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Review

MDW as a Biomarker of Sepsis

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Abstract

Sepsis is a life-threatening syndrome caused by dysregulated host response to infection and remains a major global health challenge with high healthcare burden. Early recognition is critical for improving outcomes, yet current diagnostic tools and conventional biomarkers such as C-reactive protein and procalcitonin have important limitations related to kinetics, specificity, and cost. This review examines Monocyte Distribution Width (MDW), a novel hematologic parameter derived from routine complete blood count analysis, as an emerging biomarker for early sepsis detection and prognostic assessment. MDW reflects monocyte morphological heterogeneity associated with innate immune activation and rises early in the inflammatory cascade, often at the time of initial clinical presentation. Evidence from emergency department and intensive care unit studies demonstrates that MDW provides high sensitivity and negative predictive value for early sepsis screening and performs comparably to or better than established biomarkers, particularly when integrated with clinical scoring systems and other laboratory indices. Beyond diagnosis, elevated MDW correlates with disease severity, organ dysfunction, and adverse outcomes, suggesting prognostic utility. Although promising, current evidence is limited by heterogeneity and the need for standardized cut-off values and multicenter validation. Overall, MDW represents a rapid, cost-effective adjunct that may enhance multimodal sepsis assessment and clinical decision-making.

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1. Introduction

Sepsis is a life-threatening clinical syndrome that often leads to multiple organ dysfunction syndrome and death as a result of infection. It is caused by a dysregulated host immune response to a pathogen rather than the direct effect of the microorganism on host cells [1]. The understanding of sepsis has evolved substantially over the last century. Hugo Schottmüller first laid the foundation for a modern definition in 1914, describing sepsis as a condition in which a focus has developed from where pathogenic bacteria continuously or intermittently enter the bloodstream in such a way that it causes subjective and objective symptoms [2]. Later, the 1991/1992 ACCP/SCCM Consensus (often referred to as Sepsis-1) defined sepsis as an "infection-induced Systemic Inflammatory Response Syndrome (SIRS)," aiming to establish a globally accepted and clinically applicable description as knowledge of the underlying mechanisms advanced [3,4]. The Sepsis-3 Consensus in 2016 introduced the current definition, characterizing sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection," thereby removing the SIRS concept from the definition and pointing out organ failure as the central pathophysiological feature [5].

Sepsis today represents a major global health priority. According to the World Health Organization, by 2017 an estimated 48.9 million cases and 11 million sepsis-related deaths were recorded worldwide - numbers corresponding to 20% of all global deaths, despite improvements in therapeutic management. Septic shock, a severe subset of sepsis associated with circulatory, cellular, and metabolic abnormalities, carries an even higher risk of mortality and is recognized as one of the most fatal presentations encountered in emergency departments, prompting WHO in 2017 to declare sepsis management a global health priority. It has a high mortality rate, reaching almost 35-40% when associated with septic shock, particularly among hospitalized patients [6,7].

The epidemiology of sepsis shows significant global variability, influenced by demographic, socioeconomic, and seasonal factors [8–10]. Sepsis incidence differs across racial and ethnic groups and is notably higher among African American men and populations with low socioeconomic status (SES), even after adjusting for confounding factors such as sex, birth date, and comorbidities [11,12]. Incidence also rises during the winter months, likely due to the increased prevalence of respiratory infections [13]. Elderly individuals (≥65 years) represent the majority of cases, accounting for 60-85% of all sepsis episodes, and the overall frequency is expected to further increase with population aging [14,15]. Large national datasets highlight the growing burden of sepsis. In the United States alone, over 1,665,000 sepsis cases were annually recorded between 1979 and 2000 [16]. International retrospective studies have demonstrated a marked increase in sepsis and septic shock incidence, from 13 to 78 cases per 100,000 persons between 1998 and 2009 [17]. According to the World Health Organization, by 2017 there was an estimated 48.9 million global cases of sepsis, half of which occurred in children under five years of age, and approximately 11 million sepsis-related deaths, representing nearly 20% of all global mortality [18]. Despite advances in diagnosis and treatment, sepsis continues to carry a high mortality rate [5]. Septic shock-characterized by profound circulatory, cellular, and metabolic abnormalities-further elevates the risk of death and ranks first among the causes with the highest mortality rates encountered in emergency departments [19]. These observations led the World Health Organization in 2017 to designate sepsis prevention, diagnosis, and management as a global health priority [20]. Interestingly, although incidence rates remain stable in some regions, in-hospital mortality has shown modest improvement; for example, one large observational study reported a 3% reduction in mortality between 2009 and 2014 despite unchanged sepsis admission rates [9,10]. Additionally, patients with positive and negative blood cultures have been shown to exhibit comparable disease severity and similar mortality rates, underscoring the complexity of prognostic assessment in sepsis [21]. The economic and healthcare burden of sepsis is substantial. A large systematic review estimated that sepsis-related hospitalizations increase healthcare expenditures by approximately 2.65%, accounting for 0.33% of the gross domestic product (GDP) across 26 analysed countries [22]. Beyond its financial impact, sepsis contributes to excessive- and often inappropriate-antibiotic use, increased strain on hospital resources, and significant socioeconomic consequences [23,24]. Collectively, these factors underscore the urgent need for timely recognition, prevention, and rapid intervention in sepsis management.

Timely recognition of sepsis is universally acknowledged as a critical determinant of patient outcomes. Medical literature consistently emphasizes the fact that early identification and prompt initiation of appropriate management are among the most important factors in reducing mortality, often outweighing differences in treatment protocols themselves [25,26]. In response to this need, numerous clinical scoring systems have been developed to facilitate early detection, particularly in high-pressure environments such as emergency departments. These include the Systemic Inflammatory Response Syndrome (SIRS) criteria [3], the National Early Warning Score (NEWS) [27], and the Prehospital Early Sepsis Detection system (PRESEP) [28], which primarily aim to rule out potential sepsis using simplified criteria. Other tools focus on risk stratification based on disease severity, such as the Sequential Organ Failure Assessment (SOFA) score [29,30], the quick SOFA (qSOFA) [5], the Sepsis Patient Evaluation in the Emergency Department (SPEED) score [31], and the Mortality in Emergency Department Sepsis (MEDS) score [32].

Despite their widespread use, these scoring systems have recognized limitations. Their application in emergency settings may be constrained by incomplete data due to high patient volume, and no single score provides sufficient sensitivity and specificity in order to diagnose sepsis with

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absolute accuracy [33]. Consequently, clinical judgment remains essential, and these tools should complement-rather than replace-comprehensive clinical evaluation to ensure diagnostic precision and timely intervention.

The importance of early detection is further highlighted by routine laboratory investigations, particularly the complete blood count (CBC); CBC is inexpensive, rapidly available, and universally accessible, making it a cornerstone of initial evaluation in all healthcare settings [34]. When interpreted alongside medical history, physical examination, and clinical assessment, CBC-derived parameters can support early identification of sepsis. Appropriate utilization of these tests may reduce unnecessary antibiotic prescriptions, help mitigate antimicrobial resistance, optimize resource utilization, and prevent avoidable hospital admissions, ultimately improving patient outcomes and healthcare efficiency [5,23].

Biomarkers play an increasingly important role in the diagnosis, prognosis, and clinical management of sepsis. They are defined as objectively measurable characteristics that indicate normal biological processes, pathogenic processes, or responses to therapeutic interventions [35]. In sepsis, biomarkers encompass measurable biological molecules in blood, body fluids, or tissues that reflect infection or dysregulated host response [36]. These markers may assist clinicians in assessing disease severity, predicting deterioration, and guiding therapeutic decisions.

Given the complex and heterogeneous nature of sepsis, extensive efforts have focused on identifying reliable biomarkers capable of early risk stratification. Although no single biomarker has achieved universal acceptance, several parameters derived from the CBC have shown promising diagnostic and prognostic value [34]. These CBC-based biomarkers offer distinct advantages, as the CBC is a first-line test that is widely available, inexpensive, rapidly performed, and accessible across emergency departments and intensive care units at all levels of healthcare delivery.

In recent years, the biomarkers used for the early detection of sepsis include interleukin-6 (IL-6), C-reactive protein (CRP), and procalcitonin (PCT) [36,37]. IL-6 is more specific for bacterial infection but is not readily available [38].

Lately, there has been great interest in the introduction of new biomarkers in sepsis [39]. Amongst the emerging biomarkers, the Immature Platelet Fraction (IPF) has demonstrated significant diagnostic and prognostic value [40].

Of particular interest is also the Monocyte Distribution Width (MDW), a parameter integrated into modern hematology analysers. MDW, as a prognostic marker in patients with sepsis, has been extensively studied [41,42]. MDW reflects monocyte heterogeneity-an important feature of sepsis pathophysiology-and is immediately available as part of the routine CBC without additional cost [43]. In the context of the present study, MDW is hypothesized to be a critical biomarker for early sepsis diagnosis and a valuable prognostic tool that can support clinical decision-making from the initial patient assessment onwards. It has the advantage of not being affected by age, sex, or medical interventions, unlike other inflammatory biomarkers such as CRP and PCT [44–47].

The purpose of this review is to summarize current knowledge regarding monocyte distribution width (MDW) as a biomarker of sepsis. A structured literature search was conducted in PubMed up to [Month Year] using the following keywords: (“monocyte distribution width” OR “MDW”) AND (“sepsis” OR “septic shock” OR “bacteremia”), applied to title and abstract fields. Reference lists of relevant articles were also screened to identify additional studies. Original clinical studies, observational cohorts, systematic reviews, and meta-analyses addressing the diagnostic or prognostic role of MDW in adult patients were considered. Articles were selected based on relevance to the scope of this narrative review. Only publications in English were included. This review was designed as a narrative synthesis rather than a formal systematic review.

2. Established Biomarkers in Sepsis

C-reactive protein (CRP) is a pentameric acute-phase protein synthesized primarily by hepatocytes, but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes [48]. During infection or inflammation, its levels may rise up to 1000-fold above the

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reference range, circulating initially as five dissociated monomers [49]. In bacterial infections, CRP demonstrates a sensitivity of 68-92% and a specificity of 40-67%, with concentrations beginning to increase 6 - 8 hours after the inflammatory stimulus and peaking at 36-50 hours [37,50]. CRP may serve as an early indicator of infection, while declining levels can reflect improvement or adequate antimicrobial response during treatment [51].

Procalcitonin (PCT) is a 116-amino acid peptide and the precursor molecule of calcitonin, produced by thyroid C-cells and extra-thyroidal tissues such as adipose tissue and monocytes during inflammation [52]. Its concentrations begin to rise 3-4 hours after the inflammatory trigger, peak at approximately 24 hours, and exhibit a half-life of 22-35 hours [53]. As a biomarker, PCT belongs to the group of host-response indicators that provide additional information on systemic inflammation and infection [5]. Because of its relatively rapid kinetics, PCT is widely used in clinical practice to help distinguish bacterial from non-bacterial causes of inflammation and to support early sepsis detection [54].

Interleukin-6 (IL-6) is a 21-kDa glycoprotein produced mainly by macrophages and lymphocytes, though several other cell types (e.g., endothelial cells, fibroblasts) can also release it in response to infection [55]. It plays a central role in the inflammatory cascade, contributing to cytokine amplification, fever, and acute-phase protein production. Elevated IL-6 levels have been associated with increased severity of sepsis, poorer clinical outcomes, and higher mortality risk according to multiple clinical studies [36,56–58].

Despite their widespread use, CRP, PCT, and IL-6 exhibit important limitations regarding diagnostic accuracy. Host-response biomarkers -including CRP and PCT- provide valuable supportive information but cannot independently diagnose sepsis, particularly in the emergency department where rapid clinical decisions are required [59]. CRP shows modest specificity (40-67%), meaning that its elevation is common in numerous non-infectious inflammatory states such as trauma, surgery, and autoimmune diseases, limiting its discriminatory power [50]. PCT values, while more infection-specific, may still be affected by major surgery, systemic inflammation, and certain non-septic conditions [60,61]. IL-6, though strongly associated with infection severity, also suffers from variability due to its short half-life (~2-4 hours) and rapid fluctuation in the bloodstream, which complicates its use as a standalone diagnostic marker [62]. Overall, these limitations underscore the need for more reliable early biomarkers and contribute to the growing interest in hematologic parameters such as MDW as adjunctive diagnostic tools.

3. The Role of Monocytes in Infection and Sepsis

Monocytes play a central role in the innate immune response, acting as key effector cells during the earliest phases of inflammation [63]. They rapidly respond to infectious stimuli through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), which trigger both functional and morphological changes, including increases in cell size and alterations in scatter properties that reflect their activation state [64].

Before involving adaptive immunity, they become activated by changing their morphology and increasing their size, expressing new surface proteins such as CD16 [65]. MDW reflects the early activation of the innate immune system and therefore may be slightly elevated during inflammation [66,67]. During sepsis, activation of monocytes is accompanied by significant phenotypic modulation, including the expansion of distinct subsets such as $CD14^{+}/CD16^{+}$ populations, which were shown to be markedly increased in septic patients compared with healthy controls [68]. These morphological and functional shifts underpin the principle of the Monocyte Distribution Width (MDW), a parameter that captures early monocyte heterogeneity arising during systemic inflammation and is therefore elevated in the initial stages of the host immune response [41].

Based on the expression of surface molecules CD14 and CD16, monocytes are classified into three subsets [65]:

- Classical monocytes (CD14++ [high], CD16-, ~80-90% of monocytes),
- Intermediate monocytes (CD14++ CD16+, ~5-10%),

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- Non-classical monocytes (CD14+ [low], CD16++, ~5-10%).

Classical CD14++ monocytes circulate in the blood for 1-2 days before differentiating into intermediate CD14++CD16+ monocytes or migrating to tissues [69,70]. The frequency of these subsets depends on the immune status of the patient [71]. Early studies demonstrated expansion of $CD14^{+}/CD16^{+}$ monocytes in sepsis [68], while more recent investigations highlight alterations in monocyte subsets that correlate with short-term survival in septic shock patients [72]. Additional immunophenotyping work revealed impaired antigen presentation and a shift toward non-classical differentiation during human sepsis, further illustrating how systemic inflammation drives subset re-distribution [73]. Thus, the frequency of monocyte subsets reflects the immune status of the patient and dynamically changes according to the inflammatory environment.

Monocytes are an heterogeneous population due to morphological and functional changes induced by pattern recognition receptors (PRRs) [64]. Differential activation through PRRs gives rise to subpopulations with either pro-inflammatory or anti-inflammatory roles, consistent with the broader M1/M2 conceptual framework described in the literature [74–76]. From a biological perspective, monocytes are innate immune cells of the first inflammatory phase. This dynamic plasticity allows monocytes to adapt rapidly to pathogenic threats, making them essential mediators of early host defence, but also key contributors to dysregulated inflammatory responses observed in sepsis [77].

4. Monocyte Distribution Width (MDW)

Monocyte Distribution Width (MDW), also referred to as the Early Sepsis Indicator (ESId), is a hematologic parameter that quantifies monocyte anisocytosis-i.e., the variability in monocyte cell volume in peripheral blood [78,79]. It reflects morphological and functional changes that occur during monocyte activation in systemic inflammation, including sepsis [43,80,81].

MDW is not a biological molecule like CRP or PCT, but a numerical calculation deriving from the variability in monocyte size and morphological characteristics [78]. It is generated automatically as part of the Complete Blood Count (CBC) using advanced haematology analysers such as the Beckman Coulter DxH 800/900 [82,83]. The parameter is acquired through the Coulter principle-detecting changes in electrical impedance as cells pass through a microscopic aperture-combined with conductivity and multi-angle laser light scattering (VCS/VCSn technology) to assess detailed cell morphology [84]. MDW (ESId) received FDA 510(k) authorization in 2019 for early sepsis screening in emergency department patients, underscoring its clinical relevance and reliability [82,83].

Across several cited studies, an MDW value around 20 units has frequently been used as a diagnostic threshold in early sepsis detection models, with optimal cut-offs reported between approximately 20 and 22 depending on population and setting [42,85]. For example, MDW $\geq$ 20 has been incorporated into multivariable early sepsis prediction models alongside parameters such as MEWS $\geq$ 3, WBC $\geq 11\times10^{9}$/L and NLR $\geq$ 8, and these combinations have demonstrated high diagnostic accuracy for early sepsis prediction in emergency department cohorts [79,86]. Furthermore, MDW has been shown to be significantly higher in septic patients than in non-septic febrile or non-infected patients, and serial MDW measurements demonstrate dynamic changes that correlate with clinical improvement or deterioration [78,87].

Monocytes undergo substantial morphological alterations during early activation, including increases in size and changes in cytoplasmic complexity, which are reflected in the increased heterogeneity of monocyte volume [79,87]. These changes are captured by MDW as a measure of the variability in monocyte cell volume in circulating blood [88].

Systemic inflammatory stimuli-regardless of pathogen type-induce heterogeneous activation of monocyte subpopulations, leading to a broadened size distribution that appears as elevated MDW values [78,79]. Image-based analyses, VCS/VCSn-derived parameters, and flow cytometry confirm that microbial exposure leads to broadening of the monocyte volume distribution and altered monocyte morphology [87]. Importantly, MDW accurately reflects innate immune activation rather

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than specific pathogen-driven processes and rises early in the inflammatory cascade, often at the time of first clinical presentation and at least as early as traditional biomarkers such as CRP and PCT, making it particularly useful for early sepsis recognition [42,79,85]. Additionally, studies in mixed-pathogen cohorts, including viral and fungal infections, show that monocyte activation occurs irrespective of the infecting organism and that MDW can perform as well as or better than PCT in non-bacterial sepsis, supporting the concept that MDW captures pathogen-independent innate immune activation [42].

MDW offers several practical and diagnostic advantages over conventional biomarkers such as CRP and PCT:

1. Independence from pathogen type: MDW rises during innate immune activation regardless of whether the infection is bacterial, viral, or fungal, whereas PCT and CRP may show reduced sensitivity in non-bacterial infections [47,85]. This makes MDW a non-specific but highly sensitive early inflammatory marker that reflects global monocyte activation across diverse infectious causes [89,90].

2.Faster and more cost-effective: As part of the CBC, MDW is rapidly available, inexpensive, and requires no additional blood draw, making it readily accessible in most healthcare settings [79,85]. Compared with CRP and PCT, which typically require separate immunoassays, MDW can be automatically reported within minutes on standard haematology analysers without additional laboratory resources [78].

3.Because MDW is derived from routine hematology analysis, it can be easily incorporated into everyday clinical practice without specialized testing or on-site high-complexity laboratories [85]. Its measurement is standardized on widely used automated analysers such as the Beckman Coulter DxH series, enabling broad implementation in emergency departments, intensive care units, and general wards [82,83] .

4.MDW demonstrates strong diagnostic efficiency and a high negative predictive value in early sepsis detection and can outperform or complement established biomarkers such as CRP and PCT [78,79]. In several emergency department studies and pooled analyses, MDW achieved sensitivities around 80-83%, compared with lower sensitivities for CRP and PCT at conventional cut-offs, highlighting its value for early sepsis identification and risk stratification [41,86].

5.Independent of age and sex: Although most primary studies are not specifically powered to analyse detailed age- or sex-specific reference ranges, current evidence suggests that MDW primarily reflects innate immune activation and has been applied across diverse adult populations without systematic demographic correction [79]. This supports the use of MDW as a broadly applicable biomarker in adult patients, with disease status rather than demographic variables being the main determinant of abnormal values.

5. Clinical Studies on the Role of MDW in Sepsis

Monocyte Distribution Width (MDW) is an automated hematological parameter derived from the complete blood count that reflects heterogeneity in monocyte size and serves as a surrogate marker of monocyte activation. Because monocyte morphological changes occur early during innate immune activation, MDW reflects early inflammatory responses and may increase slightly even before overt clinical manifestations of infection or sepsis [43,67,90]. Over the past decade, MDW has emerged as a rapid, inexpensive biomarker associated with systemic inflammation, infection, and sepsis, and its clinical value has been evaluated mainly in Emergency Department (ED) and Intensive Care Unit (ICU) populations, including adults with suspected sepsis and patients with COVID-19 [42,80,81,84,91].

5.1. MDW in Emergency Department Populations

Clinical trials conducted in heterogeneous adult ED populations consistently demonstrate that MDW increases early in the course of sepsis and performs comparably to, and in some studies better than, established inflammatory biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT)

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[43,79,86]. Several prospective and multicentre studies report good sensitivity of MDW for early sepsis detection at the time of ED presentation, with area-under-the-curve (AUC) values typically around 0.80-0.86 and sensitivities often exceeding 80%, supporting its role as an early screening tool [43,92,93].

MDW has been shown to rise earlier in the inflammatory cascade than CRP and, in some cohorts, earlier than PCT, particularly when measured at first ED contact [79,94]. While CRP and PCT depend on hepatic synthesis and neuroendocrine signaling, respectively, MDW reflects rapid morphological changes in circulating monocytes following immune activation, which occur within hours of pathogen or danger-signal exposure [43,86]. This biological distinction likely explains the earlier diagnostic signal of MDW observed at first clinical contact, when CRP and PCT may still be in their lag phase.

Importantly, the diagnostic performance of MDW improves when combined with clinical scoring systems such as qSOFA or MEWS, as well as with other routinely available hematological indices, including white blood cell count (WBC) and the neutrophil-to-lymphocyte ratio (NLR) [43,93,94]. These findings support the use of MDW as an early triage and rule-out biomarker in the ED, particularly because it is immediately available as part of standard CBC testing without additional cost or turnaround time [86,92].

Large observational studies further support these findings. In a cohort of 2,724 ED patients, Polilli et al. [95] reported significantly higher MDW values in patients with sepsis (25.2) and septic shock (30.7) compared with patients with infection without sepsis (22.0), non-infectious SIRS (21.2), and controls (19.0). An MDW cut-off value of 22 was identified, and MDW ≥ 22 was associated with nearly a fourfold increased risk of sepsis, with a negative predictive value of 97%, supporting its usefulness for ruling out sepsis at presentation. In this study, the strongest associations were observed when MDW was combined with elevated CRP (≥ 19.1 mg/L) and other abnormal hematological parameters.

Similarly, a prospective study by Kralovcova et al. [96] involving 1,925 ED patients showed that MDW was significantly higher in patients with infection, sepsis, and septic shock compared with non-infected individuals. MDW demonstrated good diagnostic accuracy, with 73% sensitivity and 82% specificity for infection, and 79% sensitivity and 83% specificity for sepsis. A cut-off value of 22 for predicting sepsis was consistent with previous reports, while an MDW ≤ 17 effectively ruled out infection [96]. Increased MDW values were also observed in patients with comorbidities such as diabetes, cirrhosis, or immunosuppression, likely reflecting enhanced baseline inflammatory activity.

5.2. MDW in Intensive Care Unit Patients

In critically ill adult patients, ICU-based studies and pilot investigations consistently report significantly higher MDW values in patients with sepsis compared with non-septic controls. Sepsis has been shown to be associated with increased MDW regardless of the causative pathogen, including bacterial, fungal, and viral infections, supporting MDW as a broadly applicable sepsis biomarker in the ICU [46,66,97].

Piva et al. [97] evaluated MDW in a cohort of 506 adult ICU patients classified as non-sepsis, sepsis, or septic shock. MDW values were significantly higher in patients with sepsis and septic shock compared with non-septic patients, independently of sepsis etiology, including patients with COVID-19. Importantly, MDW values decreased over time in sepsis survivors, suggesting potential utility for disease monitoring and prognostic assessment [97].

Serial MDW measurements have been associated with clinical trajectories, including improvement or deterioration, indicating that MDW may reflect disease severity and dynamic immune responses during critical illness. Overall, the ICU literature supports MDW as a complementary biomarker for early recognition of sepsis and for monitoring disease evolution when interpreted alongside clinical assessment and established laboratory markers.

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5.3. MDW in COVID-19

In patients with COVID-19, MDW has been investigated as a marker of immune activation and systemic inflammation, with multiple cohorts showing higher MDW values in infected compared with non-infected controls. Clinical studies consistently report elevated MDW values in patients with more severe COVID-19 and strong associations with adverse outcomes such as respiratory failure, ICU admission, and death [88,98,99]. These findings are consistent with the established role of monocytes in COVID-19-related hyperinflammation and sepsis-like syndromes, where activated and dysregulated monocyte subsets contribute to cytokine storm and organ dysfunction [88,100]. MDW may therefore contribute to risk stratification and prognostic evaluation in COVID-19, particularly when integrated with clinical severity indices and other inflammatory biomarkers, with several studies suggesting MDW cut-offs around 25-26 as useful thresholds for identifying high-risk patients [88,98].

MDW in trauma patients

Direct clinical trial evidence evaluating MDW specifically in trauma populations remains limited; however, available data support a biologically plausible role. Trauma-related studies highlight the central involvement of monocyte activation and dysfunction in post-traumatic immune responses, including systemic inflammation, immune suppression, and secondary infections. Marcos-Morales et al. investigated MDW as a prognostic biomarker in trauma patients admitted to the ICU and demonstrated that MDW ≥ 21 at admission was independently associated with an increased risk of multiple organ dysfunction syndrome and prolonged hospital stay, suggesting potential prognostic value in this population [101].

These findings are consistent with broader evidence showing that functional monocyte changes occur early in sepsis, characterized by expansion of pro-inflammatory $CD14^{+}CD16^{++}$ monocytes, followed by immunosuppressive phases marked by reduced HLA-DR expression on monocytes [102–104]. As MDW reflects changes in monocyte volume associated with immune activation, its relevance in trauma-associated sepsis is biologically supported, although further prospective studies are required to define its diagnostic and prognostic utility in this setting.

Comparison with CRP and procalcitonin

Early identification of sepsis relies on a combination of clinical assessment and laboratory biomarkers, among which CRP and PCT are the most widely used, although both have limitations related to delayed kinetics, cost, and variable specificity [36,37]. Several clinical studies directly comparing MDW with CRP and PCT demonstrate that MDW shows comparable or superior diagnostic performance for early sepsis detection, particularly at ED presentation [79,105,106]. In these cohorts, MDW often provides higher sensitivity and negative predictive value than CRP and PCT when measured at first contact in the ED.

Across studies, MDW cut-off values for sepsis identification are relatively consistent, most frequently ranging between about 20 and 23 units, with MDW thresholds around ≥20 or ≥22 being most commonly reported [43,96,105]. In contrast, CRP and PCT cut-offs vary more widely depending on timing and clinical context, with PCT thresholds commonly around 0.5 ng/mL or higher for suspected sepsis and CRP cut-offs spanning roughly 4-10 mg/dL in ED studies [36,105].

When evaluated as a single biomarker, MDW demonstrates high sensitivity, frequently exceeding 80% at optimal cut-offs, whereas CRP and PCT show more variable performance depending on disease stage and sampling time [71,79,105]. Specificity of MDW is moderate and generally comparable to CRP but slightly lower than PCT, reflecting MDW's sensitivity to broader immune activation rather than infection alone [71,96]. Consequently, MDW appears particularly well suited as an early screening or rule-out biomarker rather than a definitive stand-alone diagnostic test

Overall, the available clinical evidence supports MDW as a valuable adjunct biomarker for early sepsis detection and disease monitoring in adult ED and ICU settings, with additional prognostic relevance in COVID-19 and trauma populations [88,99,106]. Its main advantages include rapid availability, low cost, and high sensitivity at early time points, since it is automatically reported with the CBC without additional sampling or assay costs [43,96]. While CRP and PCT remain important

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tools for confirmation, severity assessment, and antimicrobial stewardship, MDW appears especially useful for early identification and triage when integrated into multimodal diagnostic algorithms; future studies should focus on standardized cut-off validation, head-to-head comparisons in specific populations, and evaluation of MDW-guided clinical decision pathways [71,105].

6. Clinical Significance and Applications

6.1. MDW for Early Detection of Sepsis

Monocyte Distribution Width (MDW) has emerged as a clinically valuable biomarker for the early detection of sepsis, reflecting rapid morphological changes in circulating monocytes during innate immune activation [43,89,107]. Unlike traditional inflammatory markers that rely on downstream hepatic or neuroendocrine responses, MDW increases early in the course of systemic infection, often at the time of first clinical presentation in the Emergency Department (ED) or already-hospitalized patients [105,107]. Its immediate availability as part of routine complete blood count analysis enables prompt identification of patients at increased risk of sepsis in both ED and Intensive Care Unit settings, because MDW is automatically generated on modern hematology analysers without additional sampling or cost [43,108]. As a result, MDW is particularly well suited for early screening and triage, supporting timely diagnostic evaluation and therapeutic intervention when combined with clinical scores and other CBC-derived indices such as white blood cell count and neutrophil-to-lymphocyte ratio [43,107].

6.2. Prognostic Utility of MDW

Beyond its diagnostic role, MDW has demonstrated prognostic value in critically ill patients, where higher baseline MDW values correlate with greater illness severity, need for organ support, and mortality [106]. Elevated MDW has been associated with adverse clinical trajectories and unfavourable outcomes, including the development of multiple organ failure (MOF) and prolonged ICU or hospital stay, in sepsis and COVID-19 cohorts [88,99].

Serial MDW measurements may further enhance prognostic assessment, as decreasing values over time have been observed in patients with clinical improvement, whereas persistently elevated or rising MDW levels have been linked to ongoing immune dysregulation and poor outcomes [106]. These findings suggest that MDW may serve as a dynamic biomarker for monitoring disease progression and response to treatment, particularly when interpreted alongside conventional clinical scores and other inflammatory markers [88,96].

6.3. Integration of MDW into Routine Clinical Practice

One of the major advantages of MDW is its ease of integration into everyday clinical workflows, because it is reported as part of the routine complete blood count on modern haematology analysers [43,107]. MDW is automatically generated during standard complete blood count testing without additional blood sampling, cost, or turnaround time, which makes it readily applicable in high-throughput clinical environments, including emergency departments and intensive care units [105,107]. Its standardized measurement and rapid availability support real-time clinical decision-making and facilitate widespread implementation without requiring specialized assays or infrastructure [43,89].

6.4. Combination of MDW with Other Clinical and Laboratory Indicators

The clinical utility of MDW is further enhanced when used in combination with other biomarkers and clinical scoring systems, where it contributes independent information to multivariable sepsis models [105,107]. Studies have shown that integrating MDW with established inflammatory markers such as C-reactive protein or procalcitonin, as well as with clinical scores

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including qSOFA or MEWS, improves diagnostic accuracy for sepsis and increases negative predictive value in the Emergency Department [93,105].

Similarly, combining MDW with routinely available hematological parameters, such as white blood cell count or neutrophil-to-lymphocyte ratio, increases both sensitivity and specificity for early sepsis identification and risk stratification [93,94]. These multimodal approaches position MDW as a complementary biomarker that adds independent diagnostic and prognostic value within integrated sepsis assessment algorithms rather than replacing existing clinical scores or conventional biomarkers [106].

7. Limitations and Challenges in the Clinical Use of MDW

Despite the growing body of evidence supporting the clinical utility of Monocyte Distribution Width (MDW) in sepsis, several limitations and challenges should be considered before its widespread adoption in routine clinical practice [106]. One of the main challenges in interpreting MDW data is the heterogeneity observed across published studies, with differences in reported MDW cut-off values, patient populations, clinical settings, and sepsis definitions complicating direct comparison of results [96,105]. While many studies report broadly similar thresholds for sepsis detection, variability persists due to differences in study design, timing of sample collection, and disease severity, and MDW performance appears to vary across emergency department patients, critically ill ICU patients, trauma cohorts, and individuals with COVID-19 [88,101]

The clinical implementation of MDW also requires greater standardization of measurement and interpretation, because differences in analytical platforms, laboratory protocols, and reference ranges may influence MDW values and contribute to inter-study variability [89]. Establishing standardized cut-off values, harmonized reporting methods, and clear clinical decision thresholds is essential to ensure reproducibility and reliable integration into sepsis diagnostic algorithms across institutions and healthcare systems [71,96].

Although existing studies provide promising results, much of the evidence still derives from single-centre or retrospective analyses, and truly large, multicentre, prospective studies focused specifically on MDW remain relatively scarce [105,106]. Such studies are needed to confirm diagnostic accuracy, define optimal cut-off values in different clinical contexts, and assess the impact of MDW-guided clinical decision-making on patient outcomes, including mortality, ICU length of stay, and antimicrobial stewardship metrics [71].

While MDW itself does not incur additional testing costs, its measurement depends on the availability of specific haematology analysers capable of reporting this parameter, which may limit its use in resource-constrained settings [83,107]. Furthermore, variations in analyser availability and implementation across institutions may contribute to inconsistent adoption and limit comparability between centres, reinforcing the need for technical and clinical standardization before MDW can be universally incorporated into sepsis pathways [89,109].

8. Future Directions

Future research on Monocyte Distribution Width (MDW) should focus on strengthening the current evidence base and expanding its clinical applicability across diverse patient populations and healthcare settings, as repeatedly highlighted in recent systematic reviews and expert commentaries [106,109]. There is a clear need for well-designed, large-scale prospective and multicentre studies to validate the diagnostic and prognostic performance of MDW, moving beyond the predominance of single-centre and retrospective cohorts [96,106]. Such studies should aim to confirm optimal cut-off values, assess reproducibility across different analytical platforms, and evaluate the impact of MDW-guided clinical decision-making on patient-centred outcomes, including mortality, organ dysfunction, and length of hospital stay, thereby defining the role of MDW within standardized sepsis diagnostic pathways [89,106]. Future work should also explore the integration of MDW into multimarker biomarker panels that combine inflammatory, immunological, and hematological

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indicators, an approach already suggested by studies combining MDW with CRP, PCT, and neutrophil-to-lymphocyte ratio [94,105]. The use of advanced analytical methods, including machine learning and artificial-intelligence-based models, may further enhance the predictive value of MDW by capturing complex interactions between biomarkers and clinical variables, in line with broader trends in sepsis prediction and early warning systems [96]. Such approaches could support personalized risk stratification, early warning tools, and real-time decision support in acute care settings, where rapid risk assessment is crucial for outcome improvement [106]. Expanding research into special and underrepresented populations represents another important future direction, since most MDW data currently come from general adult ED or ICU cohorts [106]. The diagnostic and prognostic utility of MDW should be evaluated in pediatric patients, immunocompromised individuals, and surgical populations, where immune responses to infection may differ substantially from those of the general adult population, and dedicated studies in these groups may reveal population-specific cut-off values and clinical applications, ultimately broadening the relevance of MDW across the spectrum of acute and critical care [89,109].

9. Conclusions

Monocyte Distribution Width (MDW) has emerged as a promising biomarker for the early detection and prognostic assessment of sepsis. By reflecting early monocyte activation, MDW provides timely information on systemic immune responses and demonstrates high sensitivity at initial clinical presentation, particularly in Emergency Department and Intensive Care Unit settings.

Importantly, MDW does not replace established biomarkers such as C-reactive protein or procalcitonin, but rather complements them by adding independent diagnostic and prognostic value. Its rapid availability, low cost, and integration into routine complete blood count testing make MDW a practical adjunct within multimodal sepsis evaluation strategies.

The use of MDW in acute and critical care environments, including the ED and ICU, has the potential to enhance clinical decision-making by supporting earlier risk stratification, timely intervention, and improved monitoring of disease progression. With further validation and standardization, MDW may become an integral component of comprehensive sepsis assessment algorithms.

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