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MONOCYTE DISTRIBUTION WIDTH – NEW SEPSIS BIOMARKER

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Abstract: *Sepsis is a global health problem, annually over 45 million patients are diagnosed and over 11 million deaths are recorded. Activation of monocytes in sepsis by the pathogen agent or hypoxia brings about functional, morphological and phenotypic changes in these cells. Monocyte Distribution Width (MDW) is a new biomarker, defined as a measure of monocyte size heterogeneity and has been approved by the Food and Drug Administration for the early diagnosis of sepsis in the adult patient in the emergency department. In intensive care services, this biomarker can be used as a prognostic index in the follow-up of patients with sepsis. The indicator is a measure of the increased morphological variability of monocytes in response to infections, regardless of bacterial, viral or fungal etiology. This new marker also has increased values in the infection with COVID-19 and correlates positively with the severity of the disease.*

INTRODUCTION

Sepsis is a global health problem that has been in the World Health Organization's line of sight since 2017. Annually, more than 45 million cases are diagnosed in the world and more than 11 million deaths are recorded due to this cause.(1) Sepsis is considered the main cause of mortality in hospitalized patients (2), but 80% of cases originate outside the hospital.(3) Therefore, the responsibility of a quick and correct diagnosis often falls to the emergency services and poor symptomatology often places great difficulty on the clinician. A new cytomorphological marker, called Monocyte Distribution Width (MDW) comes to help the doctor in assessing the severity of the infection and the risk of progression to sepsis.

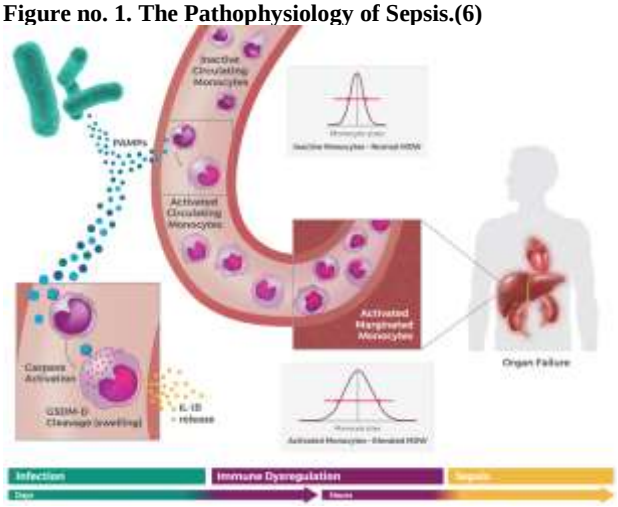
MDW is quantitatively determined by performing an automated blood count using the Early Sepsis Indicator Monocyte Distribution Width application. Venous blood is used, collected on anticoagulant type K2EDTA or K3EDTA, within a maximum of 2 hours after collection. The determination of this parameter is based on the VCSn principle: volume (V), conductivity (C) and scattering of diffused light (Sn). Monocyte volume correlates with cell size. MDW is calculated as the standard deviation of a series of monocyte volume values. This parameter is reported together with the leukocyte formula.(4)

The primary role of monocytes in the body's defence mechanisms against infections is well known. In sepsis, the activation of monocytes, directly through the action of the pathogen agent on pattern recognition receptors (PRRs) or by hypoxia, induces functional, morphological (increase in volume) and phenotypic changes in these cells. MDW is defined as a measure of monocyte size heterogeneity and has been approved by the Food and Drug Administration (FDA) as an early indicator for the diagnosis of sepsis in the adult patient in the emergency room (ER).(5)

For a long time the early diagnosis of patients who have or develop sepsis within the first 12 hours of hospital admission has been a problem.

Clinicians from the emergency services are put in a position to make a quick decision on the patient's route: he goes home, remains hospitalized in a medical ward or will be treated in an ICU ward. The alternative of sending the patient with potential sepsis home leads to a 2-fold increase in mortality and a 4-fold increase in treatment costs compared to the situation in which they remain hospitalized in the ICU ward.(1)

Figure no. 1. The Pathophysiology of Sepsis.(6)



If there is clinical suspicion of sepsis, the clinician requests the known biomarkers of sepsis: procalcitonin and lactate from the medical analysis laboratory. A percentage of 30% of patients with sepsis show minimal symptoms due to antibiotic treatments initiated at home and their diagnosis may fail.(4)

Two problems remain unsolved: the diagnosis of sepsis when the doctor does not have this suspicion and the differentiation of sepsis from the systemic inflammatory response syndrome (SIRS).

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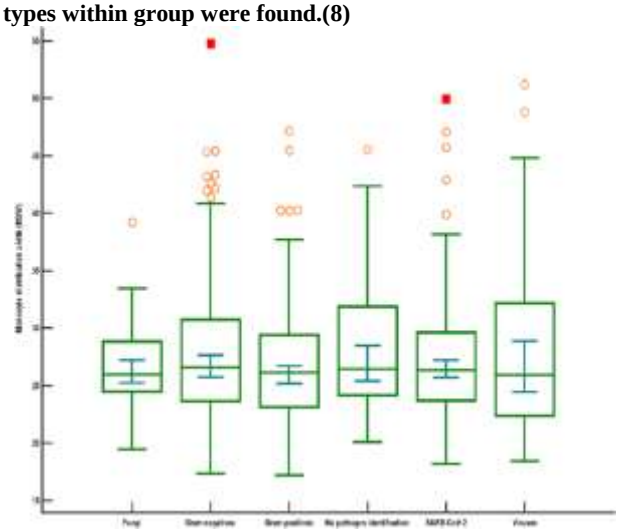
The blood count is an analysis from the standard panel used when the patient presents to a hospital service. MDW is a parameter provided automatically at the same time with the blood count result, with no impact on laboratory or ER workflow and above all, no additional cost per patient. This biomarker reduces diagnostic uncertainty and helps the clinician, under time pressure, to stratify the risks for the patient with infectious symptoms and initiate appropriate early treatment early.

Based on MDW (cut point 20.1), the differential diagnosis between sepsis, infection and systemic inflammatory response syndrome can be made with a sensitivity of 87.3% and specificity of 71.7%. If the number of leukocytes is also taken into account, the sensitivity increases to 96.8% if one of the parameters has elevated values and the specificity increases to 94.6% if both parameters have abnormal values.(7)

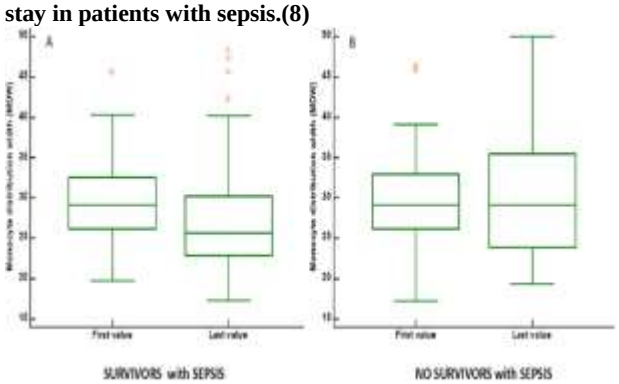
MDW is a measure of the increased morphological variability of monocytes in response to infections, regardless of bacterial, viral, or fungal etiology.(8) The most frequent biomarkers for sepsis, procalcitonin and C-reactive protein, have values dependent on the etiology of sepsis.(8)

Figure no. 2. In sepsis patients, MDW values according to bacterial, fungal or viral infection attributed as the cause of sepsis. No significant differences of MDW between organism types within group were found.(8)



MDW can be used as a prognostic index in the follow-up of patients with sepsis admitted to intensive care units. Studies show that in patients with an unfavourable evolution MDW registers a statistically significant increase throughout the hospitalization period.(8)

Figure no. 3. MDW values at the beginning and end of ICU stay in patients with sepsis.(8)



Infection with SARS-CoV-2 causes an abnormal immune response in which monocytes are deeply involved in the production of pro-inflammatory cytokines (cytokine storm) and immunoparalysis (decreased expression of HLA-DR on monocytes). Significant changes were also observed between the proportion of different monocyte subpopulations.(10)

Table no. 1. PCT and CRP values according to bacterial, fungal or viral infection attributed as the cause of sepsis.(8)

Infecting organism type	Samples	PCT, µg/L Median,IQR	Samples	CRP, mg/L Median,IQR
No sepsis	1.346	0,19 (0,07-0,54)	1.411	58 (22-120)
No definitive identification	57	2,12 (0,49-4,71)	65	96 (53,75-172,5)
Gram negatives	111	3,68 (1,32-7,10)	114	92,5 (58,0-160)
Gram positives	161	1,94 (0,38-4,49)	168	115 (58,5-160)
Viruses	52	0,49 (0,23-1,33)	52	79,5 (41,5-135)
Sars-CoV-2	224	0,51 (0,31-1,04)	233	100 (47,5-190)
Fungi	52	0,42 (0,20-0,92)	54	160 (110-220)

MDW- monocyte volume distribution width; PCT- procalcitonin; CRP- C-reactive protein; IQR- interquartile range.

Table no. 2. MDW values in patients with SARS-CoV-2 infection than those without (9)

Author	Sample size	MDW cutoff	SARS-CoV-2 infection	MDW with or without SARS-CoV-2 infection
Lin HA et al, 2020 Taiwan	150	≥20	9 (6.0%)	23.5 ± 2.1 vs 21.8 ± 5.4
Ognibene A et al, 2020 Italy	147	≥20	41 (27,9%)	27,3 ± 4,9 vs 20.3 ± 3,3
Zeng X et al, 2020 China	155	≥20.1		22.1 ± 2.3 vs 18.9 ± 2.0
Cumulative	452	-	143 (31,6%)	23,7 ± 3,0 vs 20,7 ± 4,0

All these elements may contribute to increased monocyte heterogeneity in COVID19 and increased MDW.

High viral load at first infection and repeated exposure to the virus are important factors for the evolution of the infection with COVID 19 towards severe forms. In severe forms of COVID infection, aspects not found in other respiratory viruses are described: severe eosinopenia and lymphopenia, extensive pneumonia and lung tissue damage, cytokine storm followed by acute respiratory distress and multiple organ failure. Lymphopenia causes a defect in antiviral immunity and immune regulation. Elevated levels of acute phase reactants and lymphopenia are considered early predictors of disease severity.(10)

Monitoring MDW for 5–7 days in hospitalized patients diagnosed with COVID-19 suggested the prognostic potential of this marker. A variation of less than 1 unit between the value at 7 days and the first determination indicates an unfavourable prognosis.(11)

A significant positive correlation was reported between MDW and biochemical parameters associated with SARS-CoV-2 infection (C-reactive protein, procalcitonin, lactate dehydrogenase, ferritin, D-dimers). Also, MDW values above 24.7 correlate with an unfavourable prognosis.(12)

In patients with COVID-19, MDW monitoring can help clinicians apply immunosuppressive treatments at the right time and assess the response achieved. Upon sudden worsening of the clinical condition, MDW is a specific and easy to obtain indicator of the actual severity of the patient's hyper-inflammatory state (cytokine storm). In patients with mild forms of COVID-19 who do not require hospitalization, MDW could

be used as a biomarker of disease severity to guide patient hospitalization and early initiation of therapy (specific monoclonal antibodies).

MDW, along with procalcitonin, could also be used to monitor patients with COVID infection in intensive care units.

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