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Clinical Performance of Monocyte Distribution Width for Early Detection of Sepsis in Emergency Department Patients: A Prospective Study

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Dear Editor,

Most patients with sepsis are admitted through the emergency department (ED), and their outcome is significantly worse if the diagnosis and treatment are delayed [1, 2]. Therefore, early detection and treatment of sepsis are important in ED patients. Monocyte distribution width (MDW) is increased in patients with sepsis, making it a potential marker for the early diagnosis of sepsis [3, 4]. MDW is a measurable marker that can be obtained simultaneously with complete blood count (CBC). Thus, results can be obtained quickly, and additional blood collection from the patient for sepsis evaluation is not required. We evaluated the usefulness of MDW in predicting sepsis or septic shock using the Sepsis-3 criteria in patients visiting the ED [5].

We enrolled 1,234 Korean patients aged >18 years with a fever of ≥37.5°C and/or symptoms such as hypotension and mental deterioration, whose initial evaluation included CBC and C-reactive protein (CRP) tests on suspicion of infection, conducted within two hours of presenting to the ED at Haeundae Paik Hospital, Busan, Korea, between May and August 2019. This study was approved by our Institutional Review Board (HPIRB 2018-12-003), and the requirement for informed consent was waived because there is less than minimum risk to patients when using surplus samples. Samples for CBC, white blood cell (WBC) differential count, and MDW were collected in K_2-EDTA tubes (Becton Dickinson, Plymouth, UK) and analyzed in a UniCel DxH 900 analyzer (Beckman Coulter, Inc., Brea, CA, USA). CRP and procalcitonin were measured from sera obtained by the centrifugation of samples collected in VACUETTE® CAT Serum Separator Clot Activators (Greiner Bio-One GmbH, Kremsmünster, Austria) at 1,680 ×*g* for 10 minutes. CRP was analyzed using Hitachi 7600 instrument (Hitachi, Tokyo, Japan) and Nanopia CRP (Sekisui Medical Co., Ltd., Tokyo, Japan), and procalcitonin was analyzed using cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) and Elecsys BRAHMS Procalcitonin (Roche Diagnostics GmbH). All procedures were performed according to the manufacturers' instructions. For statistical analyses, the chi-square test or Fisher's exact test was used for categorical variables, and the Mann–Whitney U test or Kruskal–Wallis test was used for continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to assess the sensitivity and specificity of MDW and blood count parameters to predict sepsis and septic shock. Optimal cut-offs for MDW and other laboratory markers were estimated using the classical Youden index. All statistical analyses were carried out using SPSS version 24.0 (IBM Corp., Armonk, NY, USA), and $P<0.05$ was considered statistically significant.

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Table 1. Comparison of demographics and laboratory biomarkers among three patient groups according to the Sepsis-3 criteria

Variable	Enrolled (N = 1,234)	No sepsis (N = 1,152)			Sepsis‡ (N = 67)	Septic shock§ (N = 15)	P‖	P¶
		No infection (N = 1,021)		Infection† (N = 131)				
		No SIRS (N = 954)	SIRS* (N = 67)					
Male sex	607 (49.2)	468 (49.1)	41 (61.2)	56 (42.7)	36 (53.7)	6 (40.0)	0.704	0.336
Age (yr)	64 (50–76)	63 (49–76)	60 (48–76)	66 (44–80)	72 (61.5–80)	70 (62.5–77.5)	< 0.001	0.598
Death	22 (1.8)	13 (1.4)	1 (1.5)	1 (0.8)	4 (6.0)	3 (20.0)	< 0.001	0.079
CRP (mg/L)	3.80 (1.00–42.50)	2.00 (0.60–10.50)	1.00 (0.50–6.20)	69.30 (17.10–130.70)	126.40 (56.80–196.30)	122.80 (80.60–156.50)	< 0.001	0.966
Procalcitonin (μg/L)	0.11 (0.04–0.46)	0.05 (0.03–0.16)	0.21 (0.03–1.29)	0.14 (0.05–0.41)	0.51 (0.13–1.54)	2.59 (1.13–8.91)	< 0.001	0.506
WBC, $\times 10^9$/L	7.77 (6.05–10.50)	7.26 (5.84–9.43)	11.10 (7.08–14.60)	10.77 (7.88–13.70)	10.90 (7.34–14.57)	16.49 (10.86–20.11)	< 0.001	0.083
Neutrophils, $\times 10^9$/L	5.18 (3.57–7.87)	4.66 (3.45–6.79)	7.79 (4.30–12.32)	8.38 (5.70–11.43)	8.91 (5.86–12.73)	14.24 (8.75–16.95)	< 0.001	0.064
Monocytes, $\times 10^9$/L	0.55 (0.41–0.73)	0.52 (0.40–0.68)	0.66 (0.50–0.98)	0.58 (0.44–0.95)	0.74 (0.53–0.91)	0.74 (0.31–1.11)	< 0.001	0.569
MDW	18.43 (16.78–21.25)	17.92 (16.53–19.77)	17.88 (16.62–20.82)	23.72 (21.15–27.35)	24.75 (22.06–28.71)	32.42 (26.44–35.90)	< 0.001	0.002

Values are presented using frequencies (percentages) for categorical data and medians (interquartile range) for continuous data.
*SIRS was confirmed if two or more criteria were present: temperature > 38°C or < 36°C, heart rate > 90/min, respiratory rate > 20/min or $PaCO_2$ < 32 mmHg, WBC count > 12.00×10^9/L or < 4.00×10^9/L, or > 10% immature bands; †Infection was determined using clinical data from cultures and relevant imaging studies performed within two days of ED admission; ‡Sepsis was defined as life-threatening organ dysfunction identified by a total SOFA score of ≥ 2 points consequent to the infection, based on the Sepsis-3 criteria [5]; §Septic shock was defined as sepsis with hypotension requiring vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and hyperlactatemia with serum lactate level of > 2 mmol/L despite adequate volume resuscitation; ‖*P* for comparison between no sepsis and sepsis plus septic shock; ¶*P* for comparison between sepsis and septic shock.
Abbreviations: SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; WBC, white blood cell; MDW, monocyte distribution width; SOFA, sequential organ failure assessment.

All laboratory markers associated with sepsis, including MDW, were higher in patients with sepsis and septic shock than in those without sepsis (Table 1). We confirmed hepatitis A in two of the 67 sepsis patients, both of whom had high MDW (28.65 and 29.32). Two of three fungal sepsis patients and both fungal septic shock patients, infected with *Candida albicans* or other yeast-like fungus confirmed by culture from urine or respiratory samples, also had high MDW (26.52, 34.71, 33.94, and 37.25, respectively). MDW increased significantly in COVID-19 patients, especially in those hospitalized in the intensive care unit [6, 7]. MDW increases with progression from infection to sepsis and is the highest in sepsis patients with severe organ dysfunction [3]. This study demonstrated that MDW was the only biomarker that differed significantly between patients with sepsis and septic shock (Table 1).

The area under the ROC curve of MDW was the highest (0.896, 95% confidence interval [CI]: 0.868–0.923), followed by that of CRP (0.894, 95% CI: 0.866–0.923), PCT (0.793, 95% CI: 0.742–0.844), and WBC count (0.692, 95% CI: 0.623–0.762). The statistically best cut-offs for predicting sepsis and septic shock were 31.750 mg/L for CRP, 0.099 μg/L for procalcitonin, 9.614×10^9/L for WBC count, and 21.935 for MDW, the latter of which is higher than that (20.0) reported by Crouser, *et al.* [4], similar to that (21.9) reported by Polilli, *et al.* [8], and lower than that (23.5) reported by Agnello, *et al.* [9]. Whole-blood samples collected in K_2-EDTA tubes reportedly yield lower MDW than those collected in K_3-EDTA tubes [9]. Therefore, the MDW cut-offs for samples collected in K_2-EDTA in those previous reports and our study were lower than those for samples in K_3-EDTA [4, 8, 9].

The highest sensitivity of 93.9% was achieved using 20 as the MDW cut-off. The highest specificity of 91.8% was achieved when the MDW cut-off of 21.935 was used in addition to a WBC cut-off of 9.614×10^9/L. The specificities of CRP and procalcitonin increased when combined with the MDW results (Table 2).

In conclusion, MDW is a useful marker for sepsis screening in the ED because it shows high sensitivity when used as a sole marker and high specificity when combined with other markers. Therefore, MDW may be useful for early detection of sepsis, prediction of sepsis severity, and effective clinical decision making, before other biomarkers or culture results and imaging interpretations become available.

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Table 2. Sensitivity and specificity of laboratory biomarkers for predicting sepsis and septic shock

Laboratory biomarker	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
MDW	21.935	84.1% (74.0–91.0)	83.0% (80.7–85.1)
	20	93.9% (85.7–97.7)	70.1% (67.3–72.7)
WBC count, $\times 10^9$/L	9.614	64.6% (53.2–74.7)	70.7% (68.0–73.3)
CRP (mg/L)	31.750	90.1% (81.0–95.3)	76.6% (74.0–79.0)
Procalcitonin (μg/L)	0.099	90.5% (80.9–95.8)	54.4% (48.8–59.8)
MDW plus WBC count, $\times 10^9$/L	MDW: 21.935		
	WBC: 9.614	54.9% (43.5–65.8)	91.8% (90.0–93.2)
	MDW: 20		
	WBC: 9.614	59.8% (48.3–70.3)	87.5% (85.4–89.3)
MDW plus CRP (mg/L)	MDW: 21.935		
	CRP: 31.750	77.8% (66.9–86.0)	88.2% (86.2–90.0)
	MDW: 20		
	CRP: 31.750	85.2% (75.2–91.8)	84.5% (82.2–86.5)
MDW plus procalcitonin (μg/L)	MDW: 21.935		
	procalcitonin: 0.099	78.4% (67.0–86.8)	73.4% (68.2–78.0)
	MDW: 20		
	procalcitonin: 0.099	83.8% (73.0–91.0)	65.3% (59.8–70.3)

Abbreviations: MDW, monocyte distribution width; WBC, white blood cell; CRP, C-reactive protein; CI, confidence interval.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Yu S, Song SA, Jun KR, and Park HY investigated and interpreted the results. Yu S, Song SA, and Jun KR curated and analyzed the data. Yu S wrote the first draft of the manuscript. Lee JN supervised the study. All authors reviewed and edited the manuscript and agreed to publish the final manuscript.

CONFLICTS OF INTEREST

None declared.

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