

# Diagnostic and Prognostic Value of Monocyte Distribution Width in Sepsis

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**Abstract:** Monocyte distribution width (MDW) is a blood monocyte morphological parameter that can be easily detected by an automated hemocyte analyzer and can provide clinicians with important information about cell volume variability in peripheral blood monocyte populations. The United States' Food and Drug Administration and Conformite Europeenne have both been cleared for their clinical application in the detection of sepsis and developing sepsis in adult patients in the emergency department (ED). Recently, MDW has been found to have an early diagnosis and predictive value for sepsis in neonates and COVID-19 patients. Here, we summarize the findings of the studies investigating the clinical application of MDW in sepsis. Under different stimuli, especially in infectious diseases, the activation of innate immunity is the host's first defense mechanism, and the change in monocyte volume is considered an early indicator reflecting the state of activation of innate immunity. Pivotal study data from a large multicenter patient cohort showed that abnormal MDW at presentation increases the odds of sepsis, considering the combination of MDW and White Blood Cell Count (WBC) as part of a standard sepsis assessment protocol for ED, which may increase the sensitivity and specificity of sepsis diagnosis. Meanwhile, MDW shares a diagnostic performance comparable to that of conventional biomarkers (C-reactive protein and procalcitonin) in sepsis. In addition, some evidence suggests that increased MDW, both in adults and neonates, may be associated with unfavorable short- and long-term outcomes, which indicates its prognostic value in sepsis. Taken together, MDW is a parameter of increased morphological variability of monocytes in response to infection, and numerous studies have shown that MDW could be used as a valuable diagnostic and prognostic index in patients with sepsis or suspected sepsis.

**Keywords:** monocyte distribution width, sepsis, diagnosis, prognosis, COVID-19

## Introduction

Sepsis is a life-threatening organ dysfunction caused by the maladjustment of the body's response to infection. Sepsis is a global public health problem that generates more than 3,000,000 hospitalizations per year. Despite advances in modern medicine, more than 5.3 million people die annually from sepsis. It remains the leading cause of death in critically ill patients in non-coronary intensive care units, with an estimated overall mortality rate of approximately 30%. It has high morbidity and mortality, especially among comorbid and hospitalized patients,<sup>1,2</sup> and its incidence is continuously increasing worldwide.<sup>3</sup> Early diagnosis and treatment of sepsis and sepsis-related organ dysfunction are critical for improving patient survival and reducing healthcare costs.<sup>4</sup> To improve survival, early recognition of sepsis has become the primary healthcare goal of many societies, promoting research and the development of optimal biomarkers for rapid diagnosis and assessment of the severity of sepsis-related diseases.

Sepsis biomarkers vary with the pathogenesis of sepsis and knowledge of regarding it. In the 1980s, pro-inflammatory cytokines that produced SIRS (TNF, IL-1 $\beta$ , and IL-6) and C-reactive protein (CRP) were the most important indicators for the early hyperinflammatory phase. In the 1990s, the increased expression of CD64 on the cell during infection was

discovered, and procalcitonin (PCT) was described as a marker of bacterial infections. In 2001, the International Conference on Sepsis included, for the first time, CRP and PCT as biomarkers of sepsis.

In addition to these biomarkers, complete blood count (CBC) and leukocyte differential (DIFF) are the most commonly used tests in clinical laboratories, and the application of CBC+DIFF in sepsis diagnosis is common.<sup>5</sup> With the introduction of new technologies and the development of analyzers capable of detecting changes in three hematopoietic cell lines, hematology analyzers have greatly improved. UniCel DxH800/900 (Beckman Coulter, Miami, Florida, USA) is used for in vitro diagnostics in clinical laboratories. The DxH800/900 system provides automated CBC, DIFF, nucleated red blood cell count, enumeration, reticulocyte analysis, and an automated method for enumeration of the total nucleated cells and red blood cells in body fluids.

The Coulter principle, under the VCSn (volume, conductivity, and scatter) technology,<sup>6</sup> could provide quantitative measurement information of the blood cell morphology (including cell size, morphology and lobulation of nucleus, intracellular granules, etc.). Monocyte distribution width (MDW), a parameter provided by the aforementioned DxH800/900 cellular analysis system, reflects the variability and heterogeneity of monocyte size in peripheral blood. This parameter has been shown to aid in the early detection of sepsis in emergency room patients, and currently, both the FDA and CE have cleared for its clinical application in the detection of sepsis and developing sepsis for adult patients in the emergency department.

As we all know, monocytes can contribute to the process of inflammation or infection by secreting cytokines;<sup>7</sup> however, there is increasing evidence that monocytes undergo morphological changes, including volume increase, during inflammatory or infectious processes and during sepsis.<sup>8–11</sup> Monocytes are important immune effector cells that protect against microbial pathogens and promote immune surveillance.<sup>12</sup> In sepsis, changes in monocytes were documented in 1993.<sup>13</sup> Monocytes perform several roles in sepsis, including antigen presentation, phagocytosis of pathogens, and production of pro- and anti-inflammatory cytokines.<sup>14</sup> Human blood monocytes are segregated into three subsets based on CD16 and CD14 expression: CD14<sup>++</sup>/CD16<sup>-</sup> classical monocytes (CM), CD14<sup>++</sup>/CD16<sup>+</sup> intermediate monocytes (IM), and CD14<sup>+</sup>/CD16<sup>++</sup> non-classical monocytes (NCM).<sup>15</sup> During inflammatory conditions, such as sepsis,<sup>16</sup> bacterial infection,<sup>17</sup> viral infection,<sup>18–21</sup> autoimmune disease<sup>22</sup> and other inflammatory diseases,<sup>23,24</sup> the changes (number, volume, function, etc.) in the three subsets are different. Nowadays, MDW, a quantitative morphological parameter for monocyte activation in peripheral blood, could be used as an indicator of inflammation at an early stage.

## The Role of MDW in Sepsis

### The Role of MDW for Emergency Department (ED) Patients

In ED patients, the prevalence of sepsis is approximately 1.2%.<sup>25</sup> Rhee et al<sup>26</sup> reported that the vast majority of sepsis patients (86.8% [95% CI, 86.7–87.0%]) had sepsis upon admission. In ED patients, non-severe sepsis without organ failure or shock has a significant difference in mortality compared to severe sepsis. Therefore, the early diagnosis of sepsis may improve patient prognosis.<sup>27</sup> Unfortunately, in the ED, the early diagnosis of sepsis has some difficulties, including the overlap of various patient symptoms, limitations of medical conditions, and time constraints.

Owing to the increasing incidence and mortality of sepsis, there is an urgent need for new and effective biomarkers for the diagnosis and monitoring of sepsis in the ED. Many studies have shown that MDW improves the early detection of sepsis during initial ED visits. Based on morphological changes in monocytes during inflammation, the sepsis index ((SI), based on MDW and mean monocyte volume (MMV)) significantly improves the accuracy of early sepsis screening and diagnosis.<sup>28,29</sup> A blind, prospective cohort study was conducted in two different emergency departments at Ohio State University by Crouser et al,<sup>30</sup> 1320 subjects were enrolled in the ED consecutively. Those patients were grouped into systemic inflammatory response syndrome (SIRS), infection, and sepsis (including sepsis, severe sepsis, and septic shock) groups, and MDW was measured using a UniCel DxH 800 analyzer. The results showed that MDW can distinguish sepsis from other conditions (AUC, 0.79; 95% CI, 0.73–0.84); moreover, it was associated with the severity of sepsis, increased with progression from mild infection to sepsis, and was highest in patients with more organ dysfunction in sepsis. A subsequent study also showed that MDW could be used as a screening tool for early identification of patients at risk of sepsis in the ED (AUC, 0.964; 95% CI, 0.945–0.984).<sup>31</sup> In a study regarding health and economics,<sup>32</sup> approximately 67% of patients benefited from MDW results due to early recognition of sepsis,

resulting in a reduction in the average duration of antibiotic use from 3.98 to 2.07 hours and a reduction in the average hospital cost of \$3046. At the hospital level, the early diagnosis of sepsis with MDW is expected to reduce the total cost by \$712,783 per hospital per year.

Sepsis 3.0 is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score by 2 points or more. However, the SOFA score can take time to obtain; thus, SIRS criteria [abnormal white blood cell count (WBC), tachycardia, tachypnea, and fever (or hypothermia)] and quick sepsis-related organ failure assessment (qSOFA) score (tachypnea, altered mental state, and hypotension) are used as surrogate methods to assist in the quick diagnosis of sepsis in the ED. Crouser et al<sup>33</sup> found that regardless of SIRS or qSOFA variables, an initial MDW >20.0% (vs. <20.0) significantly increased the incidence of sepsis; Meanwhile, according to Agnello et al<sup>34</sup> meta-analysis data, MDW plays an important role in Sepsis screening regardless of the Sepsis-2 and Sepsis-3 standard groups; therefore, MDW improved the early detection of sepsis in the initial ED and was a good complement to SIRS and qSOFA parameters. Similarly, the combination of MDW and white blood cell count (WBC),<sup>35</sup> neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR)<sup>36</sup> significantly improved the early diagnosis of sepsis. It has been proved that the diagnostic performance of MDW was comparable to that of traditional diagnostic biomarkers (PCT, CRP), and the combined diagnosis could enhance the effect to some extent, but not significantly.<sup>37,38</sup>

## The Role of MDW for ICU Patients

Patients in intensive care units (ICUs) are considered at high risk for sepsis because of surgical and invasive procedures.<sup>3</sup> Globally, sepsis leading to shock and/or end-organ failure has been identified as the most common indication for ICU admission and the leading cause of ICU death.<sup>39</sup> A pilot study in the ICU<sup>40</sup> showed that MDW levels at admission were significantly higher in patients with sepsis than in those without sepsis and those with sepsis during hospitalization. Interestingly, the MDW values were significantly higher at the time of clinical sepsis diagnosis than at admission. In addition, Polilli et al<sup>41</sup> compared patients with no sepsis, sepsis, and septic shock and found that MDW values were significantly higher in patients with sepsis or septic shock than in 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)]. Moreover, the elevation of MDW was independent of the type of sepsis-causing pathogen. Therefore, MDW can be used as a diagnostic indicator of early sepsis in ICU patients and has a strong ability to resist the interference of infectious organisms. Moreover, MDW is a good predictor of disease progression and associated prognosis.

Reports on the early diagnosis and detection of ICU sepsis using MDW combined with other indicators or compared with other indicators are gradually increasing. In a prospective study in Italy,<sup>42</sup> the AUC of MDW (0.785; 95% CI: 0.767–0.801) was comparable to that of PCT (0.759; 95% CI: 0.740–0.778), and superior to CRP (0.667; 95% CI: 0.646–0.688) and WBC (0.570; 95% CI: 0.547–0.592) in the diagnosis of sepsis in the ICU. The combination of MDW > 23 and PCT > 0.5 ng/mL had high specificity (92.6%), Youden index (0.61) and PPV (92.6%).<sup>41</sup> Therefore, the combination of MDW with other inflammatory indicators (PCT, CRP, interleukin, and leukocyte-related indicators) indicates a great potential for early diagnosis and prediction of sepsis prognosis.

## The Role of MDW in Pediatric Patients

Neonatal sepsis is a clinical syndrome caused by pathogen invasion, with nonspecific signs and symptoms, high morbidity and mortality, and difficult diagnosis.<sup>43,44</sup> The incidence of neonatal sepsis is significantly higher in low-income countries than in high-income countries,<sup>45,46</sup> and exposure time, dose, infant immune status, and pathogen virulence may affect the incidence and clinical manifestations of neonatal sepsis.<sup>43</sup> Early diagnosis of neonatal sepsis is difficult because the symptoms are non-specific, blood culture results are time-consuming, and the positive rate is low. However, using antibiotics to treat culture-negative sepsis or clinical sepsis is controversial.<sup>47</sup> Prolonged or unnecessary use of antibiotics increases the risk of other diseases (obesity, necrotizing enterocolitis, fungal infections, bronchopulmonary dysplasia, and death) in newborns.<sup>48</sup> Therefore, it is important to identify fast and effective biomarkers for the early detection and diagnosis of neonatal sepsis.

There has been very little literature on the role of MDW in neonatal sepsis. Celik et al<sup>49</sup> investigated 227 newborns [sepsis group: 116 (proven sepsis,  $n = 40$ ; clinical sepsis,  $n = 76$ ) and control group: 111] and found MDW was higher in septic patients in comparison with control group. The MDW of infants with late-onset sepsis was significantly higher than that of those with early onset sepsis. Moreover, there was no significant difference in the MDW values between gram-positive and gram-negative bacteria grown in blood cultures. An experiment was conducted by Nam et al.<sup>50</sup> In pediatric septic patients, the levels of MDW gradually increased from the control, SIRS without infection, to sepsis. In addition, MDW (AUC, 0.77; 95% CI, 0.72–0.83) showed higher AUC values than CRP (AUC, 0.74; 95% CI, 0.68–0.80), and MDW was also a valuable marker for predicting mortality.

CRP,<sup>51</sup> PCT,<sup>52</sup> IL-6<sup>53</sup> are the most widely studied inflammatory markers for the diagnosis of newborn sepsis. Although the CRP concentration correlates with disease severity, early diagnosis of neonatal sepsis is unreliable because of delayed elevation.<sup>54</sup> In addition, other non-infectious mother-to-child diseases may lead to elevated CRP levels, making it a nonspecific biomarker.<sup>55</sup> Meanwhile, the sensitivity and PPV of CRP are considered low in early-onset sepsis.<sup>56</sup> PCT increases more rapidly than CRP, which makes PCT more sensitive than CRP in the early diagnosis of neonatal sepsis,<sup>54</sup> and this increase is often associated with disease severity and mortality.<sup>57</sup> IL-6 may not be a strong predictor of neonatal sepsis owing to its high measurement cost, low sensitivity, and specificity.<sup>49</sup> Although MDW is inferior to PCT and CRP in the diagnosis of neonatal sepsis,<sup>49</sup> MDW still has certain advantages in the application of neonatal sepsis diagnosis, owing to its ease of use, fast TAT, micro blood volume requirement, and low cost.

## The Role of MDW in COVID-19 Patients

Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2 infection, most COVID-19 patients have mild or no symptoms, while some develop symptoms such as severe pneumonia, acute respiratory distress syndrome (ARDS) or multiple organ failure. Lymphocytopenia and inflammatory storms are typical in critically ill patients. Inflammatory storms occur when patients have high levels of inflammatory mediators including IL-6, IL-10, tumor necrosis factor (TNF)- $\alpha$ , and immunosuppressors.<sup>58–60</sup> Peripheral circulating monocytes participate in inflammatory storms by producing inflammatory cytokines and mediators.<sup>7,61</sup> Interestingly, significant differences were found in the function and morphology of monocytes between COVID-19 patients and healthy individuals.<sup>62</sup> Therefore, activation and morphological changes in monocytes may be used to predict changes in the condition of COVID-19 patients.

Ognibene et al<sup>63</sup> proved that in COVID-19 positive patients, MDW (mean:  $27.3 \pm 4.9$ ) was significantly higher than that of COVID-19 negative patients (mean:  $20.3 \pm 3.3$ ), and the MDW value of severe patients was also higher than that of mild patients, indicating that MDW can be used as an indicator of the prognosis or treatment effect of COVID-19. Recent studies have also shown significant increases in both the lymphoid index and MDW in COVID-19 patients, with good diagnostic performance in combination (AUC: 0.89).<sup>64,65</sup> MDW  $>20$  and NLR  $<3.2$  or NLR  $>5$  could independently distinguish COVID-19 from common upper respiratory tract infections or influenza.<sup>66</sup> Using random forest classifier, the algorithm developed based on the combination of four monocyte CPD (cellular population data, including MDW) to distinguish positive and negative COVID-19 patients also achieved good results (specificity 89.7%, sensitivity 60.5%), and it was also found that patients with sepsis often had false positives.<sup>67</sup> A recent study performed by Riva et al<sup>68</sup> showed that MDW is strongly correlated with CRP, fibrinogen, ferritin, and body temperature in COVID-19 patients, that MDW values are significantly correlated with final clinical outcome (survival/discharge vs death), and that the risk of fatal outcomes increased significantly when MDW values were higher than 26.4 (RR = 4.91, 95% CI: 1.73–13.96; OR = 7.14, 95% CI: 2.06–24.71).

## Discussion

This review summarizes the current major studies on MDW application in sepsis, suggesting that MDW serves as a new inflammatory marker and can be used as an early diagnosis and prognostic indicator of sepsis in emergency departments, ICU, neonates, children, and patients with COVID-19, and can be used to predict the progression of sepsis (Table 1).

MDW can be easily measured using an automated hemocyte analyzer (Unicel DxH800/900) together with routine blood tests. Since there is no need for additional technical requirements, the cost of each test is low and affordable (ie, a full blood cell count). Furthermore, TAT is fast, and it may be considered to be of high value in the diagnosis of fast-

**Table 1** Researches About Monocyte Distribution Width (MDW) and Sepsis

Study Period	Design Method	Country	Participants	Department	Criteria	Cutoff of MDW (U)	Anticoagulants	Other Indicators	Main Findings	References
September to November 2019	Prospective	Italy	Control (1855), infection (172), SIRS (100), sepsis (88)	ED	Sepsis-2	23.5	K3EDTA	CRP, WBC, qSOFA, blood culture, use of antibiotics	MDW levels were higher in patients with sepsis than in all other groups ( $p < 0.001$ )	[31]
	Prospective	Italy	Suspected COVID-19 patients (147)	ED		20	K2EDTA		The MDW of hospitalized patients in intensive care unit was significantly higher than that of patients with moderate and low symptoms	[63]
June 19, 2017 to January 26, 2018	Retrospective	USA	Adults (2158)	ED	Sepsis-2 Sepsis-3			qSOFA, SIRS, WBC	MDW improves the detection rate of sepsis in the ED and is a good supplementary parameter for SIRS and qSOFA	[33]
	Prospective	USA	Control (879), SIRS (203), infection (140), sepsis (98)	ED	Sepsis-2	20.5		MNV, NDW, MMV	MDW combined with WBC can increase the detection rate of sepsis	[30]
April 2017 to January 2018	Prospective	USA	Adults (2158)	ED	Sepsis-2 Sepsis-3	20		WBC	MDW value of greater than 20.0 U is effective for sepsis detection, during the initial ED encounter	[35]
Part 1: March 11, to April 5, 2020 Part 2: April 6, to April 13, 2020	Part 1: Retrospective Part 2: Prospective	France	Part 1: Control (137), COVID-19+ (322), COVID-19- (285) Part 2: Suspected COVID-19 patients (222)	ED		21.71	K3EDTA	CPD, CRP	CPD (including MDW) can improve the diagnostic efficiency of patients with COVID-19, and false-positive results are common in sepsis	[67]
February 19, to April 30, 2020	Retrospective	China	Respiratory infection (174)	ED		20		NLR	MDW and NLR can distinguish COVID-19 from influenza and upper respiratory tract infections	[66]
October to November 2020	Retrospective	Italy	control (498), infection (105), SIRS (52) and sepsis (48)	ED	Sepsis-2		K3EDTA	MMV	Compared with MDW alone, monocyte index SI (based on MDW and MMV) showed increased specificity, positive predictive value, and positive likelihood ratio	[28]
August 2, 2018, to June 27, 2019	Prospective	France, Spain	Adults (1517)	ED	Sepsis-2 Sepsis-3	21.5	K3EDTA	PCT, CRP	MDW in combination with WBC has the diagnostic accuracy to detect sepsis, and the diagnostic efficiency is equivalent to CRP and superior to PCT	[38]
January 1, 2020 to November 30, 2020	Retrospective	China	Sepsis (296), no sepsis (1184)	ED	Sepsis-2	20		CRP, NLR, PLR, qSOFA	MDW, NLR, and PLR can be used for the early detection of sepsis in the current sepsis scoring systems	[36]

(Continued)

Table I (Continued).

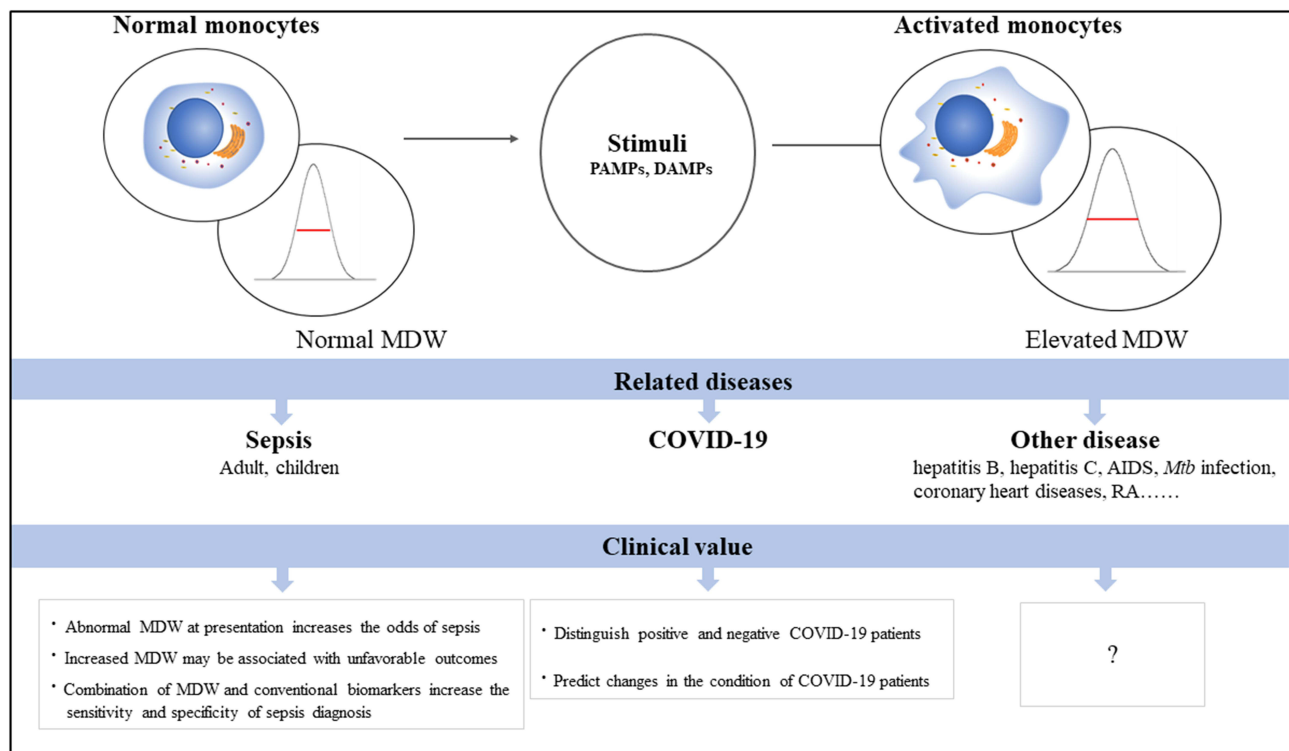
Study Period	Design Method	Country	Participants	Department	Criteria	Cutoff of MDW (U)	Anticoagulants	Other Indicators	Main Findings	References
September 2019 to March 2020	Prospective	Italy	Adults (2297)	ED ICU	Sepsis-2 (ED) Sepsis-3 (ICU)	23	K3EDTA	CRP, PCT	MDW has good diagnostic efficiency for sepsis, and the cutoff value of MDW is determined to be 23	[71]
January to June 2020	Prospective	Italy	Adults (506) (no sepsis, sepsis, septic shock)	ICU	Sepsis-3	24.63	K2EDTA	PCT, CRP	MDW values were significantly higher in patients with sepsis or septic shock in comparison to those within the no sepsis group. MDW increase is not affected by the aetiology of sepsis, even in patients with COVID-19	[42]
September 2019 to March 2020	Prospective	Italy	No sepsis (50), developing sepsis during hospital stay (16), sepsis (30)	ICU	Sepsis-3		K3EDTA	CRP, PCT	Patients with sepsis had significantly increased MDW, a reliable sepsis marker in the ICU	[40]
January 1, to December 31, 2018	Prospective	Italy	ICU patients (211)	ICU	Sepsis-3	20	K3EDTA	PCT	Values of MDW > 23 were associated with a high PPV for sepsis, whereas values of MDW ≤ 20 were associated with a high NPV	[41]
August 2017 to September 2018	Prospective	Italy	Suspected infection or sepsis (310)	Infectious Diseases Unit	Sepsis-3	22.0	K3EDTA	PCT	Incorporating MDW into current leukocyte techniques can significantly improve the detection of sepsis	[69]
July 2010 to February 2012	Prospective	Turkey	Newborns (227)					MNV, MMV, MNC, MMC MNS, MMS, NDW, CRP, PCT IL-6	MDW was higher in infants with sepsis than in controls, and in the diagnosis of neonatal sepsis was lower than that of CRP, PC and IL-6	[49]
April to September 2016	Retrospective	Korea	Pediatric patients (232)			22		WBC, DN, NDW, MPV, PDW, PMDW, IPF, CRP, PCT	WBC, DN, NDW, MDW, MPV, PDW, PMDW, and IPF were valuable markers for predicting mortality	[50]
February 14 to February 29, 2020	Retrospective	China	Suspected COVID-19 patients (147)			20.1		MNV, NDW, MMV MLV, LDW, Lymph index	MDW and lymphoid index in patients with COVID-19 were significantly higher than those in control group, and MDW and lymphoid index had good diagnostic performance for patients with COVID-19	[64]
April to June 2020	Retrospective	Italy	COVID-19 patients (87)			26.4 (threshold)	K2EDTA	CRP, fibrinogen, ferritin	MDW was significantly correlated with CRP, fibrinogen and ferritin. High MDW values are associated with prognosis and death outcomes in COVID-19 patients	[68]

**Abbreviations:** ED, emergency department; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; EDTA, ethylenediaminetetraacetic acid; CRP, C-reactive protein; WBC, white blood cell; qSOFA, Quick Sequential (Sepsis Related) Organ Failure Assessment Score; CPD, cellular population data; PCT, procalcitonin. NDW, neutrophil distribution width; MNV, mean neutrophil volume; MNC, mean neutrophil conductivity; MNS, mean neutrophil scattering; DN, neutrophil index; MMV, mean monocyte volume; MMC, mean monocyte conductivity; MMS, mean monocyte scattering; MPV, mean platelet volume; PDW, platelet distribution width; MPC, mean platelet component; PCDW, platelet component distribution width; MPM, mean platelet mass; PMDW, platelet mass distribution width; IPF, immature platelet fraction; MLV, mean lymphocyte volume; LDW, lymphocyte distribution width; Lymph index, MLV\* LDW/LC (lymphocyte conductivity); NPV, negative predictive value; PPV, positive predictive value.

progressing sepsis. Moreover, it requires simple equipment for MDW detection, which is particularly important in areas where medical facilities may be limited. Compared with other inflammatory indicators, MDW has comparable efficacy to PCT and CRP, and the combined diagnosis can also improve the diagnostic efficacy of sepsis to a certain extent. The cutoff value of MDW is heterogeneous in various studies, where the reference interval of MDW is reported to be 20–25.<sup>30,31,33,37,42,69</sup> This may be due to the type and clinical condition of the patients admitted as well as technical problems. The FDA<sup>70</sup> approved the use of whole blood vein samples of K2EDTA to detect MDW, and many laboratories use K3EDTA, which has been shown to yield higher values for MDW than K2EDTA.<sup>71</sup> The influence of anticoagulants has been reported by the manufacturer, with a 1.5 offset between K2 and K3.<sup>72</sup> Due to the demographic characteristics of the population and testing technology, a single cut-off point for MDW cannot be determined until a greater degree of standardization is achieved; hence, it is not feasible to adopt a universal cut-off point.

As shown in Figure 1, as a new inflammatory indicator, MDW can reflect the morphological changes in monocytes during inflammation, which has a positive effect on the early diagnosis of sepsis. MDW is also positively correlated with disease development and can predict disease progression. At the same time, there are also morphological changes in monocytes in some other disease processes (hepatitis B,<sup>73</sup> hepatitis C,<sup>19</sup> HIV infection,<sup>18</sup> Mycobacterium tuberculosis infection,<sup>10,17,74</sup> coronary heart diseases, and<sup>75</sup> rheumatoid arthritis<sup>22</sup>); therefore, we can speculate that MDW may also have potential application value in these diseases. In addition, peripheral blood monocytes are an important source of macrophages, and MDW can also reflect some macrophage-related functions (pathogen infection, tumor immunity, immune monitoring, etc.).

We know the activation of monocyte is an early event of pathogen infection and with no distinction between bacterial, viral or fungal infections. Upon activation, these cells undergo structural and functional modifications, enabling a broad set of immunomodulatory activities. From the studies related to the application of MDW in COVID-19, some inspiring results are obtained. Besides the diagnosis application of MDW in COVID-19 infection, the severity prediction value of MDW in these patients may indicate the pathological mechanism behind it. The dysregulation of monocytes contributes to the systemic



**Figure 1** MDW and the role of MDW in various diseases. The morphological changes of monocytes can be indicated by MDW values. Under the action of various stimuli, monocytes undergo morphological changes, which can reflect the state of host immune function and the state and process of disease.

**Abbreviations:** PAMPs, pathogen-associated molecular patterns; DAMPs, damage associated molecular patterns; *Mtb*, mycobacterium tuberculosis; RA, rheumatoid arthritis.

hyper-inflammatory response, coagulopathy and organ damage, which could be presented as cytokine storms, cardiac injury, respiratory failure and so on, characterizing the severe form of COVID-19. Interestingly, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has clearly defined sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection. The abnormal activation and dysregulation of monocyte may serve as the key factor of the sepsis onset and progression. Thus, the application of MDW in sepsis diagnosis and prognosis works from both theoretical and practical aspects. It naturally links the thought of comparison with the exploration of internal mechanism connections between sepsis and COVID-19 infection (especially in severe patients). In addition to MDW, other biomarkers related to monocyte dysregulation or abnormal excessive activation may be investigated to be used in both sepsis and COVID-19. Overall, there is no doubt that more studies are warranted to explore these hypotheses.

## Conclusion

Significant progress has been made in the treatment of patients with sepsis; however, the disease remains associated with high mortality and disability. In this review, MDW serves as an important indicator of the activation state of the immune system, is readily and rapidly obtained, plays a key role in infectious disease (sepsis, COVID-19, etc.) diagnosis and prognosis, and plays a non-negligible role in guiding the clinical diagnosis and treatment of the disease. As mentioned before, MDW serves as a morphological indicator of monocyte abnormal activation, and we speculate that MDW could be used in more niches related to dysregulation of monocyte, such as cytokine storm prediction, infection differentiation in immune compromised patients, hematopoietic stem cell transplantation monitoring and so on.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no potential competing interests.

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