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ORIGINAL RESEARCH ARTICLE

Monocyte Distribution Width (MDW) as a useful and cost-effective biomarker for sepsis prediction

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ABSTRACT

Background: Sepsis is a life-threatening condition and a major cause of hospital mortality worldwide. This study investigated the diagnostic utility of monocyte mean volume (MONO MEAN-V), monocyte distribution width (MDW), monocyte mean conductivity (MONO MEAN-C), and monocyte standard deviation conductivity (MONO Sd-C) for sepsis, compared to conventional markers.
Methods: A prospective cohort study was conducted in two centers, enrolling adult patients classified into three groups: sepsis, septic shock, and febrile. Blood was drawn from septic patients on days 1, 3, and 5 of admission. MDW and other inflammatory parameters were measured in all patients.
Results: Patients with sepsis or septic shock exhibited significantly elevated MONO MEAN-V, MDW, and MONO MEAN-C and lower MONO Sd-C compared to febrile patients. Among the biomarkers evaluated, MDW emerged as a reliable predictor of sepsis. A cut-off MDW value of 25.1 on day 1 demonstrated optimal diagnostic performance, with an area under the ROC curve of 0.84 (95% CI: 0.77-0.91), sensitivity of 75%, and specificity of 91.2%.
Conclusions: MDW appears to be a cost-effective, rapid marker for sepsis detection, performing at least as effectively as existing biomarkers. Our findings corroborate other published studies, highlighting MDW's potential to enhance early sepsis recognition.

Keywords: Biomarker, Diagnosis, MDW, Sepsis

Introduction

Sepsis, according to the Sepsis-3 conference, is a life-threatening condition characterized by the dysregulation of the host immune reaction as a response to an infection, which leads to systemic inflammation and multiple organ failure (1). The importance of organ dysfunction has been stressed during the last decade by the creation of the sequential organ failure assessment (SOFA) score in 1994, which was employed to describe the sequence of complications of severe disease and acute patient mortality under different circumstances (2,3). Septic shock is a serious complication of sepsis involving metabolic, cellular, and circulatory anomalies, which leads to an increased risk of mortality compared with sepsis alone (1). It constitutes a global health problem and indicates a steady increase in incidence, with 49 million cases and 11 million sepsis-related deaths worldwide in 2017 (4). Cases of sepsis due to fungi have increased in recent years, and the MDW is more efficient than biomarkers like C-reactive protein (CRP) and procalcitonin (PCT) (8).

Diagnosis and early detection of sepsis are crucial for improving patient survival and reducing healthcare costs (5). The use of biomarkers is vital in the early diagnosis, recognition of organ dysfunction, prognosis, and stratification of patients, leading to individualization of medical intervention. It also contributes to the avoidance of the overconsumption

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of antibiotics, which otherwise may lead to an increase in antimicrobial resistance. According to the National Institutes of Health (NIH) Biomarkers Definitions Working Group, a biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"(6).In 2001, a series of biomarkers, such as CRP and PCT, were included in the diagnosis of sepsis, and there has been an exponential growth of studies analyzing various biomarkers (5,7,8). A series of various biomarkers have been employed in the diagnosis and monitoring of sepsis; these include acute phase proteins such as high sensitivity CRP (hsCRP), complement proteins such as complement component 5amonocyte chemo (C5a) and Pentatrexin (PTX-3), cytokines such as interleukin-10(IL-10), monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-a (TNF-a), interleukin-1b (IL-1b) and interleukin-6 (IL-6), damage-associated molecular patterns (DAMPs) such as calprotectin and high mobility group box-1 protein (HMGB-1), endothelial cell and blood-brain barrier (BBB) markers such as syndecan-1, very late antigen-3 (VLA-3), angiopoietin-1 (Ang-1), angiopoietin-2 (Ang-2), claudin-5 (CLDN-5), occludin (OCLN), plasminogen activator inhibitor-1 (PAI-1), soluble intercellular adhesion molecule-1 (sICAM-1), calcium-binding protein B (S100B) and E-selectin (5).

Several other biomarkers have been explored, focusing on the parameters included in complete blood count (CBC). CBC is a simple examination and has several advantages: it is a first-line test, can be easily performed, is inexpensive, quick, and available in all medical facilities. The CBC parameters that have been studied include the absolute number of neutrophils, lymphopenia (9, 10), monocytosis or monocytopenia (11,12), eosinopenia (13), basocytopenia (14), anemia (as defined by hemoglobin (Hb) <12 g/dl) (15), an increased red cell distribution width (RDW) (>15%) (13,16,17), a low platelet (PLT) count (PC) (18), neutrophil-to-lymphocyte ratio (NLR) (19-22), monocyte-to-lymphocyte ratio (MLR)and PC-to-mean PLT volume (MPV) ratio (PC/MPV) (23-25). Novel indicators produced by modern hematology analyzers have also been employed, such as delta neutrophil index (26-28), immature PLT fraction (IPF) (29), mean neutrophils volume (NEUTRO MEAN-V), and mean monocytes volume (MONO MEAN-V) (30-31).

Monocytes play a central role in sepsis and in the mechanisms of natural and acquired immunity. A new CBC parameter provided by a modern analyzer with new-generation volume-conductivity-scatter (VSC) technology is the MDW, which depicts the anisocytosis of circulating monocytes, represents the standard deviation (SD) of a set of monocyte cell volumes and seems to be an important diagnostic and prognostic tool for the development and progression of sepsis (49). COULTER VCS established white blood cell (WBC) leukocyte-type technology using three measurements: single-cell volume, high-frequency conductivity, and laser light scattering. The combination of low-frequency current, high-frequency current, and light scattering technology provides information about each cell that can be expressed in data plots (two- and three-dimensional nephelograms), as well as surface plots).

In 2019, the Food and Drug Administration (FDA) authorized the clinical application of MDW for the detection of sepsis in adult patients in the emergency room (ER). This biomarker has also been tested in other clinical settings, such as the intensive care unit (ICU) and infectious disease units, as well as in vitro stability tests (8,32-41). The role of MDW and other monocyte parameters in sepsis prognosis has been the focus of much research in recent years.

The aim of our study was to investigate the role of MDW and other monocyte parameters in sepsis prognosis and to compare these parameters with other biomarkers widely used to predict sepsis.

Materials and Methods

Patients and identification of high-risk patients

A comparative, prospective study was carried out with 136 patients (68 patients with sepsis and 68 non-septic patients) from the Emergency Department of the General Hospital of New Ionia Konstantopouleio-Patision and Eginitio. Sepsis was defined based on the guidelines of the third international consensus on sepsis and septic shock (1). The Sepsis-3 definitions suggest that patients with at least two of the three clinical variables mentioned below may be prone to poor outcomes typical of sepsis: (1) low systolic blood pressure (SBP ≤ 100 mmHg), (2) high respiratory rate (≥22 breaths per min), or (3) altered mental status (Glasgow Coma Scale < 15). Quick SOFA(qSOFA) score includes one point for each of the above three criteria. A qSOFA score ≥ 2 with suspected infection was suggestive of sepsis or septic shock. Originally, 136 patients were screened for sepsis and were divided into two groups, with 68 patients each: those with possible infection and worse prognosis and a qSOFA score ≥2 and those without a possible infection and a qSOFA score < 2. This is how the "septic" patients came about. Patients with hematological malignancies or those undergoing recent chemotherapy or taking medications affecting the monocyte population, such as injectable growth factors, were excluded from our study. Also, pediatric cases were excluded due to the non-availability of pediatric clinics in the two survey hospitals. Patients who scored qSOFA ≥2 either came directly to the emergency department of the General Hospital of New Ionia Konstantopouleio-Patision or were already hospitalized in one of the two hospitals, and their clinical profile changed, resulting in them also having a qSOFA score ≥2. Septic patients were classified into two categories based on sepsis-3 classifications, "sepsis"and "septic shock." So, according to the aforementioned parameters, three categories of patients emerged, "febrile," "patients with sepsis," and "patients with septic shock."

Measurement of sepsis biomarkers

Several sepsis indicators have been studied (PCT, IL-6, and CRP), including The following tests were performed for all patients: CBC, prothrombin time (*PT*/INR), PT-INR-activated partial thromboplastin time (*aPTT* or *APTT*), aPTT- fibrinogen-d-dimers, serum PCT, CRP, arterial blood gas (*ABG*), lactate (LAC), serum ferritin (FER), serum TNF-α, and *IL-6*. For CBC and MDW calculation, blood samples were collected in K2

EDTA vials using the Coulter DXH900 hematology analyzer (Beckman Coulter Diagnostics SA, California, US), and PT-INR-aPTT-FIB and d-dimers were measured in sodium citrate vials using a BCS-XP Siemens analyzer (Siemens Healthcare Diagnostics, Illinois, US). For FER, CRP, PCT, TNF-a, and IL-6 serum was isolated from gel clot activator blood tubes; FER was measured by chemiluminescence immunoassay at the UniCel DxI 800 Access Immunoassay System (Beckman Coulter Diagnostics SA, California, US), CRP by immunoturbidimetric method at the Roche cobas c501 system (Roche Diagnostics, Indianapolis, USA), PCT by chemiluminescence at the Abbott Alinity C system (Abbott Diagnostics, Illinois, USA), and TNF-a and IL-6 by ELISA at the Brio 2 (Diachel). The LAC and ABGs were measured using an ABL 800 FLEX(RADIO METER) ABG analyzer. Below, the statistical analysis presents some of the biomarkers measured in the patients.

For each patient with sepsis before the initiation of antimicrobial therapy, 10 ml of blood was drawn in Bactec culture vials (one pair for each patient) and incubated for a total of 5 days in the BD Bactec™ FX Blood system (Becton Dickinson, New Jersey, US). One blood culture set was collected from patients, except for those for whom endocarditis was suspected, for whom three sets were collected. Biological samples were cultured and incubated in common culture media and were evaluated. Microbial isolates were identified using the Vitek 2 Compact system (Biomerieux SA, Craponne, France), and antibiograms were obtained using the MIC and the E-test method using the standard criteria EUCAST.

In all patients with sepsis, the hematological markers were measured from morning samples one hour after sampling on the 1st, 3rd, and 5th day to check their prognostic value for the patient's outcome. In febrile patients, the hematological markers were measured in the same way only on the 1st day. Blood cultures were taken from all patients, as well as other biological samples such as urine, sputum, bronchoalveolar lavage, and CSF, in order to identify the possible source of infection before the initiation of empirical antibiotic therapy. We evaluated the clinical history of each patient, including various comorbidities or any factors contributing to immunosuppression, co-administration of other drugs, family history of dementia, and the status of the patient.

Statistical analysis

Quantitative variables are represented by mean values (standard deviation) and median (interquartile range), while categorical variables are represented by absolute and relative frequencies. Chi-square tests were used to compare the proportions. Students' t-tests were used to compare the ages of septic patients and febrile. The Mann–Whitney test was used to compare data between the two groups. ROC curves were used to estimate the predictive ability of MONO MEAN-V, MONO MEAN-C, monocyte volume standard deviation (MONO Sd-V), and monocyte standard deviation conductivity (MONO Sd-C). The sensitivity and specificity were calculated for the optimal cut-off values. The area under the curve (AUC) was also calculated. All the reported p-values were two-tailed. Statistical significance was set at $p < 0.05$, and analyses were conducted using the SPSS statistical software (version 26.0).

Results

TABLE 1 - Sample characteristics in the total sample and by outcome

		Group				P
		Sepsis and septic shock (n = 68, 50%)		Febrile (n = 68, 50%)		
		n	%	n	%	
Gender	Women	37	54.4	35	51.5	0.731+
	Men	31	45.6	33	48.5	
Age (years), mean (SD)		73,4 (16,1)		58,1 (19,1)		**<0.001++**

+ Pearson's chi-square test; ++Student's test

One hundred thirty-six patients were included in the study. Half of them (n = 68; 50%) had sepsis or septic shock, and the other half were febrile (n = 68; 50%). The mean age of septic patients was 73.4 years (SD = 16.1 years), and the mean age of febriles was 58.1 years (SD = 19.1 years) .The majority of both groups were women, 54.4% of septic patients and 51.5% of febriles. Their characteristics are presented in Table 1 for the total sample and by outcome. A significant difference was found between septic patients and febriles, as far as age is concerned.

The comorbidities of patients with sepsis are described in Table 2. 36.8% of the patients suffered from arterial hypertension and 33.8% from heart failure.

TABLE 2 - Comorbidities

Comorbidities	n	%
Diabetes mellitus	14	20.6
Arterial hypertension	25	36.8
Heart failure	23	33.8
COPD	10	14.7
Immunosuppression	11	16.2
Other disease	53	77.9

MONO MEAN-V, MDW, MONO MEAN-C, and MONO-SdC values by a group of "septic," "septic shock," and "febrile" patients are presented in Table 3.

On the 1st day, there were significant differences in MONO MEAN-V, MDW, MONO MEAN-C, and MONO-SdC among the three groups. More specifically, after Bonferroni correction, it was found that febrile cases had significantly lower MONO MEAN-V and MDW compared to the sepsis group ($p = 0.001$ and $p < 0.001$, respectively) and significantly greater MONO MEAN-C compared to the sepsis group ($p < 0.001$). In addition, febrile patients had significantly lower MONO-SdC and MDW than the sepsis group ($p < 0.001$ for both groups) and significantly greater MONO MEAN-C than the septic shock group ($p = 0.002$). No significant differences were found between the sepsis and septic shock groups after Bonferroni correction for measurements on the 1st day. In

TABLE 3 - MONO MEAN-V, MONO MEAN-C, MDW, MONO Sd-C values by outcome. Values of p < 0.05 are marked in bold

	Group						P
	Sepsis (n = 22; 16.2%)		Septic shock (n = 46; 33.8%)		Febriles (n = 68; 50%)		
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	
MONO MEAN-V							
1st day	189.2 (11,2)	191.5 (186-195)	186.9 (12.8)	184 (178-195)	18.2 (10.3)	182 (174-188)	**0.003+**
3rd day	186.9 (11,8)	187 (181-191)	183 (9.8)	181 (179-193.5)	–	–	0.586++
5th day	182.4 (10.3)	181 (177-185)	179.9 (10.2)	182 (172.185)	–	–	0.820++
MONO MEAN-C							
1st day	119.5 (4,9)	120.5 (117-123)	120.2 (8.4)	121 (118-125)	123.9 (3.8)	123 (121.5-125.5)	**<0,001+**
3rd day	120.9 (3,1)	123 (119-123)	122.3 (5.2)	124 (120.5-125.5)	–	–	**0.030++**
5th day	122.6 (3.3)	123 (120.5-124.5)	114.7 (17.2)	121 (116-125)	–	–	0.526++
MDW							
1st day	26.3 (2.9)	26.1 (25.1-28,8)	28.8 (5.4)	29.6 (24.8-32.4)	22.6 (2.3)	22.2 (21.2-24.2)	**<0.001+**
3rd day	25.7 (3.3)	25 (23.5-27.3)	27.8 (4.8)	28.4 (23.5-31,1)	–	–	0.213++
5th day	23.3 (2.3)	23.5 (21.6-24.5)	29.1 (6.6)	29.2 (24.6-32.1)	–	–	**0.003++**
MONO Sd-C							
1st day	12.6 (11.7)	6.9 (4.8-14.6)	15.1 (12.3)	9.4 (5.4-20.3)	7.3 (4.9)	5.4 (4.8-6.3)	**<0.001+**
3rd day	25 (41.7)	6.6 (4.6-21)	13.8 (9.6)	11.1 (8.3-16,4)	–	–	0.153++
5th day	6.8 (6.3)	5.3 (4.9-5.5)	17.4 (18.1)	7 (5.1-24.1)	–	–	0.104++

+Kruskal–Wallis test; ++Mann–Whitney test

contrast, MONO MEAN-C on day 3 and MDW on day 5 were significantly greater in the septic shock group.

Some other indicators that are currently used to predict sepsis have been measured, and the results are shown in Table 4.

LAC, PCT, TNF-a, IL-6, and CRP values were significantly lower in febrile patients compared to septic patients (sepsis and septic shock).

In febrile cases, no significant correlation was found between MONO MEAN-V, MDW, MONO MEAN-C, MONO Sd-C and LAC, PCT, TNFa, IL-6, CRP, and NLR values on the 1st day (results are shown in Table 5).

In contrast, in sepsis cases, it was found that greater LAC, PCT, and CRP values were significantly associated with greater MONO MEAN-V and greater TNFa values with lower MONO MEAN-V.In addition, greater TNFa and lower NLR were significantly associated with greater MONO Sd. Furthermore, greater PCT, CRP, and NLR, as well as lower TNFa and IL-6 levels, were significantly associated with greater MDW. Lower TNFa and greater NLR were significantly associated with greater MONO-SdC.

In septic shock cases, greater TNFa values were significantly associated with lower MONO MEAN-V and higher MDW and MONO Sd-C. Also, greater IL-6 values were significantly associated with lower MONO MEAN-V and higher MDW.

The predictive ability of MONO MEAN-V, MONO MEAN-C, MDW, and MONO Sd-C between febrile and septic events during the first day was examined via ROC curves, the results of which are presented in Table 6. All factors had a significant predictive ability. More specifically, for MEAN–V, the optimal cut-off was set at 180.5, with 72.1% sensitivity and 48.5% specificity. For MEAN-C, the optimal cut-off was set at 120.5, with 48.5% sensitivity and 88.2% specificity. For MDW, the optimal point was 25.1, with 75.0% sensitivity and 91.2% specificity, and for MONO Sd-C, the optimal point was 6.9, with 58.8% sensitivity and 80.9% specificity.

Discussion

Our results indicated that MDW, a biomarker that can be easily measured using a common CBC test, can be used

TABLE 4 - LAC, CRP, PCT, TNFa, IL-6, and NLR values by outcome. Values of p < 0.05 are marked in bold

	Outcome						P
	Febriles (n = 68, 50%)			Sepsis and septic shock (n = 68; 50%)			
	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)	
LAC (mmol/L)							
Day 1	68	1.34 (0.51)	1.35 (1-1,8)	68	5.26 (3.29)	4.45 (3.1-6,8)	**<0.001**
Day 3	0	–	–	49	3.6 (3)	2.8 (2.2-4.1)	–
Day 5	0	–	–	49	2.78 (2.55)	1.8 (1.2-3.2)	–
CRP (mg/L)							
Day 1	68	151.28 (108.61)	135.5 (67-248.84)	68	202.18 (121.98)	169 (106-259.5)	**0.017**
Day 3	0	–	–	51	170.22 (97.01)	149 (90-234)	–
Day 5	0	–	–	50	144.42 (105.89)	123 (66-188)	–
PCT (ng/L)							
Day 1	68	0.47 (0.57)	0.28 (0.07-0.8)	68	22.19 (29.08)	4.7 (1.12-43.5)	**<0.001**
Day 3	0	–	–	51	11.38 (16.77)	4.62 (0.89-15.76)	–
Day 5	0	–	–	48	7.98 (18.84)	2.44 (0.51-6.01)	–
TNFa (pg/mL)							
Day 1	67	69.16 (20.57)	62.9 (54.4-84.4)	68	104.86 (31.43)	101 (76.15-135.5)	**<0.001**
Day 3	0	–	–	46	48.37 (55.02)	16.5 (15.2-129)	–
Day 5	0	–	–	43	33.84 (57.67)	5.2 (3.7-5.9)	–
IL-6 (pg/mL)							
Day 1	67	20.16 (10.12)	17.9 (12.9-26.1)	68	63.53 (46.34)	51.25 (4.1-108.4)	**<0.001**
Day 3	0	–	–	46	42.65 (44.58)	40.15 (3-103.2)	–
Day 5	0	–	–	44	80.01 (27.37)	80.85 (58.45-100.7)	–

for the detection of sepsis. The MDW and other correlated parameters, such as MONO MEAN-V and MONO MEAN-C mono, can be easily calculated from the CBC (42). This could be of crucial importance since the management of patients with sepsis remains a major problem in clinical practice.

Studies have shown the importance of MDW in detecting sepsis as a reliable diagnostic marker for the early detection of sepsis compared to classic biomarkers, such as PCT and CRP, in various patient populations (13,32-34,36,38,44-60) published a score incorporating the modified early warning score (MEWS), neutrophil-to-lymphocyte ratio (NLR), MDW, and CRP, and showed that MEWS ≥3 with white blood cell (WBC) count ≥11 × 109/L, NLR ≥8, and MDW ≥20 demonstrated the highest diagnostic accuracy in all age subgroups in detecting sepsis in an early stage (61) suggested the incorporation of MDW along with NLR and PLR to improve sepsis scores. Early detection of sepsis is crucial because it is associated with the early initiation of broad-spectrum antibiotics, which can be lifesaving for patients with sepsis (43). In conclusion, the value, mainly, of MDW as a biomarker for sepsis prediction in comparison with existing sepsis biomarkers was confirmed in this study as well as in other similar studies (43).

In our study, MDW, MONO MEAN-V, MONO Sd-C, and MONO MEAN-C acted as biomarkers for the diagnosis of sepsis since septic patients had significantly higher values of MDW, MONO MEAN-V, MONO Sd-C, and significantly lower MONO MEAN-C, on the first day. In addition, our study did not find significant differences in the abovementioned biomarkers between septic and septic shock patients on the first day. The above indicates that these biomarkers could be very useful tools for the early diagnosis of sepsis. Furthermore, significant differences were found between septic and septic shock patients for MONO MEAN-C on day 3 and MDW on day 5, indicating that some monocyte parameters could also be useful tools for the diagnosis of septic shock. These findings are in line with those of other studies that suggest the use of MDW in combination with WBC for the diagnosis of sepsis (58,63). Furthermore, our findings are in agreement with other studies that have found that increased monocyte parameters, such as MDW or MONO MEAN-V, contribute to the early diagnosis of sepsis (33,64,65). The same applies to MONO MEAN-C, as other studies have found what we have found, that septic patients have significantly lower values of MONO MEAN-C.

TABLE 5 - LAC, CRP, PCT, TNFa, IL-6, and NLR values by outcome. Values of p < 0.05 are marked in bold

			MONO MEAN-V	MONO MEAN-C	MDW	MONO Sd-C
Febriles	**LAC (mmol/L)**	rho	−0,13	0.05	−0.03	0.16
		P	0.305	0.714	0.839	0.182
	PCT (ng/L)	rho	−0.08	−0.08	−0.04	0.00
		P	0.503	0.500	0.729	0.971
	TNFa (pg/mL)	rho	−0.10	−0.02	0.06	0.08
		P	0.413	0.867	0.616	0.540
	IL-6 (pg/mL)	rho	−0.12	−0.04	0.03	0.08
		P	0.324	0,743	0.835	0.518
	CRP (mg/L)	rho	−0.18	0.00	0.06	0.11
		P	0.137	0.990	0.655	0.379
	NLR	rho	−0.16	−0.17	−0.04	0.07
		P	0.202	0.166	0.748	0.557
Sepsis	**LAC (mmol/L)**	rho	0.57	0.05	0.42	0.24
		P	**0.006**	0.841	0.053	0.276
	PCT (ng/L)	rho	0.63	−0.07	0.52	0.06
		P	**0.002**	0.760	**0.014**	0.792
	TNFa (pg/mL)	rho	−0.45	0.42	−0.61	−0.43
		P	**0.037**	**0.050**	**0.003**	**0.046**
	IL-6 (pg/mL)	rho	−0.26	0.37	−0.48	−0.35
		P	0.243	0.087	**0.023**	0.106
	CRP (mg/L)	rho	0.50	−0.16	0.48	0.22
		P	**0.017**	0.485	**0.023**	0.334
	NLR	rho	0.26	−0.53	0.69	0.51
		P	0.233	**0.011**	**<0.001**	**0.015**
Septic shock	**LAC (mmol/L)**	rho	0.10	0.04	0.39	0.27
		P	0.528	0.777	**0.007**	0.075
	PCT (ng/L)	rho	0.09	−0.07	0.19	0.22
		P	0.535	0.660	0.204	0.146
	TNFa (pg/mL)	rho	−0.34	−0.23	0.34	0.30
		P	**0.019**	0.121	**0.020**	**0.045**
	IL-6 (pg/mL)	rho	−0.31	−0.17	0.37	0.28
		P	**0.038**	0.262	**0.012**	0.064
	CRP (mg/L)	rho	0.20	−0.18	0.21	0.11
		P	0.183	0.233	0.152	0.469
	NLR	rho	−0.09	0.08	−0.22	−0.02
		P	0.540	0.605	0.138	0.903

In our study, the significant predictive ability of MONO MEAN-V, MONO MEAN-C, MDW, and MONO Sd-C was found via ROC analysis. For MONO MEAN-V, the optimal cut-off was found to be 180.5, with a sensitivity of 72.1% and specificity of 48.5%. For MONO MEAN-C, it was found to be 120.5, with a sensitivity of 48.5 % and specificity of 88.2 %. For MDW, the optimal cut-off was found to be 25.1, with a sensitivity of 75.0% and specificity of 91.2%, and for MONO Sd-C was found to be 6.9, with a sensitivity of 58.8 % and specificity of 80.9%. The cut-off of MDW is in line with other studies that find cut-offs of 20-25 units for the detection of sepsis, with values >25 generally indicating higher severity (49). Overall,

TABLE 6 - ROC analysis results

	AUC (95% ΔE)+	P	Optimal cut-off	Sensitivity (%)	Specificity (%)
MONO MEAN-V (1st day)	0.65 (0.56-0.74)	**0.002**	>180.5	72.1	48.5
MONO MEAN-C (1st day)	0.7 (0.61-0.79)	**<0.001**	<120.5	48.5	88.2
MDW (1st day)	0.84 (0.77-0.91)	**<0.001**	>25.1	75.0	91.2
MONO SD-C (1st day)	0.7 (0.61-0.78)	**<0.001**	>6.9	58.8	80.9

+Area Under the Curve (95% CI)

our results point out that MDW is an independent predictor of outcomes in septic patients administered in the ICU. The predictive value of MDW in the diagnosis of sepsis has been confirmed, and it is demonstrated why researchers are now focusing on this particular marker, as it is a monocyte parameter that can provide a low-cost, rapid, and reliable solution for the diagnosis of sepsis.

As mentioned above, patients with hematological malignancies or those undergoing recent chemotherapy or taking medications affecting the monocyte population, such as injectable growth factors, were excluded from our study. Also, pediatric cases were excluded due to the non-availability of pediatric clinics in the two survey hospitals. Moreover, the sample could have been bigger, but due to the limitations of COVID-19, this was not possible. More research should be carried out in the future. For example, the diagnostic ability of the MDW in pediatric cases and the correlation of the diagnostic ability of the MDW with various pathogenic factors should be clarified. Also, it would be useful to compare the results of our research with those of studies where the sample is larger.

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