Analysis of Monocyte Distribution Width (MDW) as a Biomarker for early Sepsis Detection in a Tertiary Care Hospital in North India

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ABSTRACT

INTRODUCTION
Early sepsis identification is vital to give specific treatment. Biomarkers for Sepsis have been studied however, none are specific. This study, Monocyte Distribution Width (MDW) was evaluated as a biomarker for sepsis and infection detection.

METHODS
356 adult patients presented to the emergency department with suspected infection or Sepsis, in whom a complete blood count with differential leucocyte count was performed, were included in the study. Patients were classified into diagnostic groups with sepsis - 2 and sepsis - 3 criteria. MDW was evaluated on the Beckman Coulter DxH 900 hematology analyser. MedCalc was used for statistical analysis to calculate Area Under the Curve (AUC), Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity, specificity, and the positive and negative likelihood ratio for MDW as a biomarker of sepsis / infection.

RESULTS
MDW values correlated with the severity of infection increased from no infection group to infection, sepsis, and septic shock. For sepsis - 2 detection, MDW demonstrated AUC 0.746, sensitivity of 81.48 %, and specificity of 59.27 % at cut off > 22.48. For infection detection with sepsis - 3 definitions, MDW demonstrated AUC 0.752, sensitivity of 73.08 %, specificity of 66.67 at cutoff > 23.02. MDW performance was similar in subgroups of patients with and without immunosuppression. In patients with 1 or 2 SIRS, sepsis probability increased 4.7 times if MDW was abnormal compared to normal; in the whole cohort, sepsis probability increased 7 times if MDW was abnormal. MDW, together with White Blood Cell Counts (WBC), showed 100 % sensitivity and NPV for sepsis - 2 identification, if either of them was abnormal.

CONCLUSION
MDW correlated with the severity of infection showed high NPV and sensitivity for sepsis - 2 detection. As complete blood counts with differential leucocyte counts are a part of routine workup in all patients, MDW can be considered a useful sepsis biomarker.

KEYWORDS
Emergency, Biomarker, Monocyte Distribution Width (MDW), Sepsis, Infection

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INTRODUCTION

Early detection of infection and Sepsis at is important to administer specific treatment, which improves a patient's outcome. Multiple publications have demonstrated that delay in specific antibiotic treatment in sepsis patients leads to increased morbidity and mortality.[1-3] Biomarkers for sepsis detection, (e.g. procalcitonin, C -reactive protein) have been studied previously, however, a reliable biomarker is still not identified.[4-6] Cell population data from hematology analysers, especially neutrophil volume, conductivity, and scatter parameters, have been studied before and shown promising sepsis detection results.[7-14] Recent studies using a monocyte parameter, Monocyte Distribution Width (MDW), showed its usefulness for sepsis identification in the Emergency Department (ED).[15-17] As MDW can be measured automatically, rapidly, and at a low cost during the routine complete blood counts with differential leucocyte counts, it is potentially a helpful sepsis biomarker. Our primary goal was to evaluate the performance of MDW as a sepsis biomarker on the patient population in the ED in a large University Hospital in North India. Earlier published studies on MDW were focused on sepsis detection using a sepsis - 2 definitions, which combines the presence of two or more SIRS criteria and confirmed or clinically strongly suspected infection; we planned to apply the same criteria for this study. In 2016, a new sepsis definition was introduced, and today, Sepsis is defined as a life - threatening organ dysfunction caused by a deregulated host response to infection. With this definition change, we think it would be of interest to look at MDW not only as a biomarker of Sepsis (with sepsis - 2 definition), but also as a biomarker for infection (with sepsis - 3 definition) because early identification of infection is critical to begin treatment and prevent patients from progressing to Sepsis with organ failure. Our second goal was evaluation of MDW as a biomarker of infection if sepsis - 3 definitions is applied for patient classification.[18]

MATERIAL AND METHODS

Adult patients (more than 18 years of age) presenting to the emergency department with suspected infection or Sepsis and in whom complete blood count with differential leucocyte count was performed at presentation and with more than 12 hours hospital stay were recruited in the study for 6 - months. Preexisting conditions, which can affect the immune status and or influence MDW, were recorded, including, (i) Conditions of chronic immune suppression - Neutropenia (absolute neutrophil count < 1,500 / µl); patients on treatment for neutropenia (Filgrastim, etc); immune suppression due to HIV, chemotherapy, recent transplant; patients on immune suppressants (≥ 2 weeks); (ii) Patients treated with antibiotics seven days prior to emergency admission and (iii) Patients with hematological malignancies. The final diagnosis was based on emergency department diagnosis and considering results of tests ordered at the time of presentation and up to 12 hours after presentation.

Diagnosis Categories According to Sepsis - 2 Definition Included[19]:

- Non - systemic inflammatory response syndrome (SIRS) / Non - Infection.
- **Infection, but no sepsis:** Infection diagnosis was based on a combination of clinical, bacteriological, cyto - or histo - pathological, and other test results according to the disease involved.
- **SIRS:** was diagnosed when patients had two or more of the following criteria
  - Temperature < 36 °C (96.8 °F) or > 38 °C (100.4 °F)
  - Heart rate > 90 /min or > 2 Standard deviation above the normal
  - Respiratory rate >20 /min, or $PaCO_2$ of <32 mm Hg (tachypnea, hyperventilation)
  - White blood cell count < 4 x 10^9 / L or > 12 x 10^9 / L or > 10 % band forms
- **Sepsis - 2:** presence of infection with at least 2 SIRS criteria.
- **Severe Sepsis:** occurs when there is tissue hypo perfusion or organ dysfunction resulting from Sepsis.
- **Septic Shock**: there is hypotension and severe Sepsis, despite adequate fluid resuscitation *(i.e.,* infusion of 20 - 30 mL / kg of crystalloids).

When assessing the diagnostic performance of MDW for sepsis - 2 detection, groups 1,2 and, 3 were combined (no sepsis group) and compared to groups 4,5, and 6 combined (sepsis group).

Diagnostic Categories Based on Sepsis - 3 Definition Included:

- No infection
- **Infection**: Infection diagnosis was based on a combination of clinical, bacteriological, cyto - or histo -pathological and other test results according to the disease involved.
- **Sepsis - 3:** Patients with organ failure (defined by SOFA score) due to deregulated response to infection
- **Septic shock**: patients with hypotension and severe Sepsis, in spite of adequate fluid resuscitation (i.e., infusion of 20-30 mL / kg of crystalloids).

When assessing the diagnostic performance of MDW for infection detection with sepsis - 3 definition, groups 2, 3, and 4 were combined (infection group) and compared to groups 1 (no infection group).

MDW Analysis

Blood was collected in K_2 EDTA tubes and analyzed within 2 hours of blood draw. MDW was obtained from Beckman Coulter D x H 900 hematology blood cell counter and reported as part of CBC - different results. For quality control, 6 C plus cell control material was used.

Statistical Analysis

For evaluating the utility of MDW as a biomarker of Sepsis, MedCalc, v.19.6.4 4 (MedCalc Software bvba, Ostend, Belgium), was used. Area Under the Curve (AUC), Positive Predictive Value (PPV), Negative Predictive Value (NPV), sensitivity, specificity, positive and negative likelihood ratio (LR + and LR -) were calculated.

RESULTS

Institutional ethics committee approved the study, which was performed following the ethical standards of Helsinki. The study cohort included 356 adult patients admitted to ED. Classification of patients into diagnostic sub-groups was done according to sepsis - 2 criteria and sepsis - 3 criteria.

Diagnostic Groups According to Sepsis - 2 Criteria Included:

- Non - systemic inflammatory response syndrome (SIRS) / Non - Infection, n = 165 (45.2 %)
- Infection, but no sepsis, n = 87 (24.4%)
- SIRS, n = 23 (6.5 %) (6.6 %)
- Sepsis - 2, n = 59 (16.6 %)
- Severe Sepsis, n = 10 (2.8 %)
- Septic Shock, n = 12 (3.4 %)

With Sepsis - 3 Classification Patients were Classified as:

- No infection, n = 250 (70.2 %)
- Infection n = 84 (23.6 %)
- Sepsis - 3, n = 10 (2, 8 %)
- Septic shock, n = 12 (3.4 %)

We performed analysis for all patients included in the study (n = 356) and then - excluded patients with conditions which can affect the immune status and or influence MDW performance (n = 326). Exclusion criteria were the following: patients with hematological malignancy (n = 26), patients on antibiotics for one week before admission to emergency (n = 13); Patients with immune suppression due to transplant (bone marrow / solid organ) or HIV (n = 12), Patients with immune suppression due to chemotherapy (n = 11), Patients on immune suppressants (≥ 2 weeks) (n = 13). This analysis strategy was applied for sepsis detection with sepsis - 2 and for infection detection with sepsis - 3 criteria. 189 healthy adult individuals were also included for MDW value analysis.

Overall Trend of MDW Value in Patients and Controls

We observed an increasing trend for MDW values with increasing the severity of infection. It was lowest in the no - infection group and maximum in the septic shock group it gradually increased for Systemic Inflammatory Response Syndrome (SIRS) group, to Sepsis - 2 group and severe sepsis group for sepsis - 2 classification. The same trend was observed with sepsis - 3 classifications: MDW values increased from non - infection group to infection and then to sepsis groups (Tables 1, 2 and Figure 1).

Parameter	AUC (95% CI)	Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95 % CI)	-LR (95% CI)	PPV (95% CI)	NPV (95% CI)	Sepsis patients (%)	Non-sepsis patients (%)	Total number
All patients included											
MDW	0.746 (0.698-0.791)	>20	93.83 (86.2 - 98.0)	40.73 (34.9 - 46.8)	1.58 (1.4 - 1.8)	0.15 (0.06 - 0.4)	31.8 (29.4 - 34.3)	95.7 (90.4 - 98.1)	81 (22.75%)	275 (77.25%)	356
		>22.48	81.48 (71.3 - 89.2)	59.27 (53.2 - 65.1)	2 (1.7 - 2.4)	0.31 (0.2 - 0.5)	37.1 (33.1 - 41.3)	91.6 (87.2 - 94.5)			
WBC as continuous variable, x 10^9/L	0.698	>11.5	74.07 (63.1 - 83.2)	60.73 (54.7 - 66.5)	1.89 (1.6 - 2.3)	0.43 (0.3 - 0.6)	35.7 (31.4 - 40.3)	88.8 (84.5 - 92.1)			
WBC x 10^9/L (normal/abnormal)	0.678	<4 or >12	74.07 (63.1 - 83.2)	61.45 (55.4 - 67.2)	1.92 (1.6 - 2.3)	0.42 (0.3 - 0.6)	36.1 (31.7 - 40.8)	88.9 (84.6 - 92.2)			
MDW and WBC combined in logistic regression	0.773	>-1.4598	77.78 (67.2 - 86.3)	66.55 (60.6 - 72.1)	2.32 (1.9 - 2.8)	0.33 (0.2- 0.5)	40.6 (35.8 - 45.6)	91 (87.0 - 93.9)			
Immunocompromised patients, patients with Ab treatment and patients with hematological malignancies excluded											
MDW	0.752 (0.701-0.798)	>20	93.33 (85.1 - 97.8)	42.63 (36.4 - 49.0)	1.63 (1.4 - 1.8)	0.16 (0.07 - 0.4)	32.7 (30.1 - 35.5)	95.5 (90.1 - 98.1)	75 (23.01%)	251 (76.99%)	326
		>22.48	80 (69.2 - 88.4)	61.35 (55.0 - 67.4)	2.07 (1.7 - 2.5)	0.33 (0.2 - 0.5)	38.2 (33.8 - 42.9)	91.1 (86.6 - 94.2)			
WBC as continuous variable, x 10^9/L	0.703	>11.5	76 (64.7 - 85.1)	59.76 (53.4 - 65.9)	1.89 (1.6 - 2.3)	0.4 (0.3 - 0.6)	36.1 (31.7 - 40.7)	89.3 (84.6 - 92.7)			
WBC, x 10^9/L (normal/abnormal)	0.678	<4 or >12	74.67 (63.3 - 84.0)	60.96 (54.6 - 67.0)	1.91 (1.6 - 2.3)	0.42 (0.3 - 0.6)	36.4 (31.8 - 41.2)	89 (84.4 - 92.3)			

MDW and WBC combined in logistic regression	0.776	>-1.2948	72 (60.4 - 81.8)	71.71 (65.7 - 77.2)	2.55 (2.0 - 3.2)	0.39 (0.3-0.6)	43.2 (37.4 - 49.2)	89.6 (85.5 - 92.6)	

Table 1. Performance of Individual Biomarkers for Sepsis - 2 Detection.

Parameter	AUC (95 % CI)	Cut - off	Sensitivity (95 % CI)	Specificity (95 % CI)	+ LR (95 % CI)	-	95 % CI)	PPV (95 % CI)	NPV (95 % CI)	Infection patients (%)	No infection patients (%)	Total number
All patients included												
MDW	0.752 (0.707 - 0.799)	> 23.02	73.08 (63.5 - 81.3)	66.67 (60.5 - 72.5)	2.19 (1.8 - 2.7)	0.4 (0.3 - 0.6)		47.5 (42.3 - 52.7)	85.7 (81.2 - 89.3)	104 (29.21 %)	252 (70.79 %)	356
WBC as continuum variable, x 10^9 / L	0.654 (0.602 - 0.703)	>11.5	67.31 (57.4 - 76.2)	61.11 (54.8 - 67.2)	1.73 (1.4 - 2.1)	0.53 (0.4 - 0.7)		41.7 (36.8 - 46.7)	81.9 (77.2 - 85.9)			
WBC x 10^9 / L (normal / abnormal)	0.653 (0.601 - 0.702)	< 4 or > 12	68.27 (58.4 - 77.1)	62.3 (56.0 - 68.3)	1.81 (1.5 - 2.2)	0.51 (0.4 - 0.7)		42.8 (37.8 - 47.9)	82.6 (77.9 - 86.5)			
Immunocompromised patients, patients with Ab treatment and patients with hematological malignancies excluded												
MDW	0.765 (0.701- 0.798)	>22.6	75.79 (65.9 - 84.0)	64.94 (58.4 - 71.1)	2.16 (1.8 - 2.7)	0.37 (0.3 - 0.5)		47.1 (41.9 - 52.3)	86.7 (81.9 - 90.4)	95 (29.14 %)	231 (70.86 %)	326
WBC as continuum variable, x 10^9 / L	0.664 (0.610 - 0.715)	> 11.5	69.47(59.2 - 78.5)	60.17 (53.5 - 66.5)	1.74 (1.4 - 2.1)	0.51 (0.4 - 0.7)		41.8 (36.8 - 46.9)	82.7 (77.7 - 86.9)			
WBC x 10^9 / L (normal / abnormal)	0.657 (0.603 - 0.708)	< 4 or > 12	69.47 (59.2 - 78.5)	61.9 (55.3 - 68.2)	1.82 (1.5 - 2.3)	0.49 (0.4 - 0.7)		42.9 (37.8 - 48.1)	83.1 (78.2 - 87.2)			

Table 2. Performance of Individual Biomarkers for Infection Detection with Sepsis - 3 Definition.

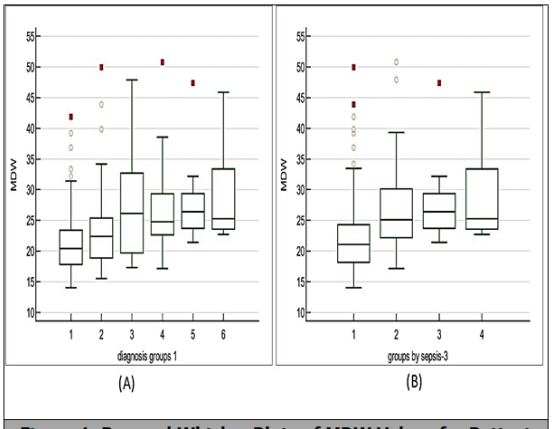

Figure 1. Box and Whisker Plots of MDW Values for Patient Groups Classified by Sepsis - 2 Criteria (A) and by Sepsis - 3 Criteria (B).

A: Groups by sepsis-2 definition: 1 = No infection, no SIRS; 2 = SIRS, 3 = Infection, 4 - sepsis, 5 = Severe sepsis, 6 = Septic shock

B: Groups by sepsis-3 definition: 1 = No infection, 2 = Infection, 3 - Sepsis, 4 = Septic shock

Diagnostic Performance of MDW and WBC for Sepsis Detection Using Sepsis - 2 Criteria

To assess MDW performance for sepsis - 2 detection, we compared positive group (Sepsis, severe Sepsis and septic shock (n = 81, 22.75 %) versus negative group: controls (no SIRS and no infection), SIRS, and infection (n = 275, 77.25 %). In receiver operating characteristic curve analysis (ROC analysis) on the whole cohort MDW demonstrated Area Under the Curve (AUC) 0.746, sensitivity of 81.48 % and specificity of 59.27 %, LR + of 2, LR- of 0.31, PPV of 37.1 % and NPV of 91.6 % at cut off > 22.48 (Table 1). At cut - off 20, recommended by manufacturer, the sensitivity was 93.83 %, specificity 40.73 %, LR + = 1.58, LR - = 0.15, PPV = 31.8 % and NPV = 95.7 % (Table 1). To analyze WBC for Sepsis - 2 detection WBC values were studied both as a continuous variable and as normal (4 – 12 x 10^9 / L) and abnormal (< 4 x 10^9 / L or >12 x 10^9 / L). For WBC as a continuous variable, the AUC was 0.698, with sensitivity of 74.07 % and specificity of 60.73 %, LR + 1.89, LR - 0.43, PPV of 35.7 % and NPV of 88.8 % at cut off > 11.5 x 10^9 / L (Table 1). Almost similar findings were observed, when analysis for WBC was done as normal/abnormal, with AUC = 0.678, sensitivity of 74.07 %, specificity of 61.45 % LR + 1.92, LR - 0.42, PPV of 36.1 % and NPV of 88.9 % (Table 1). As both MDW and WBC are available as part of CBC - Diff analysis, we combined WBC and MDW in logistic regression and demonstrated improved performance with AUC 0.773 (Table 1). After excluding from analysis immunocompromised patients, patients with antibiotic treatment before ED arrival and patients with hematological malignancies the positive group (Sepsis, Severe sepsis and Septic shock) included 75 patients (23.01%), while negative group ([No SIRS, no Infection] +SIRS + Infection) included 251 patients (76.99 %). MDW demonstrated AUC 0.752 for sepsis - 2 detection, with sensitivity of 80 %, specificity of 61.35 %, LR + of 2.07, LR - of

0.33, PPV of 38.2 % and NPV of 91.1 % at cut – off > 22.48 (Table 1). At recommended cutoff 20 the sensitivity was 93.33 %, specificity 42.63 %, LR + = 1.63, LR - = 0.16, PPV = 32.7 % and NPV = 95.5 % (Table 1). For WBC as a continuous variable, the AUC was 0.703, with sensitivity of 76 % and specificity of 59.76 %; LR + of 1.89, LR - of 0.4, PPV of 36.1 % and NPV of 89.3 % at cut - off > 11.5 x 10^9 / L (Table 1). Almost similar findings were observed, when analysis for WBC was done as normal / abnormal, with AUC = 0.678, sensitivity of 74.67 %, specificity of 60.96 %, LR + = 1.91, LR - = 0.42, PPV = 36.4 % and NPV = 89.0 % (Table 1). The combination of MDW and WBC in logistic regression demonstrated improved performance with AUC 0.776 (Table 1).

Diagnostic Performance of MDW and WBC for Infection Detection Using Sepsis - 3 Criteria: To assess MDW performance for infection detection with sepsis - 3 definition on the whole cohort, we compared positive group (infection, Sepsis, and septic shock), which included 104 patients (29.21 %) versus negative group: [(no SIRS and no Infection) and SIRS], including 252 patients (70.79 %). In this case, as biomarker of infection, MDW demonstrated AUC 0.752, sensitivity of 73.08 %, specificity of 66.67 %, LR + of 2.19, LR - of 0.4, PPV of 47.5 % and NPV of 85.7 % at cut off > 23.02 (Table 2).

For WBC as a continuous variable, the AUC was 0.654, sensitivity 67.31 %, specificity 61.11 %, LR + 1.73, LR - 0.53, PPV = 41.7 % and NPV = 81.9 % at cut - off > 11.5 x 10^9 / L (Table 2). Almost similar findings were observed, when analysis for WBC was done as normal / abnormal, with AUC 0.653, sensitivity 68.72 %, specificity 62.30 %, LR + 1.81, LR - 0.51, PPV 42.8 % and NPV 82.6 % (Table 2). After excluding from analysis immune compromised patients, patients with antibiotic treatment before ED arrival and patients with hematological malignancies, the positive group (infection, sepsis and septic shock) included 95 patients (29.14 %). In contrast, the negative group [(No SIRS, no Infection) and SIRS] included 231 patients (70.86 %). For infection detection with sepsis - 3 definitions, MDW demonstrated AUC 0.765 with sensitivity 75.79 %, specificity 64.94 %, LR + 2.16, LR- 0.37, PPV 47.1 % and NPV 86.7 % at cut - off > 22.6 (Table 2). For WBC as a continuous variable, the AUC was 0.664, with sensitivity 69.47 %, specificity 60.17 %, LR + 1.74, LR - 0.51, PPV 41.8 % and NPV 82.7 % at cut off > 11.5 x 10^9 / L (Table 2). When analysis for WBC was done as normal / abnormal, we obtained AUC 0.657, sensitivity 69.47 %, specificity 61.90 %, LR + 1.82, LR - 0.49, PPV 42.9 % and NPV 83.1 % (Table 3).

Parameter	AUC (95% CI)	Sensitivity, %	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Abnormal WBC or abnormal MDW	0.624 (0.571-0.674)	100 (95.5 - 100.0)	24.73 (19.7 - 30.3)	28.1 (26.8 - 29.5)	100
Abnormal MDW and abnormal WBC	0.725 (0.675-0.771)	67.9 (56.6-77.8)	77.09 (71.7-81.9)	46.6 (40.1-53.2)	89.1 (85.5-91.8)

Table 3. Performance Characteristics of MDW and WBC Combined in Decision Rules for early sepsis - 2 Detection in Adult ED Patients. All patients (n = 356). Upper row: Abnormal MDW or abnormal WBC indicates Sepsis. Lower row: Abnormal MDW and abnormal WBC Indicate Sepsis. Abnormal MDW > 20; Normal MDW < 20; Abnormal WBC <4 x 10^9 / L or > 12 x 10^9/L; Normal WBC 4 - 12 x 10^9 / L.

Added value of MDW to SIRS criteria: Post - test sepsis probability for patients with 1, 2, 3, and 4 SIRS criteria, with normal versus abnormal MDW results was evaluated and presented in Figure 2. All patients with 0 SIRS were not Sepsis, so results for groups with 0 SIRS were not possible. MDW was found to be complementary to SIRS parameters, especially for patients with low risk (1 SIRS criterion at presentation, and patients with 2 SIRS, which were defined as low risk, when there was no obvious site of infection) (Figure 2). MDW in patients with 1 or 2 SIRS was very useful, as sepsis probability was increased with abnormal MDW results, by 9.1 and 4.7-fold, respectively, compared to patients with a normal MDW result. Overall, for the whole cohort, abnormal MDW results increased seven times the sepsis probability when MDW was Abnormal compared to normal MDW results (29.2 versus 4.3).

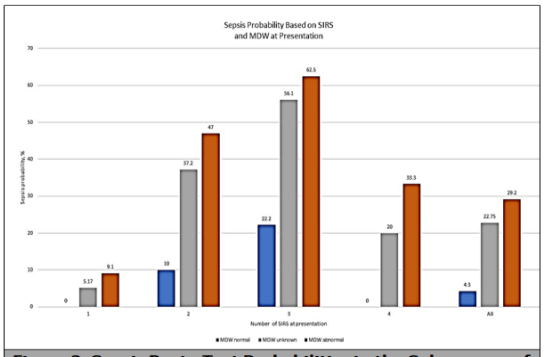

Figure 2. Sepsis Post - Test Probabilities in the Sub - group of Patients based on Mdw Value and Number of Sirs Criteria at Presentation. Normal MDW < 20; Abnormal MDW > 20.

Combinations of MDW and WBC for sepsis detection: As D x H 900 analyzer provides the possibility to create customer - defined decision rules, combining several parameters; we assessed the performance of different combinations of MDW and WBC for sepsis detection, as presented in Table 3. On taking either MDW or WBC for sepsis probability, if at least one biomarker was abnormal,

there was 100 % sensitivity and 100 % NPV for sepsis detection, implying that the sepsis probability is very low if both biomarkers are normal. However, this combination demonstrated a specificity of 24.73 %. On taking both MDW and WBC together for sepsis probability, if both biomarkers are abnormal - there was 67.90 % sensitivity, 77.09 % specificity, and 89.1 % NPV for sepsis detection (Tables 4, 5).

Groups by sepsis - 2	N	Minimum	Maximum	Mean	Median	Normal Distr.
Controls	189	14.51	25.02	18	17.7	< 0.0001
no infection no SIRS	165	14.04	41.89	21.2	20.4	< 0.0001
SIRS	87	15.53	49.9	23.3	22.4	< 0.0001
Infection	23	17.32	47.88	27.2	26.1	0.1914
Sepsis - 2	59	17.17	50.79	26.4	24.8	< 0.0001
Severe sepsis	10	21.42	47.39	28.2	26.4	0.0005
Septic shock	12	22.72	45.87	29.3	25.3	0.1191

Table 4. MDW Statistics (Patients groups Classified by Sepsis - 2 Criteria).

Groups by sepsis - 3	N	Minimum	Maximum	Mean	Median	Normal Distr.
No infection	250	14	50	21.9	21.1	<0.0001
Infection	84	17.2	51	26.6	25.1	<0.0001
Sepsis	10	21.4	47	28.2	26.4	5 E-04
Septic shock	12	22.7	46	29.3	25.3	0.119

Table 5. MDW statistics (patients groups classified by sepsis - 3 criteria).

DISCUSSION

MDW is an FDA - cleared sepsis marker for adults and used in emergency departments.[20] MDW is available on Beckman Coulter instruments - UniCel D x H 900 and UniCel D x H 69 ^{0}T (Beckman Coulter, USA). The first responders to infection are neutrophils and monocytes; therefore, an increase in cell volume is useful for early detection of Sepsis. Demonstrated that MDW values of more than 20 differentiated Sepsis from other conditions, using either sepsis - 2 criteria (AUC = 0.79) or sepsis - 3 criteria (AUC = 0.73). NPV for MDW was 93 % and 94 % for sepsis - 2 and sepsis - 3, respectively. When MDW was combined with abnormal white blood cell count, the diagnostic performance further increased (AUC = 0.85). Further study by Crouser.[21] Using MDW and SIRS or Quick Sepsis - Related Organ Failure Assessment (QSOFA) score, concluded that MDW is complementary to SIRS and qSOFA parameters that are currently used for sepsis detection. In another study that compared MDW and procalcitonin for sepsis detection in 260 patients, MDW was at least equivalent to PCT in predicting Sepsis and MDW < 20 was associated with negative blood cultures. They suggested that MDW is useful marker for early sepsis detection and can be easily provided with routine complete blood counts.[22] A recent large study conducted in two European hospitals in France and Spain demonstrated very solid MDW performance for sepsis detection, which was comparable to C - reactive protein and superior to procalcitonin. They have also found MDW to be very useful in sub - population patients with low pre - test sepsis probability.[23] Very impressive results from Italy showed good MDW accuracy for sepsis risk assessment in ED with 92 + % sensitivity and specificity. They considered MDW a potentially valuable tool for early sepsis detection by general practitioners.[24] we aimed to evaluate the performance of MDW for sepsis detection in a large University hospital in North India, and our results are in good agreement with previous publications, demonstrating solid MDW performance for sepsis - 2 detection. Abnormal MDW showed high sensitivity and NPV for early sepsis detection and, in combination with abnormal white blood cell counts, showed 100 % sensitivity and NPV for sepsis detection. We also found that in our cohort, MDW performance for sepsis detection in the ED is not affected by the immune status of the patient. After excluding patients with immune - compromised conditions (Table 1) the AUC was slightly improved, but not dramatically, which means that in this cohort MDW performance was not affected by Immune compromised conditions, by antibiotic treatment before ED arrival and by hematological malignancies. Slightly different results were obtained from a study. who demonstrated decreasing trend in the AUC of the biomarkers studied, including MDW, in immune - compromised patients compared with those in immune - competent patients. This probably can be explained by differences in the study cohort. Like other studies, we found that MDW can be useful when applied together with SIRS criteria, increasing sepsis probability when MDW is abnormal compared to normal MDW results. Several groups also reported this for MDW used together with SIRS 17,21, or with qSOFA criteria 17, 21,25. For the first time in our study, we evaluated MDW performance for infection detection when sepsis - 3 criteria are used for sepsis definition. This is very important, as

MDW, available very early in patient's assessment, as part of CBC - Diffrent analysis, can be used to alert clinicians about infection, which can result in organ failure if not recognized and treated early enough. MDW demonstrated AUC 0.752, sensitivity of 73.08 %, and specificity of 66.67 % for infection detection (with sepsis - 3 definitions) on the whole cohort and AUC 0.765 with sensitivity 75.79 %, specificity 64.94 % when immunocompromised patients were excluded. At the same time, WBC, both as a continuous variable and as normal / abnormal, showed inferior performance for infection with AUC 0.664 and 0.657, respectively. This demonstrates that MDW enhances the value of routine CBC - Diff for patients triage in the busy ED. The optimal MDW cutoff for sepsis detection defined for our patient population is higher than recommended by the manufacturer. This can be explained by the difference in the patient population, specifically because many patients arrive in the hospital when they are very sick, at the advanced stage of the disease, and these results in relatively high sepsis prevalence in our cohort (23 %). When we applied a recommended cutoff of 20 for MDW to aid in sepsis detection in the ED, it demonstrated a very high sensitivity of 93.83 %, but with compromised specificity of 40.73 %.

CONCLUSION

To conclude, MDW is a useful biomarker for early sepsis detection. Abnormal MDW results increase the probability of sepsis - 2, and normal MDW results decrease the probability of sepsis - 2 for patients in the ED. On combining MDW with white blood cell count, 100 % sensitivity and NPV was observed for sepsis detection in this study, *i.e.*, the sepsis probability is very low if both biomarkers are normal. MDW can also be considered a useful biomarker for infection detection when sepsis - 3 criteria are used. Correlation of MDW with disease severity can alert clinicians about the "need to act" upon receiving CBC - Diff results, including MDW, and potentially escalate or de - escalate patient care of course, any decision for an individual patient should not be based on MDW alone but should be made using all clinical and laboratory information available. As CBC - Different analysis is performed as a part of routine workup in all patients, with very fast turnaround time, MDW will be a very useful biomarker for sepsis detection, without additional cost involved.

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