# Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker

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WBC

NE%
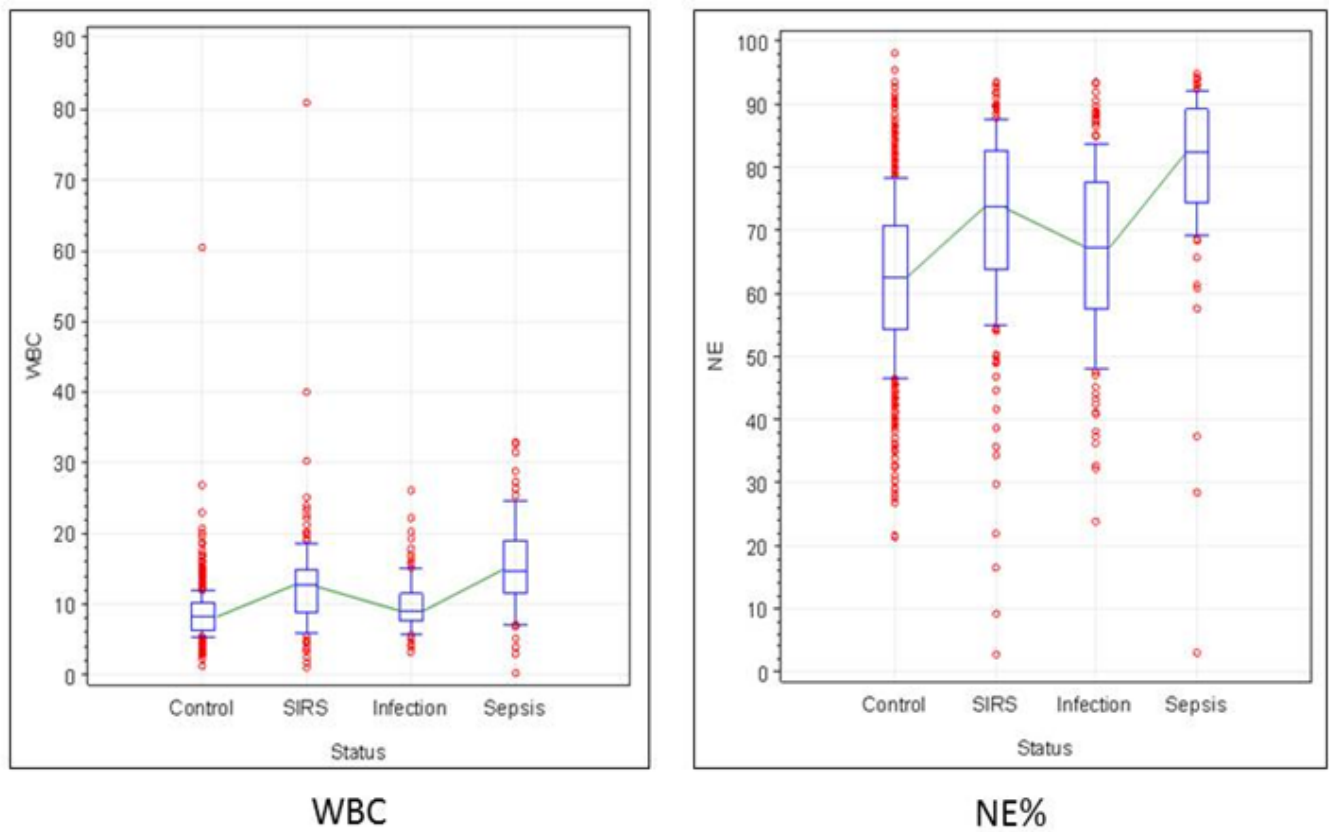
e-Figure 1. White blood count (WBC) and neutrophil percent (NE%) performance for sepsis in the ED population. Left Panel, WBC is noted to be elevated in the SIRS and sepsis groups relative to control and infection groups. Right Panel, NE% is elevated in SIRS and sepsis groups compared to control and infection groups. There was no statistically significant difference of either parameter when comparing SIRS and sepsis.
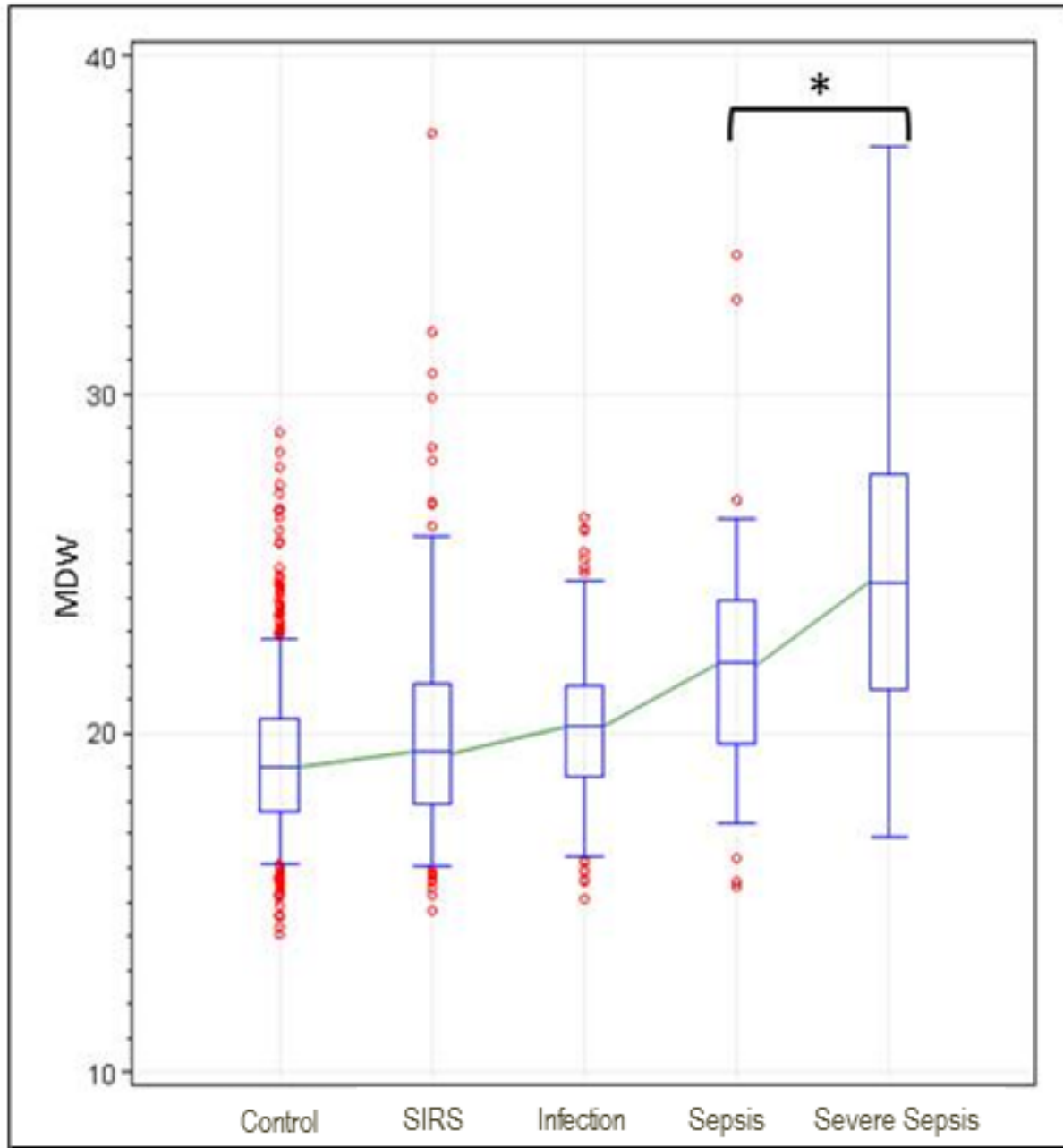
e-Figure 2. Monocyte distribution width (MDW) increases with severity of infection in the ED population. MDW is shown to incrementally increase when comparing controls, SIRS and infection groups. More dramatic increases in MDW are observed in patients with sepsis and are highest in those with "advanced sepsis" (severe sepsis + septic shock, labeled as "Severe Sepsis"). [*$P < 0.01$ advanced sepsis vs sepsis; $P < 0.001$ Advanced sepsis vs non-septic (control + infection + SIRS)].

e-Table 1: Preexisting conditions associated with macrocytosis or otherwise expected to promote impaired immune responses in the ED population.

Condition	Description
Neutropenia	Absolute neutrophil count <1,500/μL
Drugs used to treat neutropenia	Neupogen, Filgrastim, Granix, Sargramostime.
Immune compromised state	HIV infection, organ or bone marrow transplantation, malignancy, hematologic (lymphomas, multiple myeloma, acute and chronic leukemias, myelodysplastic syndromes, aplastic anemia).
Immune modulating drugs	Chronic treatments (≥2 weeks) with corticosteroids (prednisone ≥20 mg/day), anti-TNFα molecules, methotrexate (≥15 mg/week), azathioprine (≥75 mg/day), cyclophosphamide (any dose) or mycophenylate (≥1000 mg/day) or any combination of these treatments (at any dose).
Hydroxyurea	Treatment within one week
Alcoholism	As defined by the CDC (≥15 drinks/week for men; ≥8 drinks/week for women) or a blood alcohol level exceeding the legal limit (0.08%)
Current antibiotic use	Subjects treated with antibiotics within the past 7 days prior to ED presentation (i.e., recently infected).

e-Table 2. Emergency Department Population Demographics

	Summary Demographics by Group		
	Sepsis	**SIRS**	**Non-Sepsis**
Total Subjects	98	203	1222
Subject Age - Mean (Min - Max)	50 (18 - 84)	48 (18 - 89)	46 (18 - 90)
Male gender, no. (%)	43 (44%)	97 (48%)	610 (50%)
Race:			
African/Black	16	56	421
American Indian or Alaska Native	1	0	1
Asian	0	5	19
Middle Eastern	0	0	1
Native Hawaiian, other Pacific Islander	0	2	4
White	77	131	729
Unknown	4	9	47
Comorbid Illness, no. (%):			
Alcoholism	2 (2)	17 (8)	43 (4)
Malignancy	16 (16)	14 (7)	33 (3)
Renal Disease	13 (13)	14 (7)	41 (4)
Liver Disease	3 (3)	2 (3)	25 (2)
Post-Surgical	5 (5)	0 (0)	3 (0)
Bronchitis / COPD	1 (1)	8 (4)	11 (1)

e-Table 3. Summary of Cell Population Data (CPD) and CBC data from the ED population (n=1320 total) based upon clinical category.

Analyte	Status	N	Mean	Standard Deviation	Min	Max
MCV	Control	879	88.02	6.56	58.96	115.00
	Infection	140	88.32	6.13	71.75	107.67
	SIRS	203	87.93	7.75	62.36	118.78
	Sepsis	98	87.36	7.05	59.00	106.33
MMV	Control	879	176.62	8.42	158.66	228.55
	Infection	140	180.90	8.58	162.46	221.71
	SIRS	203	177.44	8.70	157.09	206.29
	Sepsis	98	186.94	11.20	163.01	220.16
MDW	Control	879	19.24	2.39	14.09	50.49
	Infection	140	20.25	2.25	15.12	26.40
	SIRS	203	19.99	3.18	14.74	37.71
	Sepsis	98	22.63	3.66	15.48	37.33
MNV	Control	879	151.38	8.73	130.47	188.25
	Infection	140	153.59	8.58	132.45	178.39
	SIRS	203	153.61	9.46	132.05	189.43
	Sepsis	98	159.09	11.01	140.53	189.16
NDW	Control	879	18.25	1.84	14.81	35.90
	Infection	140	18.75	1.90	15.09	30.21
	SIRS	203	19.50	3.33	15.38	39.34
	Sepsis	98	20.61	3.33	17.27	42.99
MO	Control	879	8.25	2.97	0.31	27.91
	Infection	140	8.60	3.18	2.97	25.77
	SIRS	203	7.73	4.42	0.95	40.64
	Sepsis	98	8.08	7.82	0.89	76.33
NE	Control	879	62.51	12.62	21.31	98.14
	Infection	140	67.01	14.31	23.78	93.56
	SIRS	203	71.38	15.27	2.62	93.71
	Sepsis	98	80.15	13.55	2.88	94.91
PLT	Control	879	235.19	80.55	10.22	660.65
	Infection	140	249.54	91.02	66.61	746.13
	SIRS	203	253.49	98.87	3.51	575.33
	Sepsis	98	259.45	117.77	15.40	635.09
WBC	Control	879	8.62	3.47	1.23	60.36
	Infection	140	10.00	3.82	3.15	26.16
	SIRS	203	12.63	7.08	1.01	80.81
	Sepsis	98	15.61	6.53	0.39	32.80

MCV = mean corpuscular volume
MMV = mean monocyte volume
MDW = monocyte distribution width
MNV = mean neutrophil volume
NDW = neutrophil distribution width
MO = monocyte %
NE = neutrophil %
PLT = platelet count in thousands
WBC = white blood cell count in thousands

e-Table 4. Cutoff values for each measure CPD and CBC parameter, and the distribution of ED patients (n=1320 total) based upon test performance.

Sepsis vs. Non-Sepsis						
Analyte	Cut-off	True Positive	False Negative	True Negative	False Positive	TOTAL
MCV	88.00	49	49	612	610	1320
MMV	180.00	69	29	822	400	1320
MDW	20.50	75	23	873	349	1320
MNV	152.00	70	28	659	563	1320
NDW	18.80	73	25	819	403	1320
MO	6.30	37	61	887	335	1320
NE	75.00	71	27	938	284	1320
PLT	250.00	45	53	734	488	1320
WBC	12.00	73	25	983	239	1320

MCV = mean corpuscular volume
MMV = mean monocyte volume
MDW = monocyte distribution width
MNV = mean neutrophil volume
NDW = neutrophil distribution width
MO = monocyte %
NE = neutrophil %
PLT = platelet count in thousands
WBC = white blood cell count in thousands

e-Table 5. Clinical accuracy of CPD parameters for sepsis detection in the ED population.

Sepsis vs. Non-Sepsis										
Parameter	AUC	95% Confidence Interval		Cut-Off	Sensitivity	95% Confidence Interval		Specificity	95% Confidence Interval	
		Lower	Upper			Lower	Upper		Lower	Upper
WBC	0.81	0.76	0.86	12.00	0.75	0.65	0.82	0.80	0.78	0.83
NE	0.83	0.79	0.88	75.00	0.73	0.63	0.80	0.77	0.74	0.79
MNV	0.69	0.63	0.74	152.00	0.71	0.62	0.79	0.54	0.51	0.57
NDW	0.77	0.73	0.82	18.80	0.75	0.65	0.82	0.67	0.64	0.70
MMV	0.76	0.71	0.81	180.00	0.70	0.61	0.79	0.67	0.65	0.70
MDW	0.78	0.73	0.84	20.50	0.77	0.67	0.84	0.72	0.69	0.74

> MDW = monocyte distribution width
> MMV = mean monocyte volume
> MNV = mean neutrophil volume
> NDW = neutrophil distribution width
> NE = neutrophil %
> WBC = white blood cell count

e-Table 6. Effect of preexisting conditions associated with altered immune status (see e-Table 1) on the performance of CPD and CBC parameters for discrimination of sepsis from SIRS in the ED population. Exclusion of ~17% of ED patients based upon conditions that are known to have risk factors for altered immune status or macrocytosis (i.e., "without" exclusion criteria) modestly improves the performance of CPD and CBC parameters in the ED population.

Parameter	Pre-Existing Conditions	AUC	95% Confidence Interval		Cut-Off	Sensitivity	95% Confidence Interval		Specificity	95% Confidence Interval	
			Lower	Upper			Lower	Upper		Lower	Upper
WBC	Without	0.73	0.64	0.82	12.00	0.81	0.67	0.90	0.39	0.32	0.47
	With [All]	0.66	0.59	0.73	12.00	0.75	0.65	0.82	0.41	0.35	0.48
NE	Without	0.76	0.69	0.84	75.00	0.79	0.64	0.88	0.52	0.44	0.59
	With [All]	0.70	0.64	0.77	75.00	0.73	0.63	0.80	0.522	0.45	0.59
MNV	Without	0.69	0.60	0.78	152.00	0.81	0.67	0.90	0.46	0.38	0.53
	With [All]	0.64	0.58	0.71	152.00	0.71	0.62	0.79	0.44	0.38	0.51
NDW	Without	0.75	0.67	0.83	18.80	0.74	0.59	0.85	0.58	0.50	0.65
	With [All]	0.68	0.61	0.74	18.80	0.75	0.65	0.82	0.52	0.45	0.59
MMV	Without	0.77	0.69	0.85	180.00	0.69	0.54	0.81	0.70	0.62	0.76
	With [All]	0.75	0.69	0.81	180.00	0.70	0.61	0.79	0.66	0.59	0.72
MDW	Without	0.78	0.70	0.87	20.50	0.79	0.64	0.88	0.68	0.60	0.75
	With [All]	0.74	0.68	0.80	20.50	0.77	0.67	0.84	0.63	0.56	0.70

The table header above spans "Sepsis vs. SIRS".

MDW = monocyte distribution width
MMV = mean monocyte volume
MNV = mean neutrophil volume
NDW = neutrophil distribution width
NE = neutrophil %
WBC = white blood cell count (in thousands)

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