ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

Type of manuscript: Original article

Title: Monocyte distribution width (MDW) in COVID-19 infection: A predictor of progression of severity ?

Running title: MDW in Covid-19

AnkitaSoni MD[1]*, VikramNarang MD[1], SaloniGoyal MD[1], Aminder Singh MD[1], DevikaBansal MBBS[1], RamneekKaur MBBS[1], HarpreetKaur MD[1].

[1]Department of Pathology, Dayanand Medical College & Hospital, Ludhiana, Punjab, INDIA.

[*]**Corresponding author information:**

Ankita Soni

Department of Pathology, Dayanand Medical College & Hospital

Address: Tagore Nagar, Ludhiana, Punjab, INDIA 141001

Contact number: 8427800689

Email: ankitatavish@gmail.com

Abstract:

Background: Monocyte distribution width (MDW) is a well-studied parameter in sepsis and septic shock. However, the data is limited in Covid-19 disease.

Aim: This study was conducted to determine the role of MDW in Covid-19 disease to triage the patients and to predict disease progression.

Material and methods: It was a propective observational study conducted during the second wave of Covid-19 pandemic. Samples of RT-PCR-proven Covid-19 cases received in haematology laboratory were included in the study. Two study groups (with CRP <25 mg/l and >25 mg/l respectively) were compared for various haematological parameters ie total leucocyte count (TLC), neutrophil (%), lymphocyte (%), monocyte (%), neutrophil-lymphocyte ratio (NLR) and monocyte distribution width. A cut-off value of MDW to differentiate both the groups were also calculated.

SPSS statistics 21version for Microsoft windows (Chicago, USA) was used for statistical analysis of data. Data were described in terms of range, mean ± standard deviation (SD), frequencies (number of cases), and relative frequencies (percentage) as appropriate. Comparison of data in the two groups was done by Student`s t-test and chi-square test as appropriate. Receiver operator curve (ROC) analysis was used to derive the cut-off point for MDW.

Results: 115 Covid-19 cases were included in the study, out of which 37 cases belonged to mild disease and 78 cases to moderate-severe disease. Of the haematological parameters difference in MDW, TLC, NLR, neutrophil (%), and lymphocyte (%) were

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

found to be statistically significant. MDW cut-off value was 21.72 with a sensitivity of 64.1% and specificity of 67.6%. ROC curve showed an area under the curve of 0.66 (95% CI, 0.552-0.761; p-value=0.007).

Conclusion: MDW is an easy, automatically calculated, rapid and reliable parameter that might help in the triage of Covid-19 patients. In this study, we found a statistically significant difference in MDW values in both the study groups which correlated with other haematological parameters including NLR and TLC.

Keywords: Covid-19, MDW, monocyte distribution width, neutrophil-lymphocyte ratio.

Introduction:

Monocyte distribution width (MDW) is a novel biomarker that has emerged as an independent factor for the early detection of sepsis and septic shock. Monocytes along with epithelial cells, dendritic cells, macrophages, and neutrophils from the first-line defense system against infectious pathogens and display volumetric changes which can be detected as MDW by most of the current haematology analyzers. MDW values increase concerning all kinds of infectious pathogens ie bacteria, fungus, viruses including the SARS-Cov-2 virus.[1] MDW in Covid-19 is a new concept and not widely studied yet. However, its role in severe Covid-19 cases as a prognostic marker has been reported by a few studies.[2-5]

The collapse of the healthcare system was witnessed throughout the world during the peaks of the Covid-19 pandemic in past, demanding a strategy to triage the patients to provide healthcare to everyone and to reduce the Covid-19 associated morbidity and mortality. As most of the Covid-19 patients have mild disease and don't require hospital admission, it is important to identify and differentiate these cases from more severe ones to utilize the healthcare facilities to their fullest.

We aimed to study and compare various haematological parameters in mild and moderate-severe Covid-19 cases and find out the cut-off value of monocyte distribution width (MDW) as a marker of progression of Covid-19 infection from mild to moderate-severe disease.

Material and methods: This was a propectivestudy conducted during the second wave of the Covid-19 pandemic, in a tertiary care centre and the procedures followed were in accordance with the institutional ethical standards and with the Helsinki Declaration. The blood samples received in haematology laboratory from COVID-19 emergency and wards were evaluated for suitability to study design. The laboratory-confirmed (by an RT-PCR test) COVID- 19 cases in which a c-reactive protein (CRP) test was also done were included in this study. However, a repeat sample from an already included patient was excluded. The cases were then divided into two groups based on the CRP-based severity grading as CRP is an established marker to grade the Covid-19 infection severity. Cases with CRP levels<25mg/l were labeled as a mild disease while the cases with CRP levels>25mg/l were labeled as a moderate-severe disease.

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

Demographic and haematological data were retrieved from the hospital-based records for all the cases. The haematological parameters included in the study were total leucocyte count (TLC), neutrophil (%), lymphocyte (%), monocyte (%), c-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), and monocyte distribution width (MDW).

Statistical analysis:SPSS statistics 21version for Microsoft windows (Chicago, USA) was used for statistical analysis of data. Continuous data were represented as mean ± standard deviation (SD) and categorical data was represented as frequencies (number of cases) or relative frequencies (percentage). Comparison of continuous data in the two groups was done by Student`s t-test and categorical data was compared by chi-square test. The 2-sided values were taken as the probability values. A P-value of less than 0.05 was considered statistically significant for the difference between comparison variables. Receiver operator curve (ROC) analysis was used to derive the cut-off point for MDW.

Results: A total of 115 patients who suited the study design were included. Of all, 37 patients had mild disease and 78 patients had moderate-severe disease. The mean (±SD) age of the study group was 53.6 (±14.95) years with the male to female ratio being 1.8:1. Mean (±SD) CRP, mean (±SD) MDW, mean (±SD) NLR, mean (±SD) TLC, mean (±SD) neutrophil percentage, and mean (±SD) lymphocyte percentage for the study group were 87.91 (±97.48), 23.01±5.66, 20.53±19.20, 13.54±6.03, 82.40±14.27 and 9.68±9.16 respectively.

Based on CRP values the study group was further divided into two groups - mild and moderate-sever. The laboratory parameters of both groups are shown in Table/Figure 1. The difference in MDW, TLC, NLR, neutrophil (%), and lymphocyte (%) were found to be statistically significant between both the groups. However, the difference in monocyte (%) and age was insignificant.

The ROC curve analysis showed an area under the curve (AUC) of 0.66 (95% CI, 0.552-0.761; p-value=0.007) for MDW to distinguish mild from moderate-severe Covid-19 cases (Table/Figure 2). The cut-off value was 21.72 with a sensitivity of 64.1% and specificity of 67.6%.

Discussion: COVID-19 was first reported in Wuhan city of China which was later named SARS-Cov-2 by World Health Organization (WHO) because of its genetic similarities with severe acute respiratory syndrome coronavirus (SARS-CoV).[6] In March 2020, it was declared a pandemic and continues to affect millions of individuals with varying clinical presentations and outcomestilltoday.

The clinical course of the Covid-19 infection is unpredictable with a wide range of symptoms ranging from asymptomatic infection to upper respiratory tract infection (URI) like symptoms to viral pneumonia. The majority of the mild Covid-19 patients recover spontaneously and do not need hospitalization. Progression to moderate or severe disease can be done on clinical grounds. Yet, it is the need of an hour to find out a parameter that can differentiate the mild cases from those requiring hospital admission and identify the progression in disease severity.

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

Numerous haematological and biochemical parameters including CRP, NLR, absolute neutrophil count, absolute lymphocyte count, lymphocyte to monocyte ratio, platelet to lymphocyte ratio, fibrinogen, procalcitonin,etc have been studied in context to Covid-19 infection. Of all, NLR[7] and CRP[8,9] are the most studied and well-established parameters for detection and prognostication of Covid-19 patients, particularly as a predictor of severe Covid-19 disease and fatal outcome. However, a limited number of studies described their role in mild Covid-19 disease with very few studies being available in the literature. Kirtana et al[9] and Wang et al[10] provided the cut-off value of CRP to differentiate mild Covid-19 cases from moderate-severe cases noted as 24.6 mg/l and 26.9 mg/l respectively. Based on which we took the value 25 mg/l to differentiate both the groups in our study.

A limited number of studies have described the role of MDW in Covid-19 infection with only 4 studies being found on Pubmed search.[2-5] These studies described the role of MDW either to differentiate Covid-19 from non-Covid-19 cases or to assess the probability of a fatal outcome. To the best of our knowledge, we conducted the first-ever study dedicated to determining a cut-off value of MDW to identify mild Covid-19 infection from those having more aggressive disease. MDW is a novel biomarker, the role of which is well-studied in the early detection of sepsis.[11] It reflects a change in circulating monocytes volume and is used as an indicator of systemic inflammation including Covid-19 infection. Monocytes increase in size with variation in cell size and produce a variety of cytokines like tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)1α, monocyte chemo-attractant protein 1 (MCP1), IL-6, etc. MDW detects the changes in monocyte biology (volume) and can automatically be reported as a part of complete blood count (CBC) by specific haematology analyzers, making it an easy and rapidly available parameter for clinicians. Lin HA et al, Ognibene A et al, and Zeng X et al compared MDW in Covid-19 patients with MDW in non-Covid-19 patients and found out that MDW value was higher in Covid-19 patients as compared to non-Covid patients with a cut-off value of ≥20, ≥20.1 and ≥20 respectively. [2,3,4]Ognibene A et al also compared the MDW value in paucisymptomatic Covid-19 patients with that in Covid-19 patients admitted to intensive-care units. The authors found a statistically significant difference in MDW values in both the groups noted as 25.4 ± 3.6 and 28.8 ± 5.3 respectively. However, there were only 41 Covid-19 patients in the study and the cut-off value of MDW was not calculated. In this study, we also found out a statistically significant difference in MDW value in mild vs moderate-severe Covid-19 disease and a cut-off value of 21.72 was calculated to differentiate both the disease groups. The observations were supported by other haematological and biochemical parameters included in our study ie NLR, absolute neutrophil count, and absolute lymphocyte count.

We think that MDW is an easily available, rapid, automatically calculated, and useful parameter in differentiating mild from moderate-severe Covid-19 disease. However, this

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

study had a few limitations. First, it was a single centre study with small sample size. Second, this was a laboratory bases study and the differentiation of mild from moderate-severe Covid-19 cases was done based on CRP and no clinical features were evaluated. Third, sequential sampling was not performed for MDW. Thus, larger prospective studies are required for validation of the findings observed in this study and for generalization of the results.

Conclusion: We believe that MDW has a significant role in Covid-19 disease and can be used as an indicator to identify the mild cases which might help in the triage of patients during peaks of this pandemic. It can indicate progression from mild to moderate-severe disease and help in the identification of severe cases at early stages which might affect the clinical outcome in such patients.

References:

1. Piva E, Zuin J, Pelloso M, Tosato F, Fogar P, Plebani M. Monocyte distribution width (MDW) parameter as a sepsis indicator in intensive care units. ClinChem Lab Med. 2021;59:1307-14
2. Lin HA, Lin SF, Chang HW, Lee YJ, Chen RJ, Hou SK. Clinical impact of monocyte distribution width and neutrophil-to-lymphocyte ratio for distinguishing COVID-19 and influenza from other upper respiratory tract infections: A pilot study. PLoS One. 2020;15:e0241262
3. Ognibene A, Lorubbio M, Magliocca P, Tripodo E, Vaggelli G, Iannelli G et al. Elevated monocyte distribution width in COVID-19 patients: The contribution of the novel sepsis indicator. ClinChimActa. 2020;509:22-4
4. Zeng X, Xing H, Wei Y, Tang Z, Lu X, Wang Z et al. Monocyte volumetric parameters and lymph index are increased in SARS-CoV-2 infection. Int J Lab Hematol. 2020;42:e266-e269
5. Riva G, Castellano S, Nasillo V, Ottomano AM, Bergonzini G, Paolini A et al. Monocyte Distribution Width (MDW) as novel inflammatory marker with prognostic significance in COVID-19 patients. Sci Rep. 2021;11:12716.
6. WHO. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (SARS-CoV-2). 1 Mar 2020.
7. Man MA, Rajnoveanu RM, Motoc NS, Bondor CI, Chis AF, LesanA et al. Neutrophil-to-lymphocyte ratio, platelets-to-lymphocyte ratio, and eosinophils correlation with high-resolution computer tomography severity score in COVID-19 patients. PLoS One. 2021;16:e0252599.
8. Statsenko Y, Al Zahmi F, Habuza T, Gorkom KN, Zaki N. Prediction of COVID-19 severity using laboratory findings on admission: informative values, thresholds, ML model performance. BMJ Open. 2021;11:e044500

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

9. Kirtana J, Kumar A, Kumar SS, Singh AK, Shankar SH, Sharma A et al. Mild COVID-19 infection-predicting symptomatic phase and outcome: A study from AIIMS, New Delhi. J Family Med Prim Care. 2020;9:5360-5
10. Wang G, Wu C, Zhang Q, Wu F, Yu B, Lv J et al. C-Reactive Protein Level May Predict the Risk of COVID-19 Aggravation. Open Forum Infect Dis. 2020;7:ofaa153
11. Polilli E, Sozio F, Frattari A, Persichitti L, Sensi M, Posata R, Di Gregorio M et al. Comparison of Monocyte Distribution Width (MDW) and Procalcitonin for early recognition of sepsis. PLoS One. 2020;15:e0227300

Table/Figure 1: Comparison of haematological and biochemical parameters in mild and moderate-severe Covid-19 disease.

S no.	**Parameters**	**Mild covid (n=38) [mean**±SD]	**Moderate-severe covid (n=77) [mean**±SD]	**p- value**
1	Age (years)	49.62±13.8	54.69±15.24	0.08
2	CRP (mg/l)	10.48±7.41	126.12±98.74	0.00
3	Monocyte distribution width (MDW)	21.12±4.45	23.9±5.96	0.01
4	TLC ($x10^3$/µl)	11.52±4.57	14.51±6.4	0.01
5	Neutrophil-Lymphocyte ratio (NLR)	14.89±17.15	23.2±19.65	0.03
6	Neutrophil (%)	77.52±14.89	84.71±13.46	0.01
7	Lymphocyte (%)	14.10±11.26	7.58±7.15	<0.001
8	Monocyte (%)	6.54±2.92	6.67±9.76	0.93

ISSN:0975-3583,0976-2833 VOL13,ISSUE05,2022

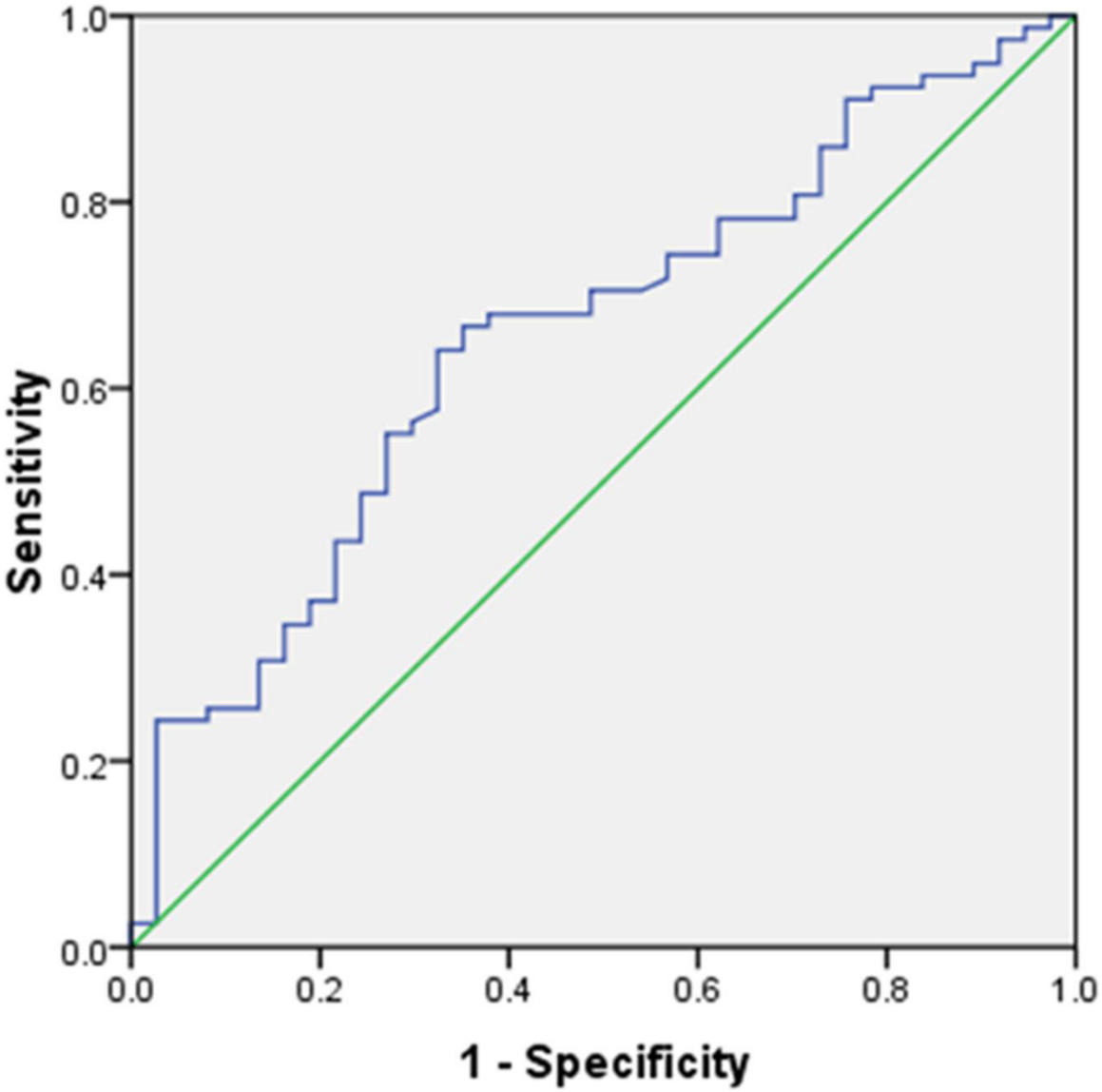

Figure legend:

Table/Figure 2: Receiver operating characteristics (ROC) curve of MDW for differentiating mild from moderate-severe Covid-19 disease (Cut-off value: 21.72; area under the curve (AUC): 0.66 with 95% CI 0.552-0.761; p-value=0.007)