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Monocyte distribution width (MDW) as an infection indicator in severe patients attending in the Emergency Department: a pilot study

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ABSTRACT

Background. The aim of the present study was to evaluate the diagnostic performance of monocyte distribution width (MDW) as a biomarker for sepsis diagnosis in severe patients attended in the Emergency Department for different conditions and not only infections.

Methods. We performed an observational study in a consecutive prospective cohort including severe patients attending the Emergency Department with different conditions. MDW and other biomarkers were determined from samples obtained during the first care of patients. The diagnostic performance of the different biomarkers was determined based on the final diagnosis at patient discharge.

Results. One hundred two patients, with a mean age of 76.7 (SD 16.5) years were included, 53 being (51.9%) male. Among the patients included, 65 (63.7%) had an infectious disease while the remaining had other different conditions. A MDW cut-off of 20.115 provided the best accuracy to identify infected patients, with a sensitivity of 89.2 (95% CI 79.4-94.7), a specificity of 89.2 (95% CI 75.3-95.7), a positive predictive value of 93.5 (95% CI 84.6-97.5), a negative predictive value of 82.5% (95% CI 68.0-91.3), a positive likelihood ratio of 8.25 (3.26-20.91), and a negative likelihood ratio of 0.12 (0.06-0.24). The area under the receiver operating characteristic curve for infection according to MDW was 0.943 (95% CI 0.897-0.989; p<0.001).

Conclusions. A MDW > 20.115 may be associated with infection and could help to distinguish between infected and non-infected patients in severe patients. These results must be confirmed in new studies due to the limited patient sample included.

Keywords: MDW, Sepsis, NEWS, SOFA, Disease Progression, Emergency Department, Intensive Care Unit

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Ancho de distribución de los monocitos como indicador de infección en pacientes graves atendidos en Urgencias: estudio piloto

RESUMEN

Introducción. El objetivo del presente estudio fue evaluar el desempeño diagnóstico del ancho de distribución de monocitos (MDW) como biomarcador para el diagnóstico de sepsis entre pacientes graves atendidos en el servicio de urgencias por diferentes afecciones y no solo por infecciones.

Métodos. Realizamos un estudio observacional en una cohorte prospectiva consecutiva que incluyó pacientes graves desde el punto de vista clínico que acudían a urgencias con diferentes patologías. El MDW y otros biomarcadores se determinaron a partir de muestras obtenidas durante la primera atención de los pacientes. Se estudio la precisión de los diferentes biomarcadores para apoyar el diagnóstico de infección, basándonos en el diagnóstico final al alta del paciente.

Resultados. Se incluyeron 102 pacientes, con una edad media de 76,7 (DE 16,5) años, siendo 53 (51,9%) del sexo masculino. Entre los pacientes incluidos, 65 (63,7%) pacientes tenían una enfermedad infecciosa y el resto otras condiciones diferentes. Un punto de corte MDW de 20,115 proporcionó la mejor precisión para identificar pacientes infectados, con un sensibilidad de 89,2 (IC 95 % 79,4-94,7), una especificidad de 89,2 (IC 95 % 75,3-95,7), un valor predictivo positivo de 93,5 (IC 95 % 84,6-97,5), un valor predictivo negativo de 82,5% (IC 95% 68,0-91,3), un coeficiente de probabilidad positivo de 8,25 (3,26-20,91), y un coeficiente de probabilidad negativo de 0,12 (0,06-0,24). El área bajo la curva característica operativa del receptor para la infección del MDW fue de 0,943 (IC del 95 %: 0,897-0,989; p<0,001).

Conclusiones. Un MDW > 20.115 se asocia a padecer una enfermedad infecciosa en un paciente grave y podría ayudar

a distinguir entre pacientes infectados y no infectados. Estos resultados deben ser confirmados en nuevos estudios debido a la muestra limitada de pacientes incluidos.

Palabras clave: ancho de distribución de monocitos, Sepsis, NEWS, SOFA, progresión de la enfermedad servicio de urgencias, unidad de cuidados intensivos

BACKGROUND

Sepsis is defined as life-threatening organ dysfunction caused by systemic and dysregulated host response to infection [1]. It is one of the leading causes of hospital mortality and has a great impact on the healthcare system. Early diagnosis of sepsis is essential for the initiation of adequate treatment to improve patient outcomes [2-4].

Nevertheless, there is no gold standard diagnostic test for sepsis and identification is based on clinical scores. Moreover, the definition of sepsis has changed over time. Multiple studies and guidelines have been published to correctly identify the presentation of sepsis and septic shock using different scores or biomarkers in infected patients [5-7]. The 3rd International Consensus Conference on the Definitions of Sepsis [8] recommends the use of Quick Sequential Organ Failure Assessment (qSOFA) to identify patients with sepsis in the Emergency Department (ED). The recently published Surviving Sepsis Campaign guidelines recommend against the use of qSOFA alone as a screening tool for sepsis or septic shock compared to the systemic inflammatory response syndrome (SIRS), National Early Warning Score (NEWS) or Modified Early Warning Score (MEWS) [9].

There is increasing evidence that monocytes undergo morphological changes, including an increase in volume, during inflammatory/infectious processes and sepsis [10-13]. Monocyte activation and the morphological changes that occur in early inflammatory response can be detected by measuring the monocyte distribution width (MDW) [1], which is a measure of the dispersion related to the mean monocyte population volume in whole blood. The incorporation of the MDW improves the detection of sepsis compared with the white blood count (WBC) alone at the time of ED admission and complements the use of the SIRS and qSOFA parameters that are currently used for this purpose [14,15]. A MDW value greater than 22.0 U is effective for the detection of sepsis based on either Sepsis-2 or Sepsis-3 criteria during the initial ED visit [16]. Therefore, as suggested by some authors, MDW may represent an early indicator of infection and sepsis [17-21].

Nonetheless, infection must first be suspected and several conditions, including anaphylaxis, gastrointestinal emergency, pulmonary disease, metabolic alterations, toxin ingestion/withdrawal, vasculitis, or spinal injury, can mimic sepsis due to the common pathophysiologic responses that these diseases present [22]. All these conditions can be deadly if not correctly diagnosed and managed appropriately. Indeed, the most common errors with therapeutic repercussion in relation to clinical diagnosis and necropsy studies are bacterial infections and cardiovascular diseases [23,24]. Data suggest that as many as 40,500 adult patients in Intensive Care Units (ICU) in the United States may die annually due to misdiagnosis [**25**]. This problem is becoming more common in the evaluation of the elderly and immunosuppressed population in the ED since they may present with atypical clinical manifestations. Differentiating between sepsis and other types of infection or disease can be difficult in the emergency setting and clinical scores or laboratory abnormalities do not provide a definitive diagnosis. However, a combination of history, physical examination, and adjunctive studies may assist healthcare providers.

The aim of the present study was to evaluate the diagnostic performance of MDW as a biomarker for sepsis diagnosis in severe patients attended in the ED setting for different conditions and not only infections.

METHODS

Study Design and Ethical Approval. This was an observational cohort study including consecutive severe patients attended in the ED from November 2020 to February 2021. The study was performed according to the principles of the Declaration of Helsinki and ethical approval was granted by the local Ethics Committee (xxx number). The study coordinator was responsible for collecting and recording all the clinical data using a standardized case report form for each patient throughout the investigation. Informed consent was not required because residual material was used and no interventions were performed beyond routine good standard clinical practices.

Study setting. The ED and Laboratory participating in the study belong to a university hospital with 800 beds and all the medical specialties available. A mean of 350 patients are attended in the ED every day.

Patient and sample selection. Adult patients ≥18 years of age evaluated in the ED with severe clinical manifestations were consecutively included in the study. Disease severity was defined as a NEWS score >5, an increase of 2 points in the Sequential Organ Failure Assessment (SOFA) score or a lactate value > 4 mmol/L. Obstetric/Gynaecology patients were excluded. This was a pilot study and it was decided to finalize the study after 4 months, independently of the sample collected.

Definition and collection of variables. Demographic variables (age. sex) as well as comorbidities were collected. Final diagnosis at hospital discharge and the source of infection in infected patients was recorded. In addition, haemodynamic data (blood pressure, heart rate, respiratory rate, alteration in consciousness according to the Glasgow score, oxygen saturation) and analytical data available during the ED evaluation were registered. The information was collected anonymously in an electronic data collection registry.

MDW determination. Upon request by the attending ED clinician, a whole-blood sample was collected in a K2-EDTA tube and analysed in a UniCel DxH-900 Hematology Analyzer (Beckman Coulter. Inc. Brea. California) within two hours of ex-

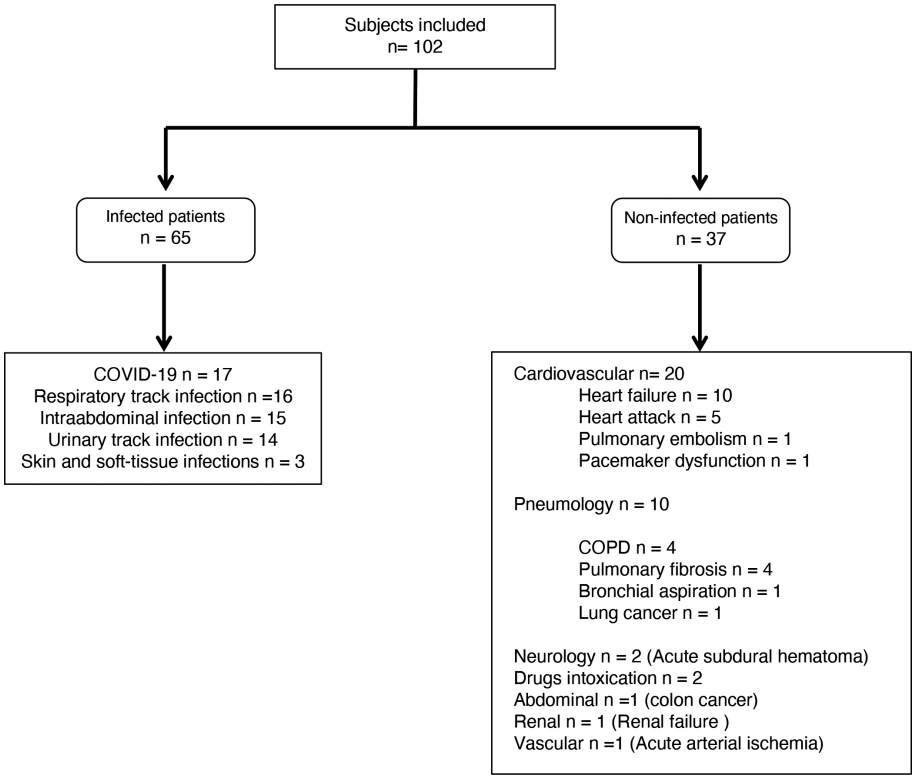


Figure 1 | **Flow diagram of the patients included in the study.**

COVID-19 (Coronavirus disease 2019); COPD: Chronic obstructive pulmonary disease

traction. This equipment uses VCS 360 technology that measures and quantifies the morphological characteristics of each cell using volume, conductivity and multiple light scattering angles, and provides a complete blood count with differential (CBC-Diff). It also measures specific cell volume parameters and the distribution of cell volumes, including MDW, and provides quantitative measurement of the amplitude of monocyte distribution calculated as the standard deviation (SD) of a set of monocyte cell volume values. The investigators were blinded to the MDW values during the collection of patient data and classification and the laboratory investigators were blinded to the patients´ diagnoses. No results of MDW were reported to the attending ED physicians and thus, decision making was not influenced by these results.

Statistical analysis. Categorical variables are expressed as numbers and percentages and the quantitative variables as means and SD [as medians and interquartile ranges (IQR) if the distribution was not normal. Normality was tested using the Kolmogorov-Smirnov test. Categorical variables were compared with the Pearson chi-square or Fisher test and quantitative variables using the Student's-t test (or the Mann-Whitney U test if the distribution was not normal). All patients were classified into 2 groups: infected and non-infected patients. The values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (LHR+) and negative likelihood ratio (LHR-) were calculated for the identification of infected patients. A receiver-operator characteristic (ROC) curve was constructed to determine the capacity of MDW to identify infected patients. A p-value of <0.05 was considered statistically significant. The statistical analyses were performed using SPSS for Windows 18.0 (SPSS Inc.. Chicago. IL). The STARD statement for reporting studies of diagnostic accuracy was used in this study [26].

RESULTS

One hundred two patients were included. The mean age was 76.7 (SD 16.5) years and 53 (51.9%) were male. Among the patients included, 65 (63.7%) had an infectious disease based on the final diagnosis at hospital discharge, and the remaining patients had other conditions (Figure 1). In 37 (56.9%) of the 65 infected patients a microorganism was isolated from samples obtained in the ED. Regarding outcomes, 9 (8.8%) patients were admitted to the ICU from the ED and 18 (17.6%) died during hospitalization.

Table 1 shows the characteristics of the sample and the

Table 1 **Characteristics of the patients included in the study based on the diagnosis or not of infection.**

	Infected patients (n=65)	Non-infected (n=37)	p
Demographic data			
Age (years) [mean (SD)]	75.8 (16.7)	78.4 (16.2)	0.415
Male [n(%)]	33 (50.8)	20 (54.1)	0.750
Comorbidity			
Cardiovascular [n(%)]	26 (47.3)	17 (60.7)	0.247
Respiratory [n(%)]	18 (32.7)	7 (25)	0.468
Immunodeficiency [n(%)]	3 (5.5)	0 (0)	0.208
Diabetes [n(%)]	20 (36.4)	10 (35.7)	0.954
Chronic renal failure [n(%)]	13 (23.6)	11 (39.3)	0.137
Chronic Liver disease [n(%)]	6 (10.9)	1 (3.6)	0.255
Cancer	6 (10.9)	4 (14.3)	0.655
Central nervous system	23 (41.8)	10 (35.7)	0.591
Clinical signs			
Temperature [median (IQR)]	36.9 (36.6-37.6)	36.6 (36.2-36.7)	0.05
Heart rate [median (IQR)]	89 (72-102)	84 (69-97)	0.44
Respiratory rate [median (IQR)]	15 (15-15)	15 (15-15)	0.188
Systolic blood pressure [median (IQR)]	121 (110-137)	140 (122-158)	0.011
Diastolic blood pressure [median (IQR)]	66 (53-76)	80 (68-93)	0.014
Oxygen saturation [median (IQR)]	95 (93-98)	98 (68-98.5)	0.639
Laboratory data			
White blood cell count (ml/mm3) [mean (SD)]	11.2 (6-16.8)	9.5 (6.6-12.7)	0.296
Creatinine (mg/dL) [median (IQR)]	1.19 (0.9-1.73)	1.13 (0.85-2.24)	0.806
Bilirubin (mg/dL) [median (IQR)]	0.9 (0.5-1.5)	0.8 (0.6-1.3)	0.952
Biomarkers			
C-reactive protein (mg/L) [median (IQR)]	11.5 (2.8-19.2)	0.94 (0.31-1.98)	<0.001
Procalcitonin (mg/dL) [median (IQR)]	0.28 (0.15-2.57)	0.10 (0.04-0.19)	0.001
Lactate (mg/dL) [median (IQR)]	1.7 (1.25-2.45)	1.3 (0.27-2.72)	0.730
Troponin (mg/dL) [median (IQR)]	0.02 (0.01-0.11)	0.19 (0.04-0.92)	0.009
MDW (U) [median (IQR)]	24.65 (22.06-30.22)	18.41 (16.72-19.50)	<0.001
Severity			
NEWS score [median (IQR)]	4 (3-5)	3 (2-4)	0.032
SOFA score [median (IQR)]	3 (2-3.5)	3 (2-4)	0.158
Outcomes			
ICU admission [n(%)]	6 (9.2)	3 (8.1)	0.848
Mortality [n(%)]	16 (24.6)	2 (5.4)	0.014

IQR: interquartile range; U: units; NEWS: National Early Warning Score; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit

Table 2 Performance of MDW to identify infection between severe patients evaluated in the Emergency Department

	Value	95% CI
Sensitivity	89.2	79.4-94.7
Specificity	89.2	75.3-95.7
Positive predictive value	93.5	84.6-97.5
Negative predictive value	82.5	68.0-91.3
LR (+)	8.25	3.26-20.91
LR (-)	0.12	0.06-0.24

LR (+): positive likelihood ratio; LR (-): negative likelihood ratio.

univariate analysis based on the diagnosis or not of infection. Statistically significant differences were observed in the temperature (higher in infected patients) and blood pressure (lower in infected patients). There were no differences in sex, age, or comorbidity between the two groups. Regarding severity, infected patients had a higher NEWS score, but there were no differences in the SOFA score. Table 1 also shows the biomarker results and the univariate analysis based on the diagnosis or not of infection. Infected patients had higher values of procalcitonin (PCT), C-reactive protein (CRP), and MDW, and lower troponin values. Regarding severity, the NEWS score was higher in infected patients while the SOFA score was similar in both groups.

An MDW cut-off of 20.115 provided the best accuracy to identify infected patients, with a Se of 89.2 (95% CI 79.4-94.7), a Sp of 89.2 (95% CI 75.3-95.7), a PPV of 93.5 (95% CI 84.6-97.5), a NPV of 82.5% (95% CI 68.0-91.3), an LHR+ of 8.25 (3.26-20.91), and an LHR- of 0.12 (0.06-0.24) (Table 2).

On comparing infected with non-infected patients, we observed a tendency of MDW (odds ratio [OR] 1.82 95%CI 0.93-3.58; p=0.08) to be significantly associated with infection (Figure 2). None of the other parameters evaluated (temperature, systolic or diastolic blood pressure, PCT, CRP, or troponin) achieved significance to identify this infected population.

The area under the ROC curve (AUROC) for infection using the MDW was 0.943 (95% CI 0.897-0.989; p<0.001), and 0.847 (95% CI 0.720-0.973; p=0.001) for PCT (Figure 3).

DISCUSSION

The MDW is a measure of monocyte anisocytosis and in this observational study it has shown good accuracy for the identification of infected patients in a cohort of severe patients attended in the ED. The best cut-off was 20.115 with a LHR+ of 8.25, a LHR- of 0.12, and an AUROC for infection of 0.943.

Diagnosis of Infection can be challenging. Multiple studies have described misdiagnosis during the initial approach in severe patients, leading to the initiation of unnecessary or erroneous treatments. Klein Klouwenberg *et al.* [27] reported that among patients admitted to the ICU for sepsis, 13% did not present an infectious disease and in the 30% it was only possible. The study concluded that the diagnosis of sepsis at admission corresponds poorly with the final diagnosis.

In clinical practice decision-making must not only be made based on biomarkers. Nonetheless, biomarkers are helpful tools for clinicians, since the use of only clinical evaluation may not be sufficiently accurate to establish the final diagnosis of the patient, especially in a setting such as the ED in which overcrowding is frequent. Our data show that MDW could be useful in a high-risk population, in which misdiagnosis could lead to erroneous treatment, and therefore, to poor patient outcomes.

The most important feature of a biomarker is its potential to change clinical decision-making. Likelihood ratios may be relevant for evaluating biomarkers and their usefulness for clinicians. An LHR+ between 5 and 10, and a LHR- between 0.1 and 0.2, indicates that the MDW has good performance to induce changes from pre-test probabilities to the final diagnosis, and thus, be clinically relevant [28]. MDW could provide information about the probability that a patient with a positive or negative test actually has or does not have infection.

Several previous studies have described the use of MDW as a screening tool for the early identification of patients at risk of sepsis in the ED [1,29,30], reporting improved detection of sepsis compared with the WBC count, CRP or SIRS, and concluding that MDW had the best discriminatory power for sepsis, based on either Sepsis-2 or Sepsis-3 criteria [14,16,17]. Piva *et al.* [31] showed that MDW values in ICU patients were significantly higher in patients with sepsis or septic shock compared to those within the non-sepsis group. In addition, increase in MDW values was not affected by the aetiology of sepsis, even in patients with COVID-19. A systematic review and meta-analysis including 10 studies including 9,475 individuals, 1,370 of whom had sepsis (742 according to Sepsis-2 and 628 according to Sepsis-3), described a pooled Se and Sp of 0.789 and 0.777 for Sepsis-2 criteria, and 0.838 and 0.704 for Sepsis-3 criteria, being data similar to that obtained in our study. The conclusion of this study was that MDW represents a reliable biomarker for the screening of sepsis [32].

The cut-offs used in these previous studies differed, ranging from 20-27, but this discrepancy can be explained by the different clinical settings in which the studies were performed or the type of study population included. The inclusion of MDW in guidelines defining its exact use and cut-off values as an early indicator of infection and sepsis is necessary since discrepancies have been observed in different studies. Another systematic review concluded that diagnostic thresholds for sepsis should be chosen taking into account the reference standard and tube type used [33]. The implementation of this biomarker in routine practice would require consensus.

PCT is the classical biomarker for the diagnosis of infection in current clinical practice, with several studies reporting the accuracy of PCT in the identification of bacterial infections

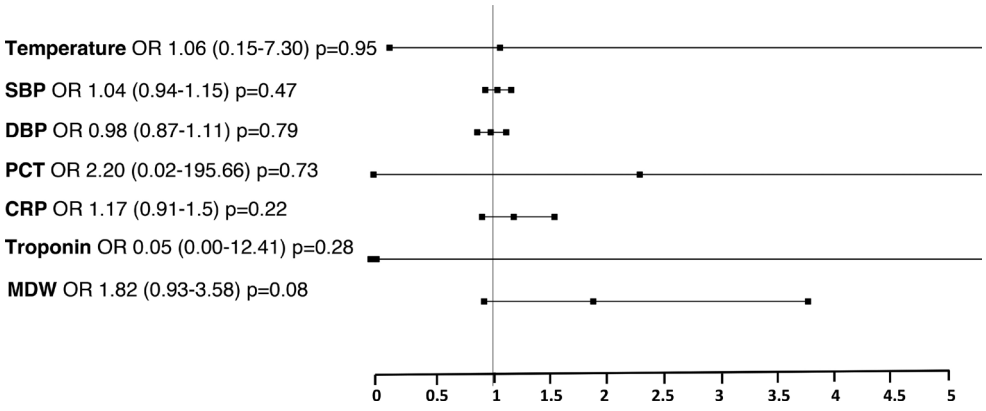
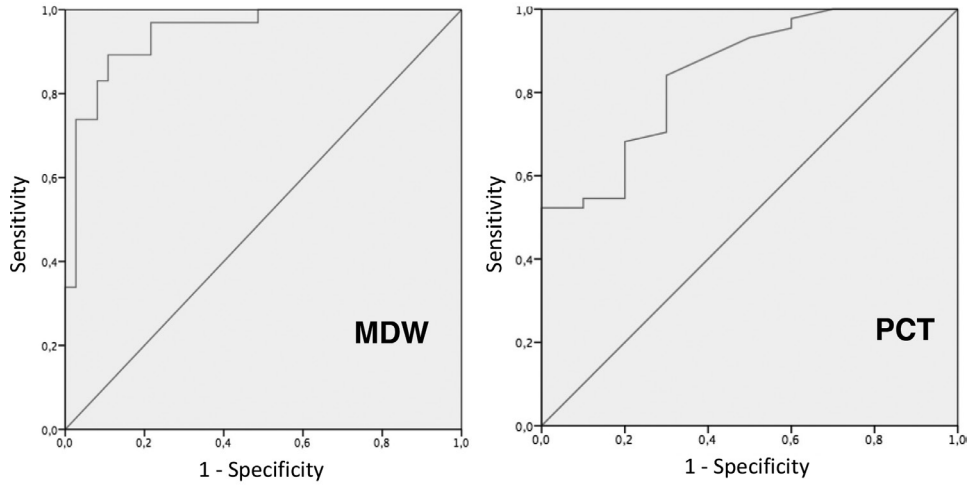


Figure 2 | **Identification of infection between severe patients attended in the Emergency department.**

SBP: systolic blood pressure; DBP: diastolic blood pressure; PCT: procalcitonin; CPR: C-reactive protein



	AUC	95% IC	P value
PCT	0.847	0.720-0.973	0.001
MDW	0.943	0.897-0.989	<0.001

Figure 3 | **ROC curve of MDW and PCT to identify infection between severe patients attended in the Emergency Department.**

and patients with bacteraemia. In our study, the AUROC to identify infected patients was higher for MDW than for PCT, albeit without statistical significance. Moreover, PCT levels provide clinicians with information about the patient´s prognosis or clinical response to antibiotic treatment and can even lead to a reduction in mortality and increase the use of short courses of antibiotics [5,6,34]. Therefore, PCT determination has several advantages compared with MDW, giving physicians additional information apart from the diagnosis. On the other hand, one of the main advantages when comparing MDW with other classical inflammatory markers is that it can be reported automatically. The CBC-Diff is routinely ordered in the ED, and thus, MDW can be determined using routine methods making it an economical, easy-to-use biomarker that can be readily available to clinicians. MDW determination does not require the collection of a different blood sample or any other special request and nor does it involve an extra cost or work. Consequently, the main advantages of MDW are the immediacy of results, accessibility in most centres, and low cost, resulting in high viability for inclusion in clinical practice. Moreover, MDW

values are elevated not only in bacterial infections, but also in virus, even in COVID-19, and fungal infections leading to the identification of infected patients and not only patients with bacterial infection [30]. Previous studies have shown that the MDW index could be a useful tool for early identification of patients at higher risk of unfavourable COVID-19 and for monitoring the progression of viral infection, clinical outcomes, and therapeutic efficacy throughout hospitalization [35].

Our study has some limitations. First, only 102 patients were included, which could influence some results. The OR of MDW for infection was 1.83 (0.93-3.58), which means there is no association between exposure and outcome. Nevertheless, a statistical trend to significance was observed (p=0.008) and the low OR may be a consequence of the limited sample size of our study. Second, this was a unicentric study which precludes the generalization of the results. However, it was performed in a university hospital, the characteristics of which have been previously described and are similar to the majority of European university hospitals. Third, its retrospective nature may limit the applications of some conclusions. Clinical trials are mandatory to change medical approaches, but this was only a pilot study that may be useful to design new studies along the same line and sample calculation.

The results of this pilot study, including severe patients attended in the ED, show that a MDW > 20.115 may be associated with the presence of infectious disease and could help to distinguish between infected and non-infected patients. A discrepancy between MDW levels and clinical approach could lead to clinicians to consider alternative diagnoses and avoid making erroneous initial diagnoses and treatments, which could lead to worse patient outcomes. The strength of this study is that it was performed in severe patients, in whom treatment decisions have a major impact on patient outcomes, including mortality. These results must be confirmed in new studies due to the limited sample of patients included.

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CONFLICT OF INTEREST

The authors declare no have conflict of interest

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