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

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## Abstract

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

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

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

their stay [median from 29.14 (IQR: 26.22–32.52) to 25.67 (IQR: 22.93–30.28)].

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

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

## Introduction

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

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

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patient survival [3]. The diagnosis of infection, usually based on positive cultures or on molecular techniques for organism identification, is time consuming and unable to make an early recognition of sepsis [4, 5]. Over the last decade several sepsis biomarkers have been proposed. Among them, procalcitonin (PCT) and C-reactive protein (CRP) have been traditionally considered in sepsis diagnosis and monitoring [6]. Nevertheless, since sepsis is related to the balance of pro-inflammatory and anti-inflammatory mechanisms, the instrument's evolution in detecting abnormalities of cells such as monocytes, that play a role in the development of sepsis-induced inflammation and immunosuppression, can provide important clinical values in disease recognition and monitoring [7].

Due to contextual features such as surgery and invasive procedures, patients in Intensive Care Units (ICU) are a high-risk population for sepsis, that is recognized as the major cause of admission and death [8, 9].

The aim of the present study is to evaluate the clinical usefulness of the MDW using the UniCel DxH 900 Beckman Coulter hematology analyzer, to early identify patients with sepsis or that became septic during their stay in ICU. Prompt recognition of sepsis is required for an appropriate antimicrobial treatment that represents an independent factor associated with a favorable outcome [10].

## Material and methods

### Patients

We conducted a prospective observational study between January and June 2020, on 506 patients admitted to the ICU of the Padua University Hospital in Italy. The inclusion criteria were: adult (>18 years) patients presenting to the ICU, who remained hospitalized for at least 24 h, enrolled no more than once, with a CBC and differential testing performed at presentation and over the entire course of the length of stay (LOS), as part of standard medical care and PCT or CRP tests ordered at the same time. Incomplete data collection, failure to determine MDW at least once, and patients with hematological disorders were exclusion criteria.

Three hundred forty six were men and 160 were women, aged from 18 to 89 years (median 68, IQR: 57–76 years). Based on historical and clinical data, severity scores, respiratory or inotropic support during their stay and all tests performed, patients were divided into three groups, as follows: 394 were defined as sepsis negative; 108 presented sepsis, four exhibited septic shock. Moreover, the two last patient groups were considered according to the outcome, based on ICU mortality.

Sepsis was clinically diagnosed according to Sepsis-3 criteria with signs of infection together with acute organ dysfunction, using the Sequential Organ Failure Assessment (SOFA) score [11]. Septic shock was recognized in the cases with hypotension requiring vasopressors and with an elevated serum lactate concentration greater

than 2 mmol/L. The infections were defined according to all tests performed, including cultures, molecular tests and imaging. All patients with suspected sepsis had one set of blood, body-fluid, central line, or intravascular device cultures collected.

### UniCel DxH 900, MDW and CBC determination

CBC and MDW were evaluated in 2,367 consecutive samples received for routine CBC as part of day-to-day clinical practice. CBC and MDW were performed once a day during the entire LOS of patients included in the study. Samples were collected in K<sub>2</sub>EDTA anticoagulated tubes (Vacutainer®, Becton Dickinson, Plymouth, UK) and analyzed within 4 h. CBC and MDW were analyzed at the same time using UniCel DxH 900 (Beckman Coulter, Inc, Brea, California). MDW values were omitted in medical reports. UniCel DxH 900 evaluates MDW, using the VCS technology. Briefly, signals obtained by bio-electrical impedance analysis of cell volumes, conductivity and Light Scatter signals can evaluate morphological changes in leukocytes, particularly in monocytes. Therefore, the value of MDW represents the width of a set of monocyte volume values, as a Standard Deviation. Maintenance, functions, and calibration were performed according to manufacturer's instructions. Internal quality control procedures were assessed using the Coulter 6C Cell Control with three levels at different concentrations. The analysis was performed by using 1.1.0 software.

Since that from the enrolled patients the study did not require any blood draws or procedures that would not already have been performed as part of standard medical care, the written informed consent was exempted. The study was conducted in accordance with the guidelines established by the Local Ethics Committee, and all data were rendered anonymous before analysis.

The repeatability of the MDW parameter was assessed by duplicate analysis of 19 specimens and also by replicate analysis of the same specimen. The reproducibility was assessed using control materials (a single lot of Coulter 6C Plus Cell Control). Using the unicel DxH 900 system stability of the MDW parameter was evaluated by testing 10 samples from zero to 7 h from blood collection. All samples were tested at each point in time and stored at room temperature, between 20 and 21 °C.

### Procalcitonin, C-reactive protein and biochemical tests determination

At the same time as the MDW, 2,128 samples were determined for C-reactive protein (CRP) and 2,035 samples for procalcitonin (PCT), as part of the clinical examination. For the determination of CRP and PCT blood samples were drawn into serum tubes and Serum CRP was determined using a nephelometric/turbidimetric technique of the Dimension Vista® System (Siemens Healthcare GmbH, Milan, Italy), according to the manufacturer's instructions. PCT was determined using chemiluminescence immunoassay (CLIA) technology with paramagnetic microparticle solid phase of the LIAISONs BRAHMS PCTs II GEN System (DiaSorin, Saluggia, Italy) according to the manufacturer's inserts. Analytical detection limits were 0.24 mg/L for CRP and 0.2 µg/L for PCT. For additional biochemical analytes (bilirubin, creatinine) blood samples were drawn into tubes containing lithium-heparin as anticoagulant and tests assessed using a Modular Analytics Cobas 8,000 (Roche Diagnostics S.p.A. Monza, Italy). Lactate was determined in plasma samples obtained using a potassium

oxalate/sodium fluoride tube, and by an enzymatic colorimetric method (Cobas c702, Roche Diagnostics S.p.A. Monza, Italy). Every test involved was part of the routine standard of care in patient's management and treatment.

### Statistical analysis

Statistical analyses were performed by MedCalc Statistical Software version 19.1 (MedCalc Software bv, Ostend, Belgium; <https://www.medcalc.org>; 2019). Differences between groups were estimated using the nonparametric Kruskal-Wallis test. For the stability the differences were evaluated using the Wilcoxon test, while calculation of the Coefficient of Variation (CV) from duplicate measurements was used to determine the repeatability. The prediction of sepsis was evaluated by receiver operating characteristic (ROC) curve analysis and their difference by the De Long method. The best cut-off was calculated using the Youden method. Rank correlation analysis was used to evaluate the degree of association between MDW and PCT with CRP. One-way analysis of variance was used to verify the difference between the mean values of subgroups for different infecting organism types. A p-value <0.05 was defined as statistically significant.

## Results

### Patient demographics and causative infecting organism type

No differences for age and sex were observed between sepsis and non sepsis patients ( $p=0.253$  and  $0.826$  respectively). The common documented origin of acquired infection was from positive blood cultures ( $n=23$ , 21%), intravascular catheters ( $n=12$ , 11%), pulmonary infections ( $n=53$ , 48%), abdominal drainage tubes ( $n=4$ , 3.5%), urinary sites ( $n=3$ , 2.5%), unknown in 16 patients (14%).

Sepsis of abdominal origin affected 3.5%, urinary origin 2.5%, chest origin 48% and blood origin 32%, while the site of infection was unknown in 14% of patients.

The documented causative microorganisms were the following: Gram negatives bacteria (25 cases, 22.32%): *Escherichia coli*, *Klebsiella pneumonia*, *Acinetobacter baumannii*, *Enterobacter cloaca*, *Pseudomonas Aeruginosa*, *Leptospira*, *Staphylococcus epidermidis*, *Enterobacter hormaecheie*, *Proteus mirabilis*; Gram positives (28 cases, 25%): *Enterococcus faecalis*, *Staphylococcus aureus*, both presenting methicillin-resistant (MRSA) and methicillin-sensitive (MSSA), *S. epidermidis*, *Staphylococcus hemoliticus*, *Streptococcus agalataiae*, *Staphylococcus hominis*, *Staphylococcus capitis*, *Citrobacter Koseri*, *Streptococcus pyogenes*; non-bacterial cause, in which causes of sepsis were virus: SARS CoV-2 (28 cases, 25%) and (seven cases, 6.25%) influenza viruses A, H1N1, and B, herpesviruses such as CMV and HSV1 and human enteroviruses; fungal

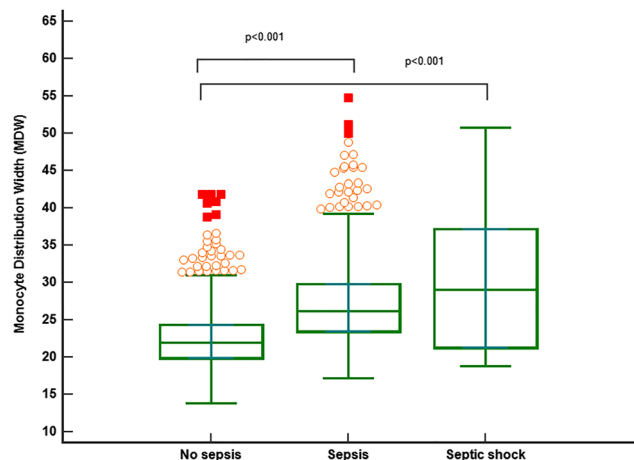
infections that were the cause of sepsis (four cases, 3.6%), were attributed to *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis* together with *Candida glabrata* and *Aspergillus fumigatus*. Among patients, 20 of them (17.86%) were culture negative, suggesting a non-bacterial cause, but without a definitive pathogen identification as cause of sepsis.

### MDW, procalcitonin (PCT) and C-reactive protein (CRP) for sepsis detection in ICU

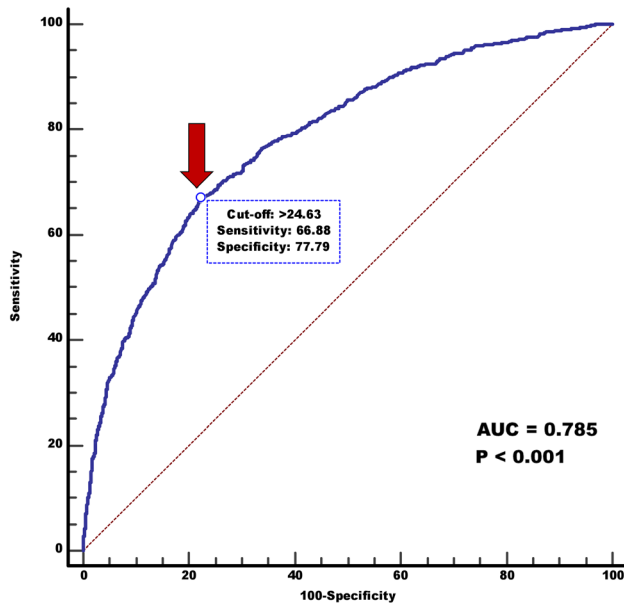
#### MDW

In ICU patients MDW was statistically higher in those with sepsis and septic shock compared to those without sepsis ( $p<0.001$ ), while no statistical differences were found between sepsis and septic shock patients, as shown in Figure 1. MDW median values were the following: no sepsis group (samples=1,540): 21.99 (IQR: 19.86–24.36) sepsis (samples=782): 26.23 (IQR: 23.48–29.83) and septic shock group (samples=45): 28.97 (IQR: 21.27–37.21). The septic shock subgroup showed the highest MDW median value.

For the prediction of sepsis, the area under the curve (AUC) of MDW, obtained by the ROC curve analysis, was 0.785 (95% CI: 0.767–0.801). The most accurate cut-off MDW value, calculated by Youden's index, was >24.63, with a sensitivity of 66.88% (95% CI: 63.5–70.2) and a specificity of 77.79% (95% CI: 75.6–79.8) while the positive (LR<sup>+</sup>) and the negative likelihood ratio (LR<sup>-</sup>) were 3.01 (95% CI: 2.7–3.3) and 0.43 (95% CI: 0.4–0.5) respectively, as shown in Figure 2. In Table 2, sensitivity, specificity with



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



**Figure 2:** ROC curve analysis of MDW in sepsis prediction and the best cut-off point in ICU.

their 95% Confidence Interval of different MDW cut points for sepsis prediction with the positive ( $LR^+$ ) and the negative likelihood ratio ( $LR^-$ ) are shown. Comparing diagnostics performance in sepsis prediction the AUC of MDW was found to be comparable with that of PCT (0.759, 95% CI: 0.740–0.778), and better than CRP (0.667, 95% CI: 0.646–0.688) and WBC (0.570, 95% CI: 0.547–0.592) ( $p < 0.001$  in both), as shown in Figure 3.

### PCT and CRP

PCT median values were statically different in the various groups ( $p < 0.001$ ), the highest values were found in the septic shock group as shown by the following results: no sepsis group (samples=1,346): 0.190  $\mu\text{g/L}$  (IQR:

0.04–0.54  $\mu\text{g/L}$ ) sepsis (samples=662): 0.855  $\mu\text{g/L}$  (IQR: 0.35–3.11  $\mu\text{g/L}$ ) and septic shock group (samples=27): 7.45  $\mu\text{g/L}$  (IQR: 4.20–13.82  $\mu\text{g/L}$ ). CRP median values were statically different in patients without sepsis in comparison to those presenting sepsis or septic shock, as follows: no sepsis group (samples=1,411): 58 mg/L (IQR: 22–120 mg/L), sepsis (samples=686): 110 mg/L (IQR: 54–170 mg/L) and septic shock group (samples=31): 83 mg/L (IQR: 39–235 mg/L) ( $p < 0.001$ ).

MDW determined in overall patients showed a positive significant correlation with PCT (Spearman's rho 0.543,  $p < 0.001$ ) and CRP (Spearman's rho 0.509,  $p < 0.001$ ), higher than that in patients with sepsis. In this group the Spearman rank correlation rho was 0.425 ( $p < 0.001$ ) for MDW with PCT and 0.423 ( $p < 0.001$ ) for MDW with CRP.

### MDW, procalcitonin, C-reactive protein and causative infecting organism type in sepsis patients

In sepsis patients, MDW, PCT and CRP values were evaluated considering the causative organism type according to bacterial, fungal or viral infection attributed as the cause of sepsis. MDW values showed no significant differences between organism types within group, as shown in Figure 4. On the contrary, significant differences for PCT and CRP were found when sepsis is classified according to the causative organism type. In fact, highest values of PCT were observed in gram negative bacteria, with a statistical difference when comparison was against no sepsis group of patients and sepsis due to gram positive bacteria, Sars-CoV-2 and fungi sepsis ( $p < 0.05$ ). This last group showed among the different groups the lowest PCT values. Concerning CRP values, a statistical difference was discovered between no sepsis patients and all groups with exception

**Table 1:** MDW, PCT and CRP values of the study population stratified in seven groups; in sepsis and shock septic patients, data were reported considering the causative organism type according to bacterial, fungal or viral infection attributed as the cause of sepsis.

Infecting organism type	Samples	MDW Median, IQR	Samples	PCT, $\mu\text{g/L}$ Median, IQR	Samples	CRP, mg/L Median, IQR
No sepsis	1,540	21.99 (19.86–24.36)	1,346	0.19 (0.07–0.54)	1,411	58.0* (22–120)
No definitive identification	78	26.95 (23.77–32.57)	57	2.12* (0.49–4.71)	65	96 (53.75–172.5)
Gram negatives	137	26.58 (23.66–30.72)	111	3.68* (1.32–7.10)	114	92.5 (58.00–150)
Gram positives	180	26.06 (23.52–29.05)	161	1.94* (0.38–4.49)	168	115 (58.5–160)
Viruses	80	25.94 (22.38–32.16)	52	0.49 (0.23–1.33)	52	79.5 (41.5–135)
Sars-CoV-2	243	26.01 (23.35–29.14)	224	0.51 (0.31–1.04)	233	100 (47.75–190)
Fungi	64	25.96 (24.5–28.8)	52	0.42 (0.20–0.92)	54	160.0* (110.0–220.0)

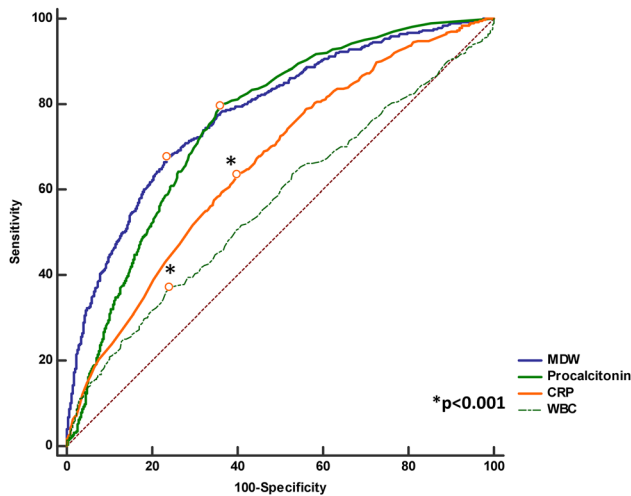
MDW, monocyte volume distribution width; PCT, procalcitonin; CRP, C-reactive protein; IQR, interquartile range. Statistical significance was calculated according to nonparametric Kruskal-Wallis test (\* $p < 0.05$ ).



**Table 2:** Sensitivity and specificity at different cut points of MDW in predicting sepsis with the positive (LR<sup>+</sup>) and the negative likelihood ratio (LR<sup>-</sup>).

MDW value (cut-off point)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR <sup>+</sup>	LR <sup>-</sup>
>20.03	95.52 (93.8–96.9)	26.49 (24.3–28.8)	1.30	0.17
>21.02	91.82 (89.7–93.6)	37.79 (35.4–40.3)	1.48	0.22
>22.0	85.29 (82.6–87.7)	50.13 (47.6–52.7)	1.71	0.29
>23.0	78.39 (75.3–81.2)	62.79 (60.3–65.2)	2.11	0.34
>24.0	70.97 (67.7–74.1)	72.34 (70.0–74.6)	2.57	0.40
>25.0	62.02 (58.5–65.4)	80.58 (78.5–82.5)	3.19	0.47
>26.01	51.41 (47.8–55)	86.36 (84.5–88.0)	3.77	0.56
>27.04	42.97 (39.5–46.5)	90.65 (89.1–92.1)	4.60	0.63
>28.01	36.06 (32.7–39.5)	93.64 (92.3–94.8)	5.67	0.68
>29.01	29.54 (26.4–32.9)	95.58 (94.4–96.6)	6.69	0.74

MDW, monocyte volume distribution width; CI, confidence interval.



**Figure 3:** ROC curves comparison of MDW, PCT, CRP and WBC for sepsis prediction. AUC estimates along with their 95% confidence interval are shown in Results.

of sepsis caused by viruses. The last group showed difference only against fungi sepsis ( $p < 0.05$ ). Results were reported in Table 1.

## MDW and patient monitoring in early onset of sepsis

In 21 patients that became septic during their stay in ICU, the evaluation of two samples at different times of MDW, PCT and CRP for early onset detection of sepsis was performed. Differences between the values before and after sepsis onset were significant for MDW ( $p < 0.0001$ ) and for CRP ( $p = 0.019$ ). The median for MDW showed a value of

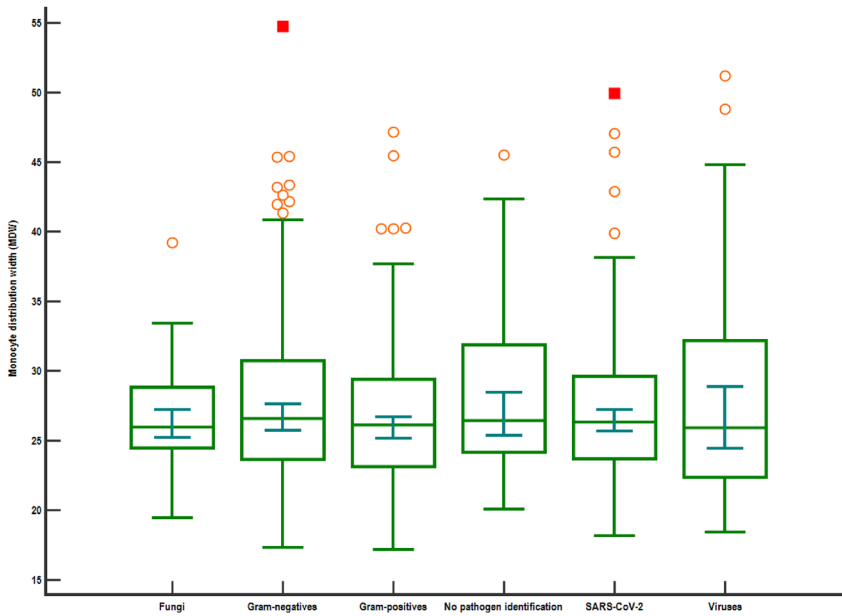
21.33 (IQR: 19.47–21.72) when patients were admitted with a non-infective diagnosis, that subsequently increased to 29.19 (IQR: 27.46–31.47) when patients developed an ICU-acquired sepsis. The CRP median values were 51.5 mg/L (IQR: 23.5–99.5 mg/L) in comparison to 93.0 mg/L (IQR: 66.0–185.0 mg/L). The PCT median values were not statistically significant ( $p = 0.92$ ), being 1.87  $\mu\text{g/L}$  (IQR: 0.48–3.12 mg/L) in comparison to 1.42  $\mu\text{g/L}$  (IQR: 0.43–4.17  $\mu\text{g/L}$ ).

## MDW as a prognostic tool in the sepsis patient's follow-up

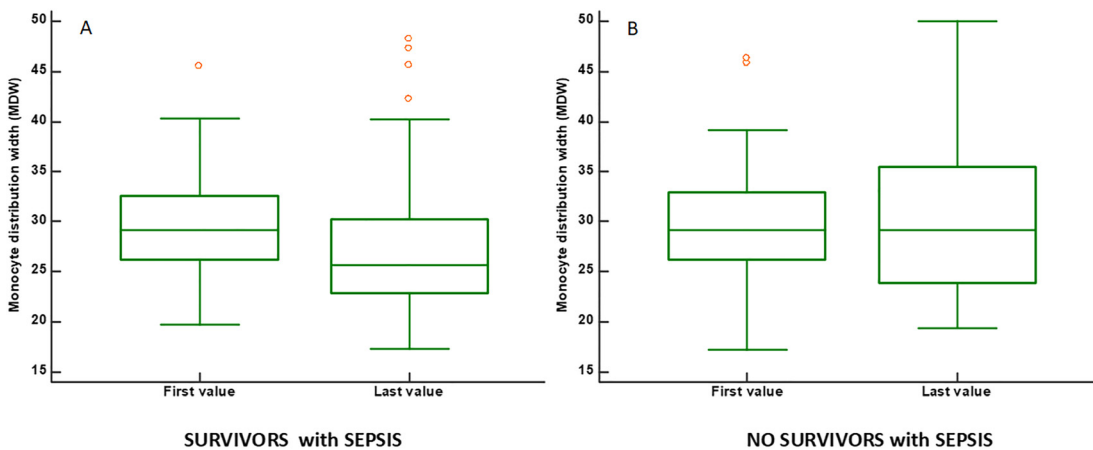
In patients with sepsis or septic shock MDW values were assessed on the basis of clinical outcomes, and in particular death. MDW was evaluated at the time of sepsis diagnosis and at the end of the ICU stay. In survivors ( $n = 81$ ), at the beginning of sepsis, MDW median values were 29.14 (IQR: 26.22–32.52), while at the end-point of their ICU stay values were 25.67 (IQR: 22.93–30.28) ( $p = 0.0002$ ). In non survivors ( $n = 31$ ) initially, MDW median values were 29.19 (IQR: 26.21–32.94), and remained 29.13 (IQR: 23.88–35.39) until the final end-point. In the case of patient survivors there were no statistically significant differences, while they were observed in patients when progression of sepsis became severe and the clinical outcome was death. Data is shown in Figure 5A, B.

## Performance characteristics

The coefficient of variation (CV%) of MDW, evaluated from duplicate measurements of 19 samples, was 4.12%. The range of values was from 15.4 to 29.47, with an overall mean value of 20.45. The mean  $\pm$  SD of the first run was  $20.56 \pm 4.16$ , while that of second run was  $20.34 \pm 3.83$ . The CV assessed by 10 replicate analysis of the same specimen with a high value of MDW, was 4.15% (mean  $\pm$  SD:  $27.10 \pm 2.25$ ). The CV between days ( $n = 15$ ), calculated using the level 3 of COULTER 6C control was 3.22% (mean  $\pm$  SD:  $36.17 \pm 2.33$ ). The MDW parameter was found to be stable for up to 7 h for a range of values from 15.49 to 31.63. The overall median was 17.96 (IQR: 15.91–20.96) at zero time and 17.66 (IQR: 17.11–21.8) at 7 h after blood collection, with a storage at room temperature of the samples. Median difference was 0.55 (95% CI from  $-0.81$  to 1.65); six samples showed a positive difference, while four displayed a negative difference. At 4 h the overall median for MDW was 17.86 (IQR: 16.31–19.36); difference was 0.11 (95% CI from  $-1.53$  to 1.06).



**Figure 4:** In sepsis patients, MDW values were shown considering the causative organism type 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.



**Figure 5:** MDW values at the beginning and end of ICU stay in patients with sepsis. In survivors there were no statistically significant differences (A), while these differences were observed in patients when progression of sepsis became severe and the clinical outcome was death (B).

## Discussion

Clinically difficult to define, sepsis diagnosis remains a challenge, despite the fact that it is a life-threatening organ dysfunction due to a dysregulation of host response in the presence of infection [11]. Because of the high mortality rate, sepsis has for a long time been recognized by the World Health Organization as a global health priority. Although its precise incidence is unknown, a recent paper estimated that 11 million adult deaths worldwide are due to sepsis, i.e., 19.7% of deaths [12]. Last year, in its first report on the global epidemiology and burden of sepsis, the World Health Organization (WHO) referred sepsis as “the

final common pathway to death” for severe infectious diseases, with an estimated mortality for patients treated equal to 26.7% in hospital and 42.6% in ICUs, without significant differences between WHO regions [9]. Nearly one in four (24.4%) cases of sepsis is acquired in ICU, and nearly half of all cases (48.7%) during hospitalization [9]. The significance of hospital or ICU acquired sepsis is also emphasized by our findings because, during the period study, all our sepsis cases (100%) had originated during the hospital stay and were the reason for ICU admission, while 5.06% of sepsis cases originated in ICU. In patients enrolled for the study, the mortality rate was 27.68%, lower than that mentioned by the WHO for ICUs, and closer to

that reported at the hospital setting outside of ICU. In order to decrease mortality, many studies have shown that patients need early administration of effective and appropriate treatments, antibiotics and the adoption of a bundle of evidence-based care [13, 14]. Therefore, the cornerstones of sepsis care remain its early recognition.

Currently, no single laboratory test or specific stand-alone biomarker has sufficient sensitivity and specificity to timely and accurately diagnosis sepsis [15, 16]. Among the most available, PCT has been FDA-approved for the assessment of risk for developing sepsis in critical patients admitted in ICU, but PCT presents more than one limitation and needs to be interpreted in the clinical context [17, 18]. C-reactive protein is an interesting biomarker, with a low cost in comparison to PCT, with a valuable diagnostic and prognostic value, but unlikely to rule out infection as the cause of inflammation [15]. Microbiological tests, that are the “gold standard”, are evolving in modern molecular-based technologies, nanotechnology, or microfluidics for point-of-care testing, but up to 30–50% of sepsis presentations are culture negative, and viral or fungi sepsis, although very rare, should be considered in laboratory testing used for clinical evaluation of sepsis [19–21].

Automatically available as part of CBC and differential, MDW is an FDA-cleared parameter intended for the early detection of sepsis in adult patients at the Emergency Department. In our study, MDW showed good accuracy for sepsis detection in ICU. In sepsis patients, MDW showed high values not only in sepsis due to Gram negative or positive bacteria, but also when sepsis was caused by fungal or viral infections, even in SARS-CoV-2. On the contrary, the highest values of PCT were observed in gram negative bacteria sepsis, with low values in fungi and viral sepsis, particularly in Sars-CoV-2. As shown by ROC curve analysis, the diagnostic accuracy for MDW was comparable to that of PCT and higher than those of PCR and WBC. Our best cut-point for MDW associated with sepsis was 24.63, a higher value than those reported in other studies, probably because they were performed in different clinical settings such as Infectious Diseases Units or Emergency Departments [22–25]. Our study confirm previously reported data by Agnello et al., even if slightly different values of MDW should be due to the use of K2EDTA tube instead of K3EDTA [26, 27]. The MDW cut-off value should be discussed and evaluated on the basis of the clinical setting in which the studies have been performed. In ICU, the severity of patient characteristics or admitting diagnostics can explain the need for a specific cut-off. In addition, MDW is significantly related to disease severity. Among the sepsis group, in survivors, differently from non-survivors, MDW values decrease in correlation with the

effective clinical outcome, highlighting the association between MDW and mortality and the association with clinical prognostication. Nevertheless, providing this new parameter to clinicians, laboratory scientists should interpret MDW taking into consideration the clinical context, mandatory for the correct diagnosis, as well as understanding the limitations in some patients, for example those with hematological diseases that were not included in our study. Appropriate materials for internal quality control (IQC) and external quality assessment (EQA) are needed to provide useful information on the compliance with established performance specifications, particularly for values near to the cut-off. This study presents some limitations including the need to evaluate the possible integration of the MDW information with other hematological indices. In particular, recently published systematic reviews highlight the prognostic value of another hematological index that is the red blood cell distribution width (RDW) that has been found may be a useful predictor of mortality [28, 29].

In conclusion, changes in functional properties related to monocytes have been reported in early sepsis, when monocytes with the inflammatory phenotypes (CD14<sup>+</sup>CD16<sup>++</sup>) increase in blood, and in the immunosuppression state of sepsis, when the expression of HLA-DR in monocytes is decreases [30–32]. MDW, a parameter that reflects a change in circulating monocytes volume in response to pro-inflammatory signals from infectious organisms referred to as pathogen-associated molecular patterns, can have potential clinical applications for early sepsis detection in hospital and ICU settings.

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**Competing interests:** Authors state no conflict of interest.

**Informed consent:** Not applicable.

**Ethical approval:** Not applicable.

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