

Monocyte Distribution Width (MDW) as a New Tool for the Prediction of Sepsis in Critically Ill Patients: A Preliminary Investigation in an Intensive Care Unit

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Research

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Abstract

Background. Monocyte Distribution Width (MDW), a simple proxy marker of innate monocyte activation, can be used for the early recognition of sepsis along with Procalcitonin.

Objectives. To explore the added value of MDW as an early predictor of ensuing sepsis in patients hospitalised in an Intensive Care Unit.

Methods: We performed an observational prospective monocentric study to estimate the analytical performance of MDW in detecting ensuing sepsis in a sample of consecutive patients assisted in an Intensive Care Unit for >48h for any reason. Demographic and clinical characteristics, past medical history and other laboratory measurements were included as potential predictors of confirmed sepsis in multivariate logistic regression.

Results: A total of 211 patients were observed, 129 of whom were included in the final sample due to the suspect of ensuing sepsis; of these, 74 (57%) had a confirmed diagnosis of sepsis, which was best predicted with the combination of MDW>23.0 and PCT>0.5 ng/mL (Positive predictive value, PPV: 92.6, 95%CI: 82.1-97.9). The best MDW cut-off to rule out sepsis was ≤ 20.0 (Negative predictive value, NPV: 86.4, 95%CI: 65.1-97.1). Multivariate analyses using both MDW and PCT found a significant association for MDW>23 only (OR:17.64, 95%CI: 5.53-67.91).

Conclusions: We found that values of MDW>23 were associated with a high PPV for sepsis, whereas values of MDW <20 were associated with a high NPV. Our findings suggest that MDW may help clinicians to monitor ICU patients at risk of sepsis, with minimal additional efforts over standard of care.

Introduction

Approximately 5 to 10% of septic patients are directly hospitalized to an Intensive Care Unit (ICU) because of septic shock, while 8–10% of all patients admitted in the ICU may be at risk of developing sepsis or septic shock during their hospital stay [1–4]. Sepsis has been reported as a major cause of increased morbidity, length of stay, and mortality among patients hospitalized in ICU for any cause [3, 5]. The risk of developing sepsis is often associated with pre-existing chronic medical conditions, e.g. diabetes, chronic inflammatory or immune disorders, obesity, cancer and heart diseases [5]. The survival of patients developing sepsis in the ICU is strictly related to early diagnosis, as well as to a prompt start of appropriate medical interventions [2, 3]. The early recognition of sepsis may be hampered by the ambiguous clinical features and by the low sensitivity and specificity of current laboratory biomarkers. As a consequence, defining new strategies for an efficient and timely diagnosis of sepsis, both at ICU admission and during ICU stay, is a well-recognized research priority [2, 6]. Several methods have been proposed for the identification of sepsis and the stratification of risk in ICU patients. Updated guidelines for sepsis management (SEPSIS-3) recommend the use of SOFA (Sequential Organ Failure Assessment) score, in order to recognize ensuing sepsis [3]. Among biomarkers of sepsis, procalcitonin (PCT) is acknowledged as the single best parameter for patients in the ICU [6–8]. Daily or twice-daily assessments

recently improved sensitivity and drove therapy de-escalation [2, 9, 10]. Even with serial PCT measurements, however, sensitivity and specificity in the prediction of sepsis were not higher than 75% [11, 12]. Serial presepsin measurements were lately suggested to complement PCT, with additional costs [13]. Several limitations, however, including the impact of renal function and immune status on physiological variations of presepsin levels, hampered both standardization and scale up of presepsin use [14].

Recent evidence highlighted the potential role of Monocyte Distribution Width (MDW), a relatively simple proxy of innate monocyte response to bacterial or fungal bloodstream invasion, as a convenient biomarker for early recognition of sepsis [15]. Monocytes are known to increase their size upon activation in bacteriemic or fungemic patients; as a consequence, measuring the spread of monocyte size in reading chambers of new generation hematologic analyzers represents a new potential tool to monitor ensuing sepsis [15]. We already showed the potential benefit of MDW evaluations to diagnose sepsis in patients admitted to an Infectious Diseases Ward [16].

In the present study, we investigated whether adding MDW monitoring to serial PCT evaluations may rise the ability to detect ensuing sepsis in patients hospitalized in our ICU for any reason.

Patients And Methods

Design of the study

We performed an observational, prospective study for the estimation of analytical performance of MDW in recognition of sepsis or septic shock in patients hospitalized at the ICU of the General Hospital of Pescara (Abruzzo, Italy). The hospital is an urban 650-bedded tertiary facility of regional reference for adult traumas and acute diseases of neurosurgical interest. The ICU facility is a single, 11-bed unit, receiving critically ill patients from regional emergency departments, as well as from medical and surgical units in the hospital. The study was conducted in accordance with the amended Declaration of Helsinki. The local Health Administrative Board reviewed in detail the study plan prepared by the ICU and Laboratory Staff of the Pescara General Hospital. General written informed consent was available from all patients upon hospital admission, authorising the use of anonymised clinical and laboratory data for institutional research purposes. Specific informed consent was not considered required, as confidentiality was guaranteed and no specific interventions were performed beyond the ordinary good standard clinical practices (measurement of blood cell volumes and indices). Data were collected between January 1st, 2018 and December 31st, 2018 for all patients admitted to the above described ICU. To avoid inclusion of patients destined to short-term ICU stay, patients were consecutively enrolled after 48 h of hospitalization in the ICU. Demographic and clinical characteristics of patients, past medical history, and laboratory measurements were collected. During the follow-up period, enrolled patients who died from any cause were classified as non-survivors. We focused our analysis on patients with a suspicion of sepsis during stay at the ICU, comparing those with and without a confirmed diagnosis of sepsis according to the following definitions.

Definitions

Sepsis and septic shock were diagnosed according to the diagnostic criteria of the Sepsis-3 classification (2016) [3]. Criteria for organ dysfunction were: sepsis-induced hypotension; lactate above normal upper limits; urine output < 0.5 mL/kg/h for > 2 h despite adequate fluid resuscitation or creatinine > 2.0 mg/dL (176.8 µmol/L); acute lung injury, with PaO₂/inspired oxygen fraction (FiO₂) < 250 mmHg in the absence of pneumonia or acute lung injury with PaO₂/FiO₂ < 200 mmHg in the presence of pneumonia; bilirubin > 2.0 mg/dL (34.2 µmol/L); platelet counts < 100,000/mm³.

Microbiological definitions and methodology

Gram negative alert organisms considered were: meropenem/imipenem resistant *Klebsiella pneumoniae*; meropenem/imipenem resistant *Pseudomonas aeruginosa*; meropenem/imipenem resistant *Acinetobacter baumannii*. Gram positive alert organisms were methicillin resistant *Staphylococcus aureus* and methicillin resistant *Coagulase Negative Staphylococcus*. Identification and sensitivity assays were performed at the central Microbiology Unit, Pescara General Hospital, using the Vitek2 system (bioMérieux, France), Accelerate Pheno Test (Accelerate Diagnostics, US), GeneXpert (Cepheid, US), as well as disc diffusion methods and agar MIC determinations (antibiotic discs and MIC test strips by Liofilchem, Italy) according to the EUCAST 2017 guidelines. All methods were not modified across the study period.

Laboratory parameters and MDW determination

Blood cell counts (Red Blood Cells, RBC; White Blood Cell Count, WBC; Hemoglobin, HGB; Hematocrit, HCT; Mean Cell Volume, MCV; Mean Cell Hemoglobin Concentration, MCHC; Mean Platelet Volume, MPV; Platelet Cell Width, PDW; Red Cell Distribution Width, RDW), platelet indices and MDW determinations were analyzed with the hematologic analyzer UniCel DxH800 (Beckman Coulter, Inc, Brea, California). Monocyte distribution width (MDW) was measured as described in Chaves et al. (2005) [17]. Briefly, MDW is estimated in the adult population utilizing Volume, Conductivity, and Scatter (VCS) technologies. VCS parameters can detect morphologic changes in immature and reactive cells, similarly to microscopic evaluation of a peripheral blood smear. MDW was analyzed on the first blood sample at hospital entry and then every day with the daily control of Complete Blood Count (CBC); MDW values were omitted in medical reports, because they were assessed for research purposes only, and were retrieved for statistical analyses. Values of MDW were paired with PCT values for monitoring of sepsis in ICU patients. All determinations of MDW were obtained from a K3EDTA whole-blood venous sample, assayed within 2 hours of collection, in the same tubes of blood used for other CBC determinations. Turnaround time for such measurements was within the time of CBC counts. Quality control was performed by monitoring performances of diagnostic processes using commercial controls. Controls with known characteristics were analyzed daily in the same way as samples, and results of the analyzed controls were compared with standard characteristics using statistical methods calculated by the same instrument. Quality control of CBC and cell population data including MDW were performed daily with both COULTER® 6C Cell Control, enabling monitoring of system performance for all directly measured and calculated

parameters, and COULTER LATRON CP-X Control, a suspension of stable polystyrene particles of uniform size with a diameter CV \leq 3.0%. Latron CP-X was used as part of the daily quality control procedure, to monitor the stability of the electrical processing and the fluidic flow rate systems used to measure the volume, conductivity and light scattering characteristics of cells as they pass through the flow cell. COULTER S-CAL Calibrator was used in the UniCel DxH800 to determine the calibration factors for directly measured CBC parameters; differential blood counts were not required. Cell Population Data parameters were derived from monocytes and lymphocytes and use of a calibrator was not required. Producers of hematological analyzers do not provide any unit for MDW and other positional parameters, as previously published [18, 19]. Positional parameters derive from an algorithmic application that transforms femtoliters in positions on the x-axis of the scatterplot, of entity proportionate to the value of the cell volume [16].

Statistical analysis

All results were analysed using the confirmed status of sepsis as the main outcome of interest. The following demographic and clinical factors were used for descriptive analysis: age, gender, presence of comorbidity, SOFA score, SAPS II (Simplified Acute Physiology Score) score, previous antibiotic exposure (defined as treatment for at least one week with either quinolone, beta-lactam, or carbapenem prescribed in the month preceding hospitalization), previous surgery (defined as surgery in the month preceding ICU admission or during ICU stay), blood counts, other available biomarkers of sepsis (PCT in nearly all cases) and microbiological isolates, including Multi Drug Resistant Organisms, MDRO(s).

Significance levels and 95% confidence intervals were based on an alpha = .05. The differences between patients with or without confirmed sepsis were tested using chi-square for categorical variables, while t-student and non-parametric Kruskal–Wallis rank tests were used for normal and non-normal continuous variables respectively [20].

The reliability of MDW and PCT in predicting sepsis was investigated through ROC analysis of varying thresholds, including the calculation of sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and the Area Under the Curve (AUC) [21]. Optimal thresholds for MDW and PCT were defined as those achieving the maximum value of Youden index. Cut-offs for ROC analysis were defined based upon the results obtained from the maximum level above, as well as from previous literature, including a value of 20.0 for high NPV to rule out sepsis [15, 16] and 22.0 as the best statistical cut-off for the prediction of sepsis [16, 22]. ROC curves were produced along with their 95% confidence bands, using all possible cut-offs of MDW and PCT. The De Long's test for two correlated ROC curves was used to test the significance of the difference in terms of AUC. The level of association between different combinations of optimal thresholds for MDW, PCT and a confirmed status was sepsis was measured using odds ratios with 95% confidence intervals, adjusting for relevant demographic and clinical characteristics using multivariate logistic regression [23]. All analyses were performed using the R statistical language [24].

Results

The total population of consecutive patients entering the ICU in the reference period included N = 211 patients; of these, N = 31 (14.6%) patients were excluded because of underlying conditions potentially associated with immune dysregulation, as AIDS (N = 6), recent bone marrow transplantation (N = 5), malignancy (N = 12) and other haematologic diseases (N = 8), all possibly influencing monocyte size and activation in response to infection [15]. The main diagnoses for N = 180 patients included in the study cohort are shown in Table 1. The most frequent causes of admission in ICU were intracerebral haemorrhage (17.8%), cardiovascular failure (14.4%); polytrauma (12.8%); respiratory failure (11.1%) and stroke (8.9%). A total of N = 51 patients were excluded from the target study group as they did not show signs of suspected sepsis during their ICU stay.

Table 1
Main diagnoses at ICU admission [N (%)]

	Study Cohort	Target sample
Diagnosis	(n = 180)	(n = 129)
Intracerebral haemorrhage	32 (17.8)	24 (18.6)
Cardiovascular failure	26 (14.4)	19 (14.7)
Polytrauma	23 (12.8)	19 (14.7)
Respiratory failure	20 (11.1)	11 (8.5)
Acute ischemic Stroke	16 (8.9)	12 (9.3)
Acute kidney failure	10 (5.6)	5 (3.9)
Head trauma	9 (5.0)	6 (4.7)
Brain surgery	9 (5.0)	5 (3.9)
Acidosis in metformin use	5 (2.8)	3 (2.3)
Septic shock	4 (2.2)	4 (3.1)
Hemorrhagic shock	4 (2.2)	3 (2.3)
Peritonitis	3 (1.7)	3 (2.3)
Acute pancreatitis	2 (1.1)	2 (1.5)
Coma in encephalitis	2 (1.1)	2 (1.5)
Consequence of Duodeno-cephalo-Pancreatectomy	1 (0.6)	1 (0.8)
Anaphylactic shock	1 (0.6)	1 (0.8)
Other	13 (7.2)	9 (7.0)

Alongside N = 4 patients with septic shock at ICU presentation, additional N = 125 patients presented a suspicion of sepsis during hospitalization. Therefore, N = 129 patients, forming the target sample for the present investigation, underwent blood cultures and other microbiological and biochemical assays. Their baseline characteristics were in fair overlap with those of the whole study cohort.

Demographic and clinical characteristics of patients included in the target sample are reported along with laboratory parameters in Table 2.

Table 2
Demographics, Clinical characteristics and laboratory parameters of the target sample*

	Sepsis		Target Sample	
Variables	No	Yes		p
N	55 (43.0)	74 (57.0)	129 (100.0)	
<i>Categorical [N (%)]</i>				
Male Gender	32 (58.0)	50 (68.0)	82 (63.6)	0.270
Septic shock	-	21 (28.4)	21 (16.3)	-
Bacteremia	5 (9.0)	53 (72.0)	58 (45.0)	< 0.001
Mortality	11 (20.0)	30 (40.5)	41 (31.8)	0.010
<i>Continuous Normal [mean (SD)]</i>				
Age, years	63.11 (17.40)	61.86 (16.06)	62.40 (16.61)	0.680
CCI	3.40 (2.50)	3.42 (2.30)	3.41 (2.40)	0.960
SAPS II [†]	49.13 (13.70)	49.07 (16.07)	49.09 (15.06)	0.980
SOFA [†]	6.22 (2.95)	7.99 (3.71)	7.23 (3.51)	0.004
SOFA ^{††}	6.13 (2.69)	8.06 (3.63)	7.63 (3.52)	0.058
Length of stay at ICU (days)	11.49 (6.96)	14.09 (9.96)	12.98 (8.87)	0.099
<i>Continuous Non Normal [median (IQR)]</i>				
MDW	21.00 (20.00-22.30)	25.60 (23.10-29.00)	23.00 (21.00-27.00)	< 0.001
PCT, ng/mL	0.21 (0.12-0.96)	4.15 (0.60-27.00)	0.95 (0.19-10.20)	< 0.001
CRP, mg/L	108.60 (41.64-161.71)	123.73 (60.57-218.13)	118.96 (55.28-190.70)	0.070
WBC*10 ³ /μL	10.35 (8.15-14.50)	10.90 (7.80-15.80)	10.80 (8.00-15.40)	0.950
*CCI: Charlson Comorbidity Index; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; PCT: Procalcitonin; CRP: C-Reactive Protein; MDW: Monocyte Distribution Width; WBC: White Blood Cell Count; [†] at ICU admission; ^{††} at sepsis diagnosis, available for 58 patients.				

Significant differences between patients with and without sepsis were found for mortality rates (40.5% vs 20.0% $p = 0.01$), average SOFA score at entry (7.99 vs 6.22, $p = 0.004$), median values of PCT (4.15 ng/mL vs 0.21 ng/mL, $p < 0.001$) and MDW (25.6 vs 21.0, $p < 0.001$). No association was found for age, male gender, Charlson Comorbidity Index (CCI), WBC, C-Reactive Protein (CRP) and length of stay (Table 2).

The summary ROC curves based upon all possible cut-offs of MDW, PCT, along with their superimposed confidence intervals, are shown in Fig. 1. The values of AUC achieved for both parameters showed to be rather comparable, with MDW achieving AUC = 0.84 (95%CI: 0.77–0.91) slightly above PCT, at an overall value of AUC = 0.81 (95%CI: 0.73–0.88). Levels of accuracy for alternative thresholds of MDW and PCT are shown in Table 3. Optimal thresholds according to the Youden index were found for MDW = 23.0 and PCT = 0.5 ng/mL, respectively.

Table 3
Results of ROC analysis of dichotomized values in the prediction of sepsis

Test predictors	N (%)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	AUC (95%CI)
MDW > 20.0	126 (97.0)	95.9 (88.5– 99.1)	35.8 (23.1– 50.2)	67.3 (57.4– 76.2)	86.4 (65.1– 97.1)	0.66 (0.59– 0.73)
MDW > 22.0	126 (97.0)	79.5 (68.4– 88.0)	71.7 (57.7– 83.2)	79.5 (68.4– 88.0)	71.7 (57.7– 83.2)	0.76 (0.68– 0.83)
MDW > 23.0	126 (97.0)	75.3 (63.9– 84.7)	88.7 (77.0– 95.7)	90.2 (79.8– 96.3)	72.3 (59.8– 82.7)	0.82 (0.75– 0.89)
PCT > 1*	128 (99.2)	64.9 (52.9– 75.6)	77.8 (64.4– 88.0)	80.0 (67.7– 89.2)	61.8 (49.2– 73.3)	0.71 (0.63– 0.79)
PCT > 0.5*	128 (99.2)	77.0 (65.8– 86.0)	70.4 (56.4– 82.0)	78.1 (66.9– 86.9)	69.1 (55.2– 80.9)	0.74 (0.66– 0.82)
MDW > 20.0 and PCT > 0.5*	126 (97.0)	74.0 (62.4– 83.5)	77.8 (64.4– 88.0)	81.8 (70.4– 90.2)	68.9 (55.7– 80.1)	0.76 (0.68– 0.83)
MDW > 22.0 and PCT > 0.5*	126 (97.0)	71.2 (59.4– 81.2)	88.9 (77.4– 95.8)	89.7 (78.8– 96.1)	69.6 (57.3– 80.1)	0.80 (0.73– 0.87)
MDW > 23.0 and PCT > 0.5*	126 (97.0)	68.5 (56.6– 78.9)	92.6 (82.1– 97.9)	92.6 (82.1– 97.9)	68.5 (56.6– 78.9)	0.80 (0.74– 0.87)
PCT: Procalcitonin; MDW: Monocyte Distribution Width; PPV: Positive Predictive Value; NPV: Negative Predictive Value, *unit of measurement: ng/mL						

Sensitivity was highest for MDW > 20.0 (95.9; 95%CI: 88.5–99.1), while specificity was best for MDW > 23.0 and PCT > 0.5 ng/mL (92.6; 95%CI: 82.1–97.9). The De Long test did not reject the hypothesis of a true difference in AUC equal to zero ($Z = 1.0296$, $p = 0.30$, Fig. 1). The best cut-offs to predict sepsis were MDW > 23.0 and PCT > 0.5 ng/mL (PPV: 92.6, 95%CI: 82.1–97.9), whereas the best cut-off to rule out sepsis was MDW < 20.0 (NPV: 86.4, 95%CI: 65.1–97.1).

In terms of AUC, high values were found for MDW > 23.0 (0.82; 95%CI: 0.75–0.89), MDW > 22.0 and PCT > 0.5 ng/mL (0.80; 95%CI: 0.73–0.87) and MDW > 23.0 and PCT > 0.5 ng/mL (0.80; 95%CI: 0.74–0.87). Multivariate analyses were run using three different logistic regression models including age, male gender, CCI, SAPS II, SOFA at entry as adjustment terms. Results are shown in Table 4. Although no adjusting terms were found to be significantly associated with the outcome, they were left in the model to make sure that the ORs calculated for different combinations of MDW and PCT were taking into account all relevant potential confounders. The models showed different predictive values for selected combinations of thresholds of MDW and PCT. In particular, Model 1 found a significant association for MDW > 23 (OR: 22.65, 95%CI: 8.28–73.70), while Model 2 found a significant association for PCT > 0.5 ng/mL (OR: 7.26, 95%CI 3.05–18.46). When using both terms in the multivariate logistic regression, Model 3 still found a significant association for MDW > 23 (OR:17.64, 95%CI: 5.53–67.91), but a non-significant result for PCT > 0.5 (OR:1.58, 95%CI: 0.46–5.09, Table 4).

Table 4
Results of Logistic regression models to predict the status of confirmed sepsis in the sample

	Model 1		Model 2		Model 3	
Variables	OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
Age	1.00 (0.95–1.04)	0.8459	1.02 (0.98–1.07)	0.2944	1.00 (0.95–1.05)	0.9284
Male gender	2.30 (0.78–7.36)	0.1397	1.62 (0.66–4.10)	0.2952	2.30 (0.78–7.44)	0.1419
CCI	1.00 (0.73–1.38)	0.9899	0.85 (0.62–1.15)	0.2833	0.97 (0.69–1.35)	0.8366
SAPS II	0.98 (0.93–1.03)	0.4172	0.97 (0.93–1.01)	0.0924	0.98 (0.93–1.03)	0.4042
SOFA at entry	1.18 (0.98–1.46)	0.0963	1.24 (0.04–1.51)	0.0196	1.17 (0.96–1.45)	0.1337
MDW > 23	22.65 (8.28–73.70)	0.0000	-	-	17.64 (5.53–67.91)	0.0000
PCT > 0.5 ng/mL	-	-	7.26 (3.05–18.46)	0.0000	1.58 (0.46–5.09)	0.4527

We also calculated sensitivity, specificity, PPV and NPV of different MDW cut offs for the prediction of positive blood cultures. Best sensitivity and specificity were obtained for MDW values < 20 and > 23, respectively (Table 5). In terms of AUC, highest values were found for MDW > 22.0 (0.72; 95%CI: 0.64–0.79). Notably, at a cut off of 20, the NPV reached 100%, since all bacteremic patients had MDW values > 20.

Table 5
Results of ROC analysis of values of MDW in the prediction of positive blood cultures

Variables	N	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	AUC (95%CI)
MDW > 20	126	100.0 (93.6–100.0)	31.4 (20.9–43.6)	53.8 (43.8–63.7)	100.0 (84.6–100.0)	0.66 (0.60–0.71)
MDW > 21	126	92.9 (82.7–98.0)	44.3 (32.4–56.7)	57.1 (46.3–67.5)	88.6 (73.3–96.8)	0.69 (0.62–0.75)
MDW > 22	126	82.1 (69.6–91.1)	61.4 (49.0–72.8)	63.0 (50.9–74.0)	81.1 (68.0–90.6)	0.72 (0.64–0.79)
MDW > 23	126	71.4 (57.8–82.7)	70.0 (57.9–80.4)	65.6 (52.3–77.3)	75.4 (63.1–85.2)	0.71 (0.63–0.79)

Discussion

Improvements in the management of sepsis in critically ill patients may yield a better quality of care [25]. In this study, we found that MDW helped early identification of sepsis in patients hospitalized in the ICU. Notably, the ROC curve analysis highlighted that using the combined cut-offs of MDW > 23.0 and PCT > 0.5 ng/mL yielded a PPV of 92.6% for sepsis, whereas a MDW cut-off of 20 alone had a NPV of 86.4%. Previous studies showed that changes in volume of monocytes are a well-documented consequence of monocyte activation upon bloodstream infections as part of innate immunity response [25, 26]. To date, four large clinical studies investigated the ability of MDW to predict sepsis, but they enrolled only patients in Emergency Departments [15, 22, 28, 29]. Crouser et al. demonstrated that MDW was able to discriminate sepsis from SIRS and that the magnitude of MDW elevations correlated with infection severity and organ dysfunction, with MDW values rising in parallel with the severity of ensuing sepsis [15]. Recently, Crouser et al (2020) demonstrated that inclusion of MDW during the initial evaluation of ED patients may enhance the odds of early sepsis detection by 6-fold for Sepsis-2 and 4-fold for Sepsis-3 assessments [28]. An additional prospective study described, for the first time, the ability of MDW to predict sepsis in a cohort of 260 consecutive patients hospitalized in an Infectious Diseases ward. In this study, the authors demonstrated that the AUCs of MDW and PCT overlapped in predicting sepsis [16]. In the present study, we followed a cohort of consecutive patients hospitalized in the Pescara General Hospital ICU, in order to evaluate the possible role of MDW in recognizing sepsis during hospital stay. Indeed, it is well known that body temperature, heart rate, as well as organ function and tissue perfusion, are frequently abnormal in this setting for reasons different from ensuing sepsis, and in many ICU

patients systemic inflammation and bacterial colonization at a single or even multiple sites are common conditions, per se not meaning ensuing sepsis [3, 29, 30]. In such patients, it is crucial to establish when empirical antimicrobials should be started, as microbiological assays often require, even under the best established diagnostic work plans, hours to days to provide their results, which may be relevant in unstable patients [31]. Inflammatory biomarkers, determined daily throughout the patient's stay, may be potentially useful to pick up early ensuing sepsis in ICU patients [8, 32, 33]. To date, PCT was documented as the best biochemical marker, with a large base of evidence supporting PCT-guided therapy de-escalation and outcome prediction. The ability of PCT to detect sepsis when creeping in a critical patient, however, is still a matter of debate, with a PPV not higher than 75% in all published series [4, 34–40]. As a consequence, we compared the AUC of MDW and PCT for PPV and NPV of these two biomarkers, revealing that MDW had better AUC than PCT, although this difference did not reach a clear statistical significance. Additionally, we found that different combinations of thresholds for MDW and PCT may predict sepsis efficiently (Table 3), as combining MDW at a threshold of 23 and PCT at a threshold of 0.5 ng/mL, the PPV rose to an unprecedented 92.6%, as this result was never reported so far for PCT alone. In addition, we also demonstrated that all patients with MDW < 20 had invariably negative blood cultures, with a NPV of 100% for bacteremia. Interestingly, our procedure can be extremely convenient to improve the surveillance of sepsis, as MDW values can be provided daily by a haematological analyser used for checking ordinary parameters of blood cell counts, in the run of only few minutes, so that even serial determinations during the ICU stay of patients may well be considered free of any additional cost. These findings suggest that MDW can significantly help identifying sepsis among critically ill patients in clinical practice. Although the adoption of MDW as a tool for the detection of sepsis in the ICU may already appear as appealing and efficient in view of our present results, further prospective studies are necessary to support and confirm the results of our exploratory investigation. Indeed, several limitations of our study design should be considered. First, despite of our diagnoses of sepsis were based on current Sepsis-3 standards, a misclassification may have occurred in some cases. Nevertheless, this problem should not have affected the significance of our results, due to the combined use of both MDW and PCT on the same patients. Second, the study involved a limited number of patients, enrolled at a single ICU, which may cast issues on the generalisability of our results, due to variations in clinical practices. However, the demographic, clinical and laboratory characteristics of target patients were comparable with those of patients assisted under the same conditions in most western countries [41]. Third, the composition of the target sample was clearly affected by the specific exclusion criteria that were used. In particular, the immune status of the excluded conditions, e.g. acquired immunodeficiency, long term steroid or other immune suppressive treatments, may influence monocyte volumetric variations upon bloodstream infections, thus limiting, once more, the generalisability of our results.

Conclusions

We explored the potential value of MDW as a new and easy-to-obtain biomarker of ensuing sepsis in the ICU, finding an optimal threshold of MDW > 23 with a high (> 90%) PPV in combinations with values of PCT > 0.5 ng/mL. Further prospective and multicentric investigations are needed to validate the role of

MDW, testing the same hypothesis in broader populations and different practices, possibly within a wider array of inflammation parameters and biomarkers.

Abbreviations

CCI: Charlson Comorbidity Index; SAPS: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment; PCT: Procalcitonin; CRP: C-Reactive Protein; MDW: Monocyte Distribution Width; ICU: Intensive Care Unit; CBC: Complete Blood Count; PPV: Positive Predictive Value; NPV: Negative Predictive Value.

Declarations

Ethics approval and consent to participate:

The study was conducted in accordance with the amended Declaration of Helsinki. The local Health Administrative Board reviewed in detail the study plan prepared by the ICU and Laboratory Staff of the Pescara General Hospital.

Consent for publication:

Specific informed consent was not considered required, as confidentiality was guaranteed and no specific interventions were performed beyond the ordinary good standard clinical practices (measurement of blood cell volumes and indices).

Availability of data and materials:

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

Authors declare no conflicts of interest related to this manuscript content.

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Authors' contributions:

E.P., G.P. and A.F. contributed to the study design, data extraction, quality assessment and writing of the manuscript. D.I.G., J.E.E., A.S. and G.G. retrieved clinical data and prepared the datasets for analysis. F.C. analysed and interpreted data, and contributed in writing the manuscript. E.P., G.P. and A.F. contributed in writing and revising the manuscript for important intellectual content. All authors approved the final manuscript.

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Figures

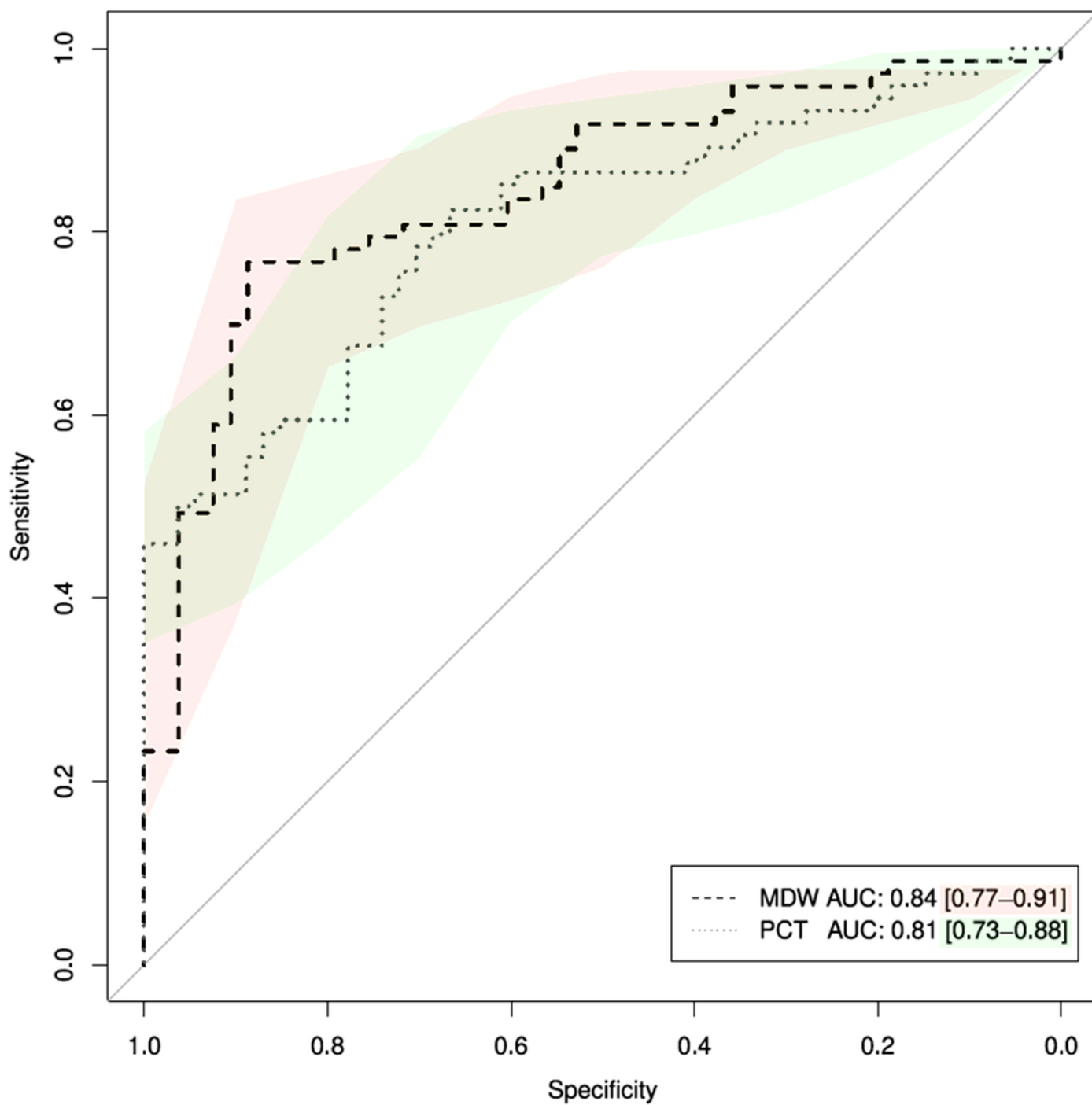


Figure 1

ROC curves comparing the overall prediction levels of different combinations of MDW, PCT