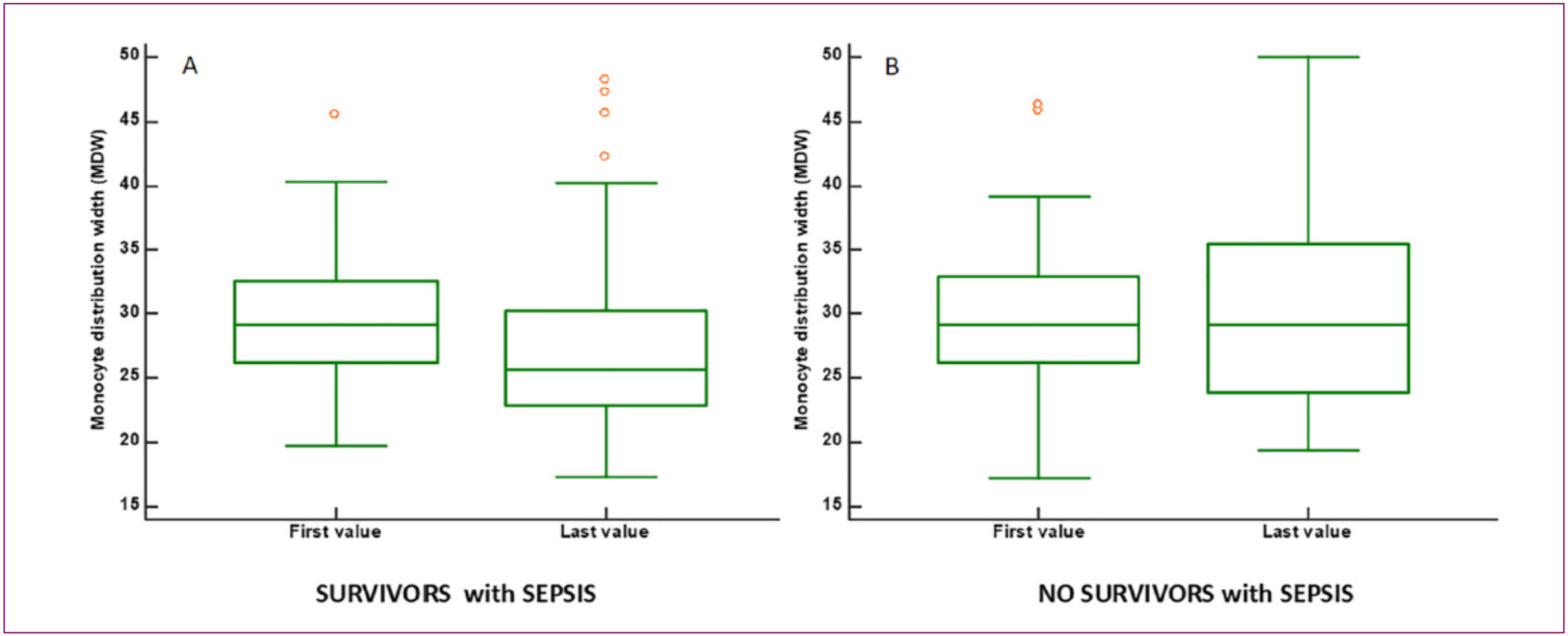
Cutoff 21.5 for K3 EDTA



Clin Chem Lab Med 2021; https://doi.org/10.1515/cclm-2021-0192

* MDW is not intended for patients in ICU

MDW in ICU*



Clin Chem Lab Med 2021; https://doi.org/10.1515/cclm-2021-0192

* MDW is not intended for patients in ICU

MDW in COVID-19*

*For scientific discussion only. The measurement of MDW on the UniCel DxH 900 analyser is intended for use with adult patients presenting to the emergency department, on whom a white cell differential test has been ordered, as an aid in the early detection of patients with or developing sepsis.

MDW IN COVID-19*

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Elevated monocyte distribution width in COVID-19 patients: The contribution of the novel sepsis indicator

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ARTICLE INFO

Keywords:
Monocyte distribution width
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ABSTRACT

Introduction: Interesting results regarding the contribution of MDW (Monocyte Distribution Width) in the Infectious Disease Unit have been reported. An observational study is ongoing at San Donato Hospital with the aim to evaluate the contribution of MDW in the diagnostic pathway in adult patients entering in the ED setting and tested for SARS-CoV-2.

Material and method: COVID-19 symptomatic and paucisymptomatic patients presenting to ED (Emergency Department), have been enrolled consecutively. Whole blood venous samples have been collected on K2 EDTA for MDW determination, at the same time a nasopharyngeal swab for SARS-CoV-2 RNA detection have been collected.

Results: One hundred six patients were negative for SARS-CoV-2 with MDW mean value of 20.3 ± 3.3, while forty-one were positive for SARS-CoV-2 with higher MDW mean value of 27.3 ± 4.9 ($P < 0.005$). The ROC curve analysis has been evaluated showing MDW AUC of 0.91. Finally twenty-three patients hospitalized in high-intensity care unit showed an MDW value higher than the eighteen patients presenting few symptoms (28.8 ± 5.3 vs 25.4 ± 3.6 respectively, $P < 0.05$).

Discussion: Monocytic population, in Covid19 disease, are the first elements of innate immunity to be involved, these changes are the basis of the modification of the MDW, with evident efficacy in term of sensitivity, particularly in the studied Covid19 patients. Moreover the patients hospitalized in high-intensity care unit showed significantly elevated MDW respects to middle or low symptomatic one, suggest including this parameter as prognostic marker or of therapy efficacy, integrated with other laboratory findings.

1. Introduction

Due to the COVID-19 outbreak, Tuscany Region adopted countermeasures to cope with this emergency.

Among these countermeasures, separate pathways for patients suspected of COVID infection have been activated at every Emergency Departments and a Coronavirus test has been recommended at the onset of symptoms. To ensure the safest and the appropriate location, all the hospitalized patients have been tested for the virus [1]. As the WHO also pointed out, testing is a crucial phase for preventing virus transmission at community level [2]. The Arezzo hospital in Tuscany (San Donato Hospital) moved accordingly and nasopharyngeal swab for viral RNA detection has been collected.

Monocyte Distribution Width (MDW) is an *in vitro* diagnostic parameter automatically reported in the Complete Blood Count with differential (CBC-Diff) and routinely requested at the Emergency Department. It has been demonstrated that an elevated MDW value is effective for early detection of sepsis in adult patients presenting at the Emergency Department (ED) [3,4].

Interesting results regarding the contribution of MDW in the Infectious Disease Unit have been reported, with MDW showing a Receiver Operating Characteristic (ROC) curve Area Under the Curve (AUC) nearly overlapping the PCT one [MDW AUC 0.87; PCT AUC 0.88] [5].

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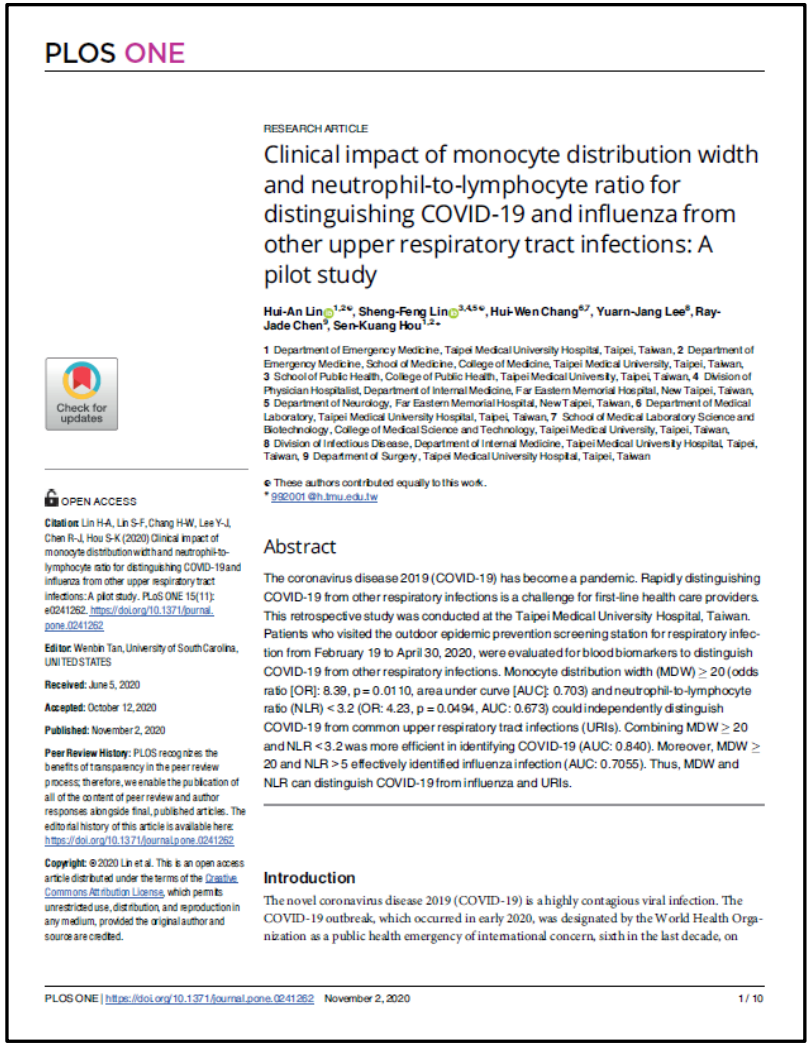

PLOS ONE

RESEARCH ARTICLE

Clinical impact of monocyte distribution width and neutrophil-to-lymphocyte ratio for distinguishing COVID-19 and influenza from other upper respiratory tract infections: A pilot study

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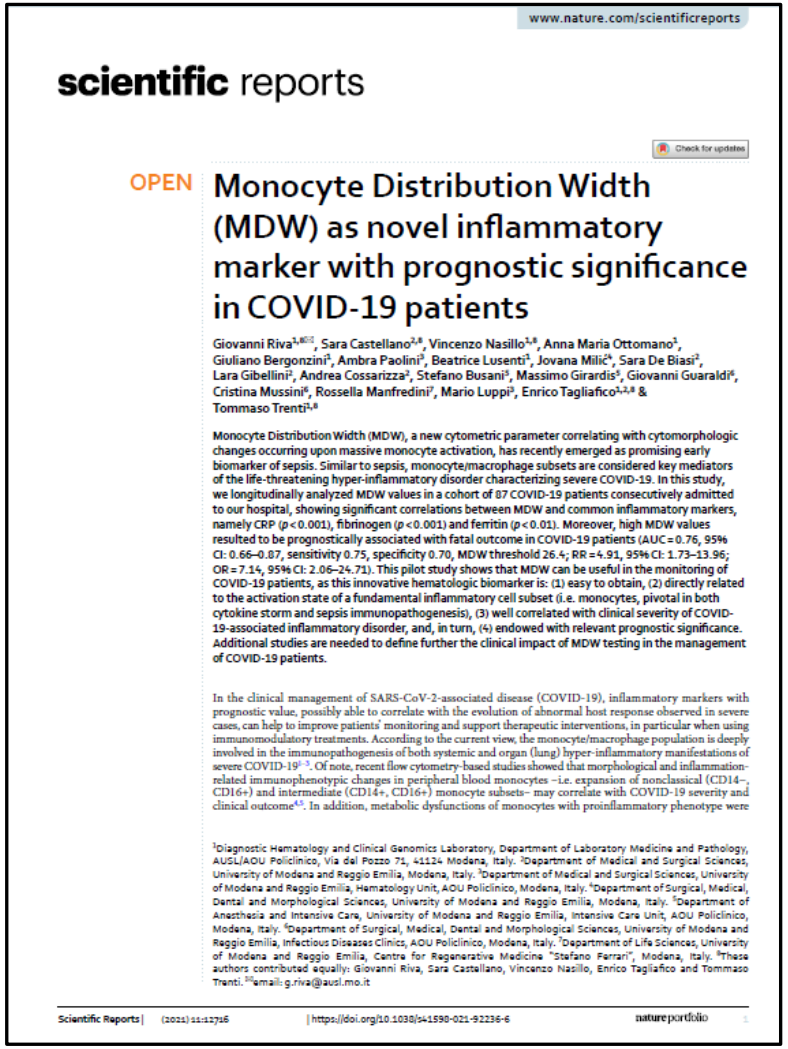
Abstract

The coronavirus disease 2019 (COVID-19) has become a pandemic. Rapidly distinguishing COVID-19 from other respiratory infections is a challenge for first-line health care providers. This retrospective study was conducted at the Taipei Medical University Hospital, Taiwan. Patients who visited the outdoor epidemic prevention screening station for respiratory infection from February 19 to April 30, 2020, were evaluated for blood biomarkers to distinguish COVID-19 from other respiratory infections. Monocyte distribution width (MDW) ≥ 20 (odds ratio [OR]: 8.39, p = 0.0110, area under curve [AUC]: 0.703) and neutrophil-to-lymphocyte ratio (NLR) < 3.2 (OR: 4.23, p = 0.0494, AUC: 0.673) could independently distinguish COVID-19 from common upper respiratory tract infections (URIs). Combining MDW ≥ 20 and NLR < 3.2 was more efficient in identifying COVID-19 (AUC: 0.840). Moreover, MDW ≥ 20 and NLR > 5 effectively identified influenza infection (AUC: 0.7055). Thus, MDW and NLR can distinguish COVID-19 from influenza and URIs.

Introduction

The novel coronavirus disease 2019 (COVID-19) is a highly contagious viral infection. The COVID-19 outbreak, which occurred in early 2020, was designated by the World Health Organization as a public health emergency of international concern, sixth in the last decade, on



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Monocyte Distribution Width (MDW) as novel inflammatory marker with prognostic significance in COVID-19 patients

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Monocyte Distribution Width (MDW), a new cytometric parameter correlating with cytomorphologic changes occurring upon massive monocyte activation, has recently emerged as promising early biomarker of sepsis. Similar to sepsis, monocyte/macrophage subsets are considered key mediators of the life-threatening hyper-inflammatory disorder characterizing severe COVID-19. In this study, we longitudinally analyzed MDW values in a cohort of 87 COVID-19 patients consecutively admitted to our hospital, showing significant correlations between MDW and common inflammatory markers, namely CRP ($p < 0.001$), fibrinogen ($p < 0.001$) and ferritin ($p < 0.01$). Moreover, high MDW values resulted to be prognostically associated with fatal outcome in COVID-19 patients (AUC = 0.76, 95% CI: 0.66–0.87, sensitivity 0.75, specificity 0.70, MDW threshold 26.4; RR = 4.91, 95% CI: 1.73–13.96; OR = 7.14, 95% CI: 2.06–24.71). This pilot study shows that MDW can be useful in the monitoring of COVID-19 patients, as this innovative hematologic biomarker is: (1) easy to obtain, (2) directly related to the activation state of a fundamental inflammatory cell subset (i.e. monocytes, pivotal in both cytokine storm and sepsis immunopathogenesis), (3) well correlated with clinical severity of COVID-19-associated inflammatory disorder, and, in turn, (4) endowed with relevant prognostic significance. Additional studies are needed to define further the clinical impact of MDW testing in the management of COVID-19 patients.

In the clinical management of SARS-CoV-2-associated disease (COVID-19), inflammatory markers with prognostic value, possibly able to correlate with the evolution of abnormal host response observed in severe cases, can help to improve patients' monitoring and support therapeutic interventions, in particular when using immunomodulatory treatments. According to the current view, the monocyte/macrophage population is deeply involved in the immunopathogenesis of both systemic and organ (lung) hyper-inflammatory manifestations of severe COVID-19[1–3]. Of note, recent flow cytometry-based studies showed that morphological and inflammation-related immunophenotypic changes in peripheral blood monocytes –i.e. expansion of nonclassical (CD14−, CD16+) and intermediate (CD14+, CD16+) monocyte subsets– may correlate with COVID-19 severity and clinical outcome[4,5]. In addition, metabolic dysfunctions of monocytes with proinflammatory phenotype were

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*For scientific discussion only. The measurement of MDW on the UniCel DxH 900 analyser is intended for use with adult patients presenting to the emergency department, on whom a white cell differential test has been ordered, as an aid in the early detection of patients with or developing sepsis.

MDW in COVID-19*

Monocyte/macrophage subsets are considered key mediators of the life-threatening hyper-inflammatory disorder characterizing severe COVID-19

- MDW values increase with increasing COVID-19 severity, from mild to moderate, to severe disease [1,2]
- MDW values are prognostically associated with fatal outcome in COVID-19 patients [1,2]
- MDW can be considered a useful tool in predicting the severity of COVID-19 disease and patient outcome

[1] S. Naseem et al. Abstract accepted for ISICEM 2021, Brussels, Belgium
[2] G. Riva et al. Nature Scientific Reports, (2021) 11:12716

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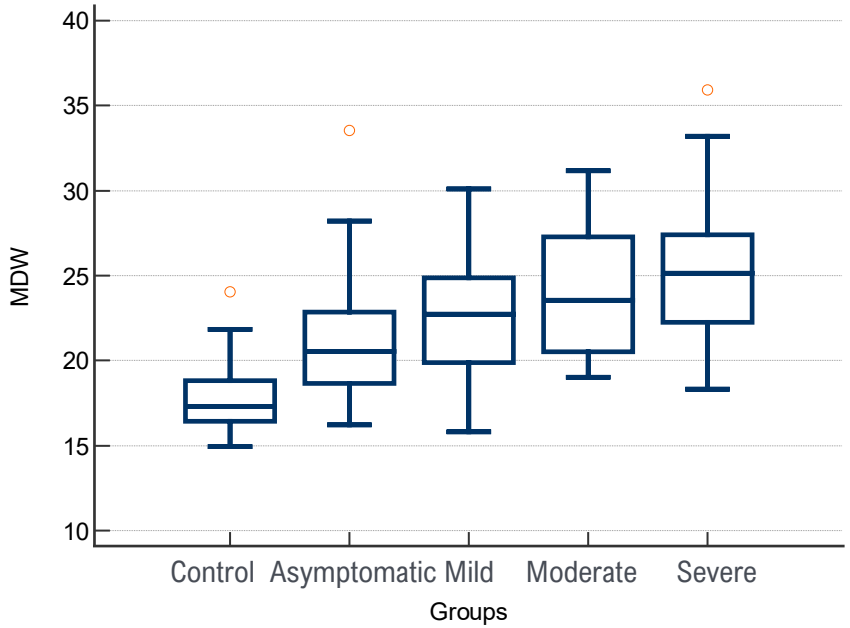
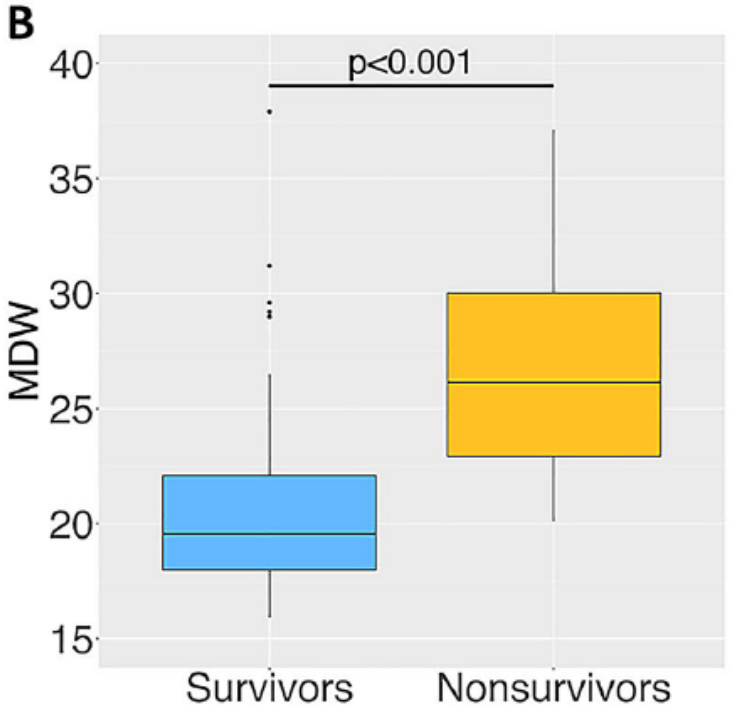
MDW in COVID-19



MDW results in patient subgroups, according to disease severity.

S. Naseem et al. Abstract presented at ISICEM 2021, Brussels, Belgium, August 31st – September 3rd 2021.



Boxplot comparison for 'last MDW' median values between survivor and non-survivor groups.

Riva et al. Nature Scientific Reports, (2021) 11:12716

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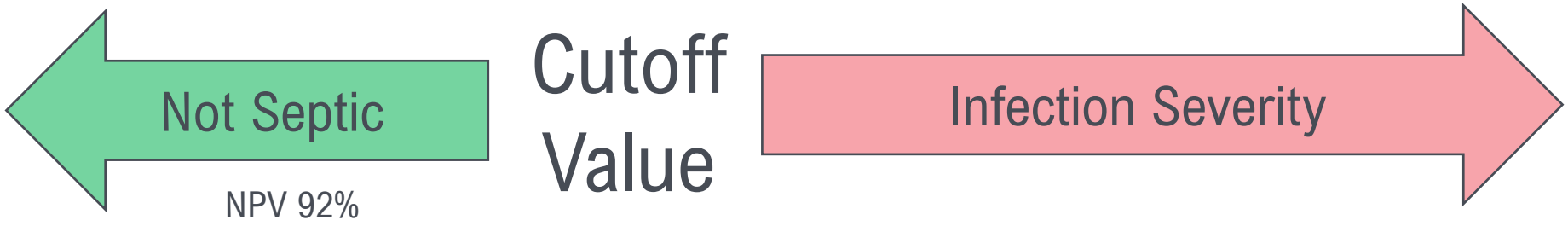
HOW TO USE MDW

- **Marker of Severity of Infection**
  - To assist clinically with reclassifying a patient based on level of severity
    - Higher MDW values equate to higher relative risk of severe infection
    - Data point to assist on decisions to transfer, admit and/or treatment decisions



Summary

SEPSIS ADVISORY BOARD

CONSENSUS ON MDW UTILITY: KEY RECOMMENDATIONS

- **MDW indicates the probability of severe infection and risk of sepsis** in the Emergency Department (ED). This is consistent with understanding of monocytes physiology and behavior pointing to infectious etiology of systemic inflammation in an innate immune response
- Include MDW in the patient **triage/evaluation protocols in initial clinical assessment**
- Use MDW **systematically** together with clinical signs/SOC to improve the accuracy of sepsis/severe infection diagnosis in ED if CBC-Diff ordered and to alert of patients in whom physician **does not yet have a suspicion**
- Abnormal MDW values can **trigger commonly ordered sepsis workup test** according to standards of care.

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