Retrospective study on the efficacy of monocyte distribution width (MDW) as a screening test for COVID-19

Kentaro Wakamatsu (wakamatsu.kentaro.fe@mail.hosp.go.jp)
National Hospital Organization Omuta National Hospital

Zenzo Nagasawa
Faculty of Fukuoka Health Care, International University of Health and Welfare

Kouta Katsuki
National Hospital Organization Omuta National Hospital

Hiroyuki Kumazoe
National Hospital Organization Omuta National Hospital

Masayo Yasuda
National Hospital Organization Omuta National Hospital

Sae Kawamoto
National Hospital Organization Omuta National Hospital

Ayano Kawamura
National Hospital Organization Omuta National Hospital

Tsuyoshi Ueno
National Hospital Organization Omuta National Hospital

Ruriko Kiyotani
National Hospital Organization Omuta National Hospital

Izumi Fukui
National Hospital Organization Omuta National Hospital

Sanae Maki
National Hospital Organization Omuta National Hospital

Nobuhiko Nagata
Fukuoka Sanno Hospital

Masayuki Kawasaki
National Hospital Organization Omuta National Hospital

Hozumi Yamada
Keitendo Koga Hospital

Research Article

Keywords: Coronavirus disease 2019 (COVID-19), Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Monocyte Distribution Width (MDW), DxH 900, Monocyte

Posted Date: June 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1757985/v1

Abstract

Purpose: Pathogenic genetic testing for Coronavirus disease 2019 (COVID-19) can detect viruses with high sensitivity, however there are several challenges. In the prevention, testing, and treatment of COVID-19, more effective, safer, and convenient methods are desired. We evaluated the possibility of monocyte distribution width (MDW) as an infection biomarker in COVID-19 testing.

Methods: The efficacy of MDW as a screening test for COVID-19 was retrospectively assessed in 80 patients in the COVID-19 group and 232 patients in the Non-COVID-19 group (141 patients with acute respiratory infection, 19 patients with non-respiratory infection, 1 patient with viral infection, 11 patients who had received treatment for COVID-19, 1 patient in contact with COVID-19 patients, and 59 patients with non-infectious disease).

Results: The median MDW in 80 patients in the COVID-19 group was 23.3 (17.2-33.6), and the median MDW in 232 patients in the Non-COVID-19 group was 19.0 (13.6-30.2) ($P < 0.001$). When the COVID-19 group was identified using the MDW cut-off value of 21.3 from the Non-COVID-19 group, the area under the curve (AUC) was 0.844, and the sensitivity and specificity were 81.3% and 78.2%, respectively. Comparison of MDW by severity between the COVID-19 group and patients with acute respiratory infection in the Non-COVID-19 group showed that MDW was significantly higher in the COVID-19 group for all of mild, moderate I, and moderate II disease.

Conclusions: MDW (cut-off value: 21.3) may be used as a screening test for COVID-19 in fever outpatients, etc.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and cases of COVID-19 have been reported globally. The World Health Organization (WHO) declared a pandemic in March 2020. In Japan, it is widely known as an unprecedented infection in the 21st century. For example, the government issued a declaration of emergency depending on the increase in the number of infected people and the degree of strain on medical institutions.

In the prevention, testing, and treatment of COVID-19, more effective, safer, and convenient methods are desired. Pathogenic genetic testing by polymerase chain reaction (PCR) is performed to confirm the presence or absence of SARS-CoV-2. Pathogenic genetic testing for COVID-19 can detect viruses with high sensitivity, however there are several challenges: for example, dedicated analytical equipment and skilled human resources are required, it takes several tens of minutes to several hours to obtain results, and reagent cost per test is relatively high.

In recent years, automated hematology analyzers for laboratory testing have made remarkable progress, and recent hematology analyzers can be used to analyze not only complete blood count (CBC) (including red blood cell (RBC) count, white blood cell (WBC) count, and platelet count parameters) and WBC

differentiation, but also detailed information on WBC. In WBC analysis using an automated hematology analyzer, UniCel DxH 900 Series Coulter Cellular Analysis System (Beckman Coulter, K.K.; DxH 900), cell volume and internal cell structure are analyzed based on detecting and measuring changes in electrical resistance and scattered laser light of flow cytometry, and conductivity of cells. These parameters are also utilized as numerical values. Since WBC analysis by an automated hematology analyzer can be performed in around 1 minute, clinical laboratories use this analysis as a daily routine examination in hematology testing. Monocyte distribution width (MDW) is a unique parameter of DxH 900 showing monocyte volume distribution width. In the US, DxH 900 which measures MDW as an Early Sepsis Indicator, has been approved by the United States (US) Food and Drug Administration (FDA) as a device to assess risk for sepsis. In Europe, DxH 900 has received a Conformité Européenne (CE) mark. MDW has been attracting attention as a new biomarker. There are reports indicating that MDW is useful for early diagnosis of sepsis in the emergency department and differentiating systemic inflammatory response syndrome (SIRS) and sepsis [1-8].

In severe infections such as sepsis, cytokine storm and activation of WBC are known to occur [9-13], and morphological change of monocytes [14] and cytokine storm have been reported in COVID-19, which is an infectious disease [15-16]. Therefore, the usefulness of MDW as an index of COVID-19 has been reported [17-19].

In this study in order to explore the possibility of MDW as an infection biomarker in COVID-19 testing, we analyzed MDW in the COVID-19 group by severity of mild, moderate I, and moderate II [20] and MDW in the Non-COVID-19 group as a comparator and evaluated the clinical usefulness of MDW.

Methods

1. Patient Enrollment

Among 88 patients diagnosed with COVID-19 by PCR testing among patients who visited National Hospital Organization Omuta National Hospital between April and September 2021, 80 patients whose MDW was measured on hospital admission (severity: mild: 18 patients, moderate I: 46 patients, and moderate II: 16 patients) were included in the study. This study also included 232 people who were suspected to have COVID-19 or were diagnosed with Non-COVID-19 based on SARS-CoV-2 PCR screening testing before hospital admission. In the study, a comparative evaluation was performed retrospectively using blood samples collected at the initial visit. Severity was classified as mild, moderate I, and moderate II according to the Medical Practice Guidelines Version 6.2 [20]. and severity of Non-COVID-19 was classified according to the same criteria. The details of patient background are shown in Table 1 and Table 2.

In the diagnosis of COVID-19, nasopharyngeal swabs were collected from patients and the samples are analyzed by a fully automated genetic analyzer, Smart Gene (Mizuho Medy, Co., Ltd.). In addition, MDW in EDTA 2K-added whole blood venous sample was measured by DxH 900 (Beckman Coulter, K.K.).

Pneumonia was diagnosed by 2 radiologists and 1 pulmonologist based on chest **Computed Tomography (**CT) findings at the initial visit to the hospital.

This study was conducted after being approved by the ethics committee of National Hospital Organization Omuta National Hospital (Approval No.: 3-19).

2. Detection method of SARS-CoV-2 with Smart Gene (nasopharyngeal swab samples)

Reagent of Smart Gene consists of test cartridges with all reagents required for purification, amplification, and detection of nucleic acids and dedicated extraction reagent solution. Analysis was performed according to the manufacturer's instructions. A nasopharyngeal swab was collected from a patient using a sterilized cotton swab recommended by the kit (Nipro sponge swab TYPE R, Nipro Corporation) and suspended with dedicated extraction reagent solution. Then, 4 drops (approximately 110 μL) of the suspended sample were dripped into a test cartridge, and analysis was performed using Smart Gene. Nucleic acid purification, reverse transcription reaction, and PCR are performed for up to 45 cycles. The sample was defined positive when the result exceeded the threshold from 23 cycles of PCR [21-23].

3. Evaluated items at the initial hospital visit

At the initial visit, age, sex, presence or absence of pneumonia, WBC, MDW, C-reactive protein (CRP), and oxygen saturation of peripheral artery (SpO2) were evaluated.

4. Evaluation of diagnostic performance for COVID-19 using MDW

A Receiver Operating Characteristic (ROC) analysis on the usefulness of MDW was performed in the COVID-19 group and the Non-COVID-19 group. Non-COVID-19 group consists of patients suspected to have COVID-19 and diagnosed with Non-COVID-19 based on SARS-CoV-2 PCR screening testing before hospital admission.

5. Discrimination performance of MDW between COVID-19 and acute respiratory infection

MDW values were compared by severity between the COVID-19 group and patients with acute respiratory infection in the Non-COVID-19 group.

6. Assessment of Factors associated with MDW

Since patients in the COVID-19 group were younger than patients with acute respiratory infection in the Non-COVID-19 group, a multiple regression analysis was performed for factors associated with MDW in these 2 groups to exclude age factor.

7. Statistical analysis

Data were expressed as median and quartile, and nonparametric analysis was performed since the data distribution did not show a normal distribution. Mann-Whitney U test was used for the test between 2

groups, and Kruskal-Wallis test was used for the test among 3 and 4 groups. Diagnostic performance for COVID-19 and Non-COVID-19 was assessed by ROC analysis. Multiple regression analysis was performed for factors associated with MDW. In the significant test, $P < 0.05$ was regarded as statistically significant. All the statistical analyses were performed using Excel statistics, Bellcurve for Excel (version 3.21, Social Survey Research Information Co., Ltd.).

Results

1. Background of the COVID-19 group

The median age was 49 years of age, and the disease was more severe with increasing age. CRP and MDW increased with increasing severity (Table 1). MDW was not significantly different between mild and moderate I patients, but statistically higher in moderate II patients than in mild and moderate I patients (P <0.01) (Fig. 1).

2. Background of the Non-COVID-19 group

The Non-COVID-19 group included 141 patients with acute respiratory infection, 19 patients with non-respiratory infection, 1 patient with viral infection (generalized herpes zoster), 11 patients who had received treatment for COVID-19 [median time from onset to testing: 43 days (11 to 140 days)], 1 patient in contact with COVID-19 patients, and 59 patients with non-infectious disease (Table 2). The median age was 70 years of age in the Non-COVID-19 group, which was higher than that in the COVID-19 group. In general, CRP and MDW showed increased values in infectious disease, and statistically differences were observed among the 4 groups of acute respiratory infections, non-respiratory infections, patients who had received treatment for COVID-19, and non-infectious disease ($P < 0.01$). Although there was no significant difference between patients with acute respiratory infection and patients who had received treatment for COVID-19, MDW was statistically higher than in the group of non-infectious disease. MDW was statistically higher in the group of non-respiratory infection than other groups, and results showed no significant difference between the group of patients who had received treatment for COVID-19 and the group of non-respiratory infection (Fig. 2).

3. Evaluation of diagnostic performance for COVID-19 using MDW

ROC analysis was performed to evaluate for the diagnostic performance of MDW, CRP, and WBC in the COVID-19 group and the Non-COVID-19 group. The results revealed that MDW (area under the curve (AUC): 0.844) had higher diagnostic performance than WBC (AUC: 0.737) and CRP (AUC: 0.621). At the MDW cut-off value of 21.3, the sensitivity and specificity were 81.3% and 78.2%, respectively (Fig. 3).

4. Background of acute respiratory infection in the Non-COVID-19 group

The Non-COVID-19 group included 80 patients with mild infection, 52 patients with moderate I infection, and 9 patients with moderate II infection. The median age was 69 years in the Non-COVID-19 group, which was higher than that in the COVID-19 group (Table 2). CRP and MDW increased with increasing

severity. Since the number of moderate II patients was small, MDW was not significantly different between moderate I and moderate II patients ($P < 0.01$). However, MDW was significantly higher in moderate I and moderate II patients compared to mild patients (Fig. 4).

5. Discrimination performance of MDW between COVID-19 and acute respiratory infection

Since MDW value increased with increasing severity, MDW by severity was compared and analyzed between the COVID-19 group and patients with acute respiratory infection in the Non-COVID-19 group. MDW in each severity was significantly higher in patients with COVID-19 compared with patients with acute respiratory infection in the Non-COVID-19 group (Fig. 5).

6. Relationship between MDW and other clinical parameters

Since the COVID-19 group were significantly younger than patients with acute respiratory infection in the Non-COVID-19 group, factors associated with MDW were evaluated. As a result, COVID-19 and CRP were found to be independent factors associated with MDW. Since age was not a factor associated with MDW, it was considered possible to compare MDW by severity between the COVID-19 group and patients with acute respiratory infection in the Non-COVID-19 group (Table 3).

Discussion

In Japan, COVID-19 is diagnosed mainly by pathogenic genetic testing or antigen testing. Since genetic testing is more sensitive than antigen testing, pathogenic genetic testing is widely used for definitive diagnosis for COVID-19 in Japan [24, 25]. However, dedicated equipment and skilled human resources are required to perform genetic testing, and strict infection control measures are required for collection of nasopharyngeal swabs. There are other challenges: for example, it takes from several tens of minutes to several hours to obtain results [24] and reagent cost per test is relatively high. Therefore, it is desirable that COVID-19 screening can be performed easily in a routine clinical examination.

MDW generated by DxH 900 which was evaluated in this study, is a new cytometric parameter that reflects monocyte changes in cell volume caused by the activation of monocytes. The result is obtained in around 1 minute with routine CBC and WBC differential testing without the need for ordering additional tests. Therefore, MDW values can be easily confirmed as a routine clinical examination. Therefore, MDW can be considered a promising screening test parameter for COVID-19 if its diagnostic performance for COVID-19 is superior.

Originally, monocytes play an important role in the innate immune system against infection, and are believed to be involved in phagocytosis, antigen presentation, cytokine production, and activation of acquired immune system. Also, activation of monocytes is considered to result in the expression of various functions and the diversity of morphology [9-14]. Similarly, neutrophil volume and distribution width are changed, however, Crouser et al. evaluated MDW in patients in the emergency department and

reported that MDW was superior in detecting sepsis patients and effective as the initial biomarker to aid in diagnosis [1-3].

In addition, Ognibene et al. reported that MDW may be useful as a diagnostic aid for COVID-19 based on an observational study analyzing 147 patients suspected to have COVID-19 presenting to the emergency department [17]. The mean MDW in 41 SARS-CoV-2-positive patients was 27.3 ± 4.9, and that in 106 patients negative for SARS-CoV-2 was 20.3 ± 3.3 ($P < 0.01$). ROC analysis showed AUC of 0.91 and MDW was quite effective in distinguishing SARS-CoV-2-positive patients from negative patients. It was reported that the sensitivity, specificity, positive predictive value, and negative predictive value were 98%, 65%, 51.9%, and 98.6%, respectively at the MDW cut-off value of 20 [17]. Although our results were not superior to the results of this report, this study showed that MDW was highly effective in distinguishing SARS-CoV-2-positive patients from negative patients with AUC of 0.844. At the MDW cut-off value of 21.3, the sensitivity and specificity were 81.3% and 78.2%, respectively. Although the specificity was inferior to that of antigen testing [26], it was considered that MDW could be used as a screening test in daily clinical practice.

The study of MDW reported by Ognibene et al. includes the fact that the age of SARS-CoV-2-positive patients is higher than that of negative patients, and COVID-19 severity and breakdown of SARS-CoV-2 negative patients were not shown in the study. In our study, although the age of patients in the COVID-19 group was lower than that of patients with acute respiratory infection in the Non-COVID-19 group, multiple regression analysis showed that age was not a factor associated with MDW. Therefore, it was considered possible to compare MDW by severity between the COVID-19 group and patients with acute respiratory infection in the Non-COVID-19 group.

In diagnosis for outpatients with fever, it is required to differentiate COVID-19 patients from Non-COVID-19 with acute respiratory infection. We compared Non-COVID-19 with acute respiratory infection by severity. MDW in each severity was significantly higher in the COVID-19 group compared with patients with acute respiratory infection in the Non-COVID-19 group. These results suggest that COVID-19 is associated with more substantial morphological diversity of monocytes than Non-COVID-19 patients with acute respiratory infection, suggesting that SARS-CoV-2 has a higher ability to activate cytokine production and adaptive immunity. Furthermore, COVID-19 and CRP were found to be independent factors associated with MDW, suggesting that MDW (cut off value: 21.3) may be used as a screening test for COVID-19 in fever outpatients.

On the other hand, some patients with non-respiratory infection also showed increased MDW values. This may be attributable to the fact that many severe patients were included in the non-respiratory infection group because CRP was high. It is interesting that increased MDW values were observed in one patient with generalized herpes zoster, which is a viral infection. Since MDW is not a specific marker for COVID-19, it should be noted that MDW increases also in severe infections such as sepsis.

Although this study is limited by the fact that it is a single center study and does not include severe patients, it is the first study to evaluate MDW for COVID-19 in Japan, and it is considered significant

because there have been no reports of studies evaluating MDW by severity and it has been demonstrated that age is not a factor associated with MDW.

MDW can be performed easily in a short time as a routine clinical examination without using nasopharyngeal swab samples. Therefore, MDW is expected to be used as a screening test for COVID-19 before PCR testing. Furthermore, it is expected to be widely used clinically as a screening test at various medical institutions such as small and medium-sized hospitals and clinics where the introduction of genetic testing has been difficult.

Declarations

Conflict of interest The authors declare to have no conficts of interest and no competing interests.

Financial interests: The authors declare they have no financial interests.

Ethical approval This study was conducted after being approved by the ethics committee of National Hospital Organization Omuta National Hospital (Approval No.: 3-19).

Authors' contributions K. W. assisted with study design and interpretation of the data, had full access to the study data, assumes responsibility for the integrity of the data and the accuracy of the analysis, and drafted the manuscript. Z. N., K. K., M. Y., T. I., A. K., T. U., S. M., N. N., M. K., and H. Y. assisted with study design and interpretation of the data and edited the initial draft of the manuscript. I. F. and R. K. contributed to data collection and management. H. K. contributed to categorization of patients with COVID-19.

Acknowledgements None.

Funding No funding was received for conducting this study.

References

1. Crouser ED, Parrillo JE, Seymour C, Angus DC, Bicking K, Tejidor L, et al. Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker. CHEST. 2017;152:518-26.
2. Crouser ED, Parrillo JE, Seymour CW, Angus DC, Bicking K, Esguerra VG, et al. Monocyte Distribution Width: A Novel Indicator of Sepsis-2 and Sepsis-3 in High-Risk Emergency Department Patients. CritCare Med. 2019;47:1018-25.
3. Crouser ED, Parrillo JE, Martin GS, Huang DT, Hausfater P, Grigorov I, et al. Monocyte distribution width enhances early sepsis detection in the emergency department beyond SIRS and qSOFA. Journal of Intensive Care. 2020;8:33.
4. Woo A, Oh DK, Park CJ, Hong SB, et al. Monocyte distribution width compared with C-reactive protein and procalcitonin for early sepsis detection in the emergency department. PLOS ONE. 2021. https://doi.org/10.1371/journal.pone.0250101

5. Hausfater P, Boter NR, Indiano CM, Abreu MC, Marin AM, Pernet J, et al. Monocyte distribution width (MDW) performance as an early sepsis indicator in the emergency department: comparison with CRP and procalcitonin in a multicenter international European prospective study. Crit Care. 2021;25:227. https://doi.org/10.1186/s13054-021-03622-5.
6. Agnello L, Bivona G, Vidali M, Scazzone C, Giglio RV, Iacolino G, et al. Monocyte distribution width (MDW) as a screening tool for sepsis in the Emergency Department. Clin Chem Lab Med. 2020. https://doi.org/10.1515/cclm-2020-0417.
7. Agnello L, Sasso BL, Giglio RV, Giulia B, Gambino1 CM, Cortegiani A, et al. Monocyte distribution width as a biomarker of sepsis in the intensive care unit: A pilot study. Annals of Clinical Biochemistry: International Journal of Laboratory Medicine. 2021;58(1):70-7.
8. Piva E, Zuin J, Pelloso M, Tosato F, Fogar P, Plebani M, et al. Monocyte distribution width (MDW) parameter as a sepsis indicator in intensive care units. Clin Chem Lab Med. 2021;59(7):1307-14.
9. Guo C, Li B, Ma H, Wang X, Cai1 P, Yu Q, et al. Single-cell analysis of two severe COVID-19 patients reveals a monocyte-associated and tocilizumab-responding cytokine storm. NATURE COMMUNICATIONS. 2020;11:3924.
10. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39:517–28.
11. Mukherjee R, Barman PK, Thatoi PK, Tripathy R, Das BK, Ravindran B. Non-classical monocytes display inflammatory features: validation in sepsis and systemic lupus erythematous. Scientific Reports. 2015;5:13886.
12. Sprangers S, Vries TJ, Everts V. Monocyte Heterogeneity: Consequences for Monocyte-Derived Immune Cells. Journal of Immunology Research. 2016;1475435:1-10.
13. Cormican S, Griffin MD. Human Monocyte Subset Distinctions and Function: Insights From Gene Expression Analysis. Frontiers in Immunology. 2020;11:1070.
14. Kaur G, Sandeep F, Olayinka O, Gupta G. Morphologic Changes in Circulating Blood Cells of COVID-19 Patients. Cureus. 2021;13(2):e13416.
15. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
16. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
17. Ognibene A, Lorubbioa M, Maglioccaa P, Tripodo E, Vaggelli G, Iannelli G, et al. Elevated monocyte distribution width in COVID-19 patients: The contribution of the novel sepsis indicator. Clinica Chimica Acta. 2020;509:22–4.
18. Lin HA, Lin SF, Chang HW, Lee YJ, Chen RJ, Hou SK, et al. 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(11):e0241262.
19. 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.

Scientific Reports. 2021;11:12716.

20. Novel Coronavirus Infection (COVID-19) Medical Practice Guidelines Version 6.2. 2022. https://www.mhlw.go.jp/content/000888608.pdf.
21. Kiyasu Y, Owaku M, Akashi Y, Takeuchi Y, Narahara K, Mori S, et al. Clinical evaluation of the rapid nucleic acid amplification point-of-care test (Smart Gene SARS-CoV-2) in the analysis of nasopharyngeal and anterior nasal samples. Journal of Infection and Chemotherapy. 2022;28:543-7.
22. Wakamatsu K, Katsuki K, Ikeda T, Ueno T, Kiyotani R, Fukui I, et al. Clinical performance evaluation of “Smart Gene SARS-CoV-2 Detection Reagent”. Annals of The Japanese Respiratory Society. 2021;10(3):229-35.
23. Wakamatsu K, Katsuki K, Ikeda T, Ueno T, Kiyotani R, Fukui I, et al. Study of Threshold Cycle (Ct Value) in SARS-CoV-2 RT-PCR test with Smart Gene. Jpn J Med Pharm Sci. 2021;78(5):643-51,
24. Yanagihara K. Clinical Examinations: Mutual Understandings and Adequate Usage Suitable for a New Era. Topics: VIII. Laboratory diagnosis of infectious diseases including test for COVID-19: current issues and challenges. The Japanese Society of Internal Medicine. 2020;109(12):2509-16.
25. Guidelines for pathogen testing for novel coronavirus infection (COVID-19) version 4.1. 2022 https://www.mhlw.go.jp/content/000841541.pdf.
26. Yamakawa K, Fujimoto Y, Miyamoto K, Oshima T, Suzuki T, Nagata N, et al. Development of Rapid Immunochromatographic Enzyme Immunoassay for SARS-CoV-2 nucleocapsid Antigen. Jpn J Med Pharm Sci. 2020;77(6):937-44.

Tables

Table 1 Background of the COVID-19 group

	Age	Male / Female	WBC(/μL)	CRP (mg/dL)	MDW
Total (N=80)	49 (15-87)	45 / 35	4,600 (2,300-12,500)	1.65 (0.02-25.48)	23.3 (17.2-33.6)
Mild (N=18)	35 (15-72)	7 / 11	4,600 (2,300-7,700)	0.65 (0.06-3.62)	23.0 (17.2-29.0)
Moderate Ⅰ (N=46)	41 (18-87)	26 / 20	4,600 (2,400-9,500)	1.64 (0.02-10.42)	22.6 (18.1-33.6)
Moderate II (N=16)	64.5 (54-82)	12 / 4	5,000 (2,500-12,500)	7.81 (0.38-25.48)	26.8 (22.2-33.0)

Data are expressed as median(range)

Abbreviation: WBC: white blood cell, CRP: C-reactive protein, MDW: Monocyte Distribution Width

Table 2 Background of the Non-COVID-19 group

	Age	Male/ Female	WBC(/μL)	CRP(mg/dL)	MDW
Total (N=232)	70 (13-96)	109 / 123	6,700 (500-21,100)	0.565 (0.01-31.46)	19.0 (13.6-30.2)
Acute respiratory infection (N=141)	69 (15-92)	67 / 74	7,200 (500-21,100)	1.59 (0.01-31.46)	19.4 (15.0-28.2)
Mild (N=80)	54.5 (15-92)	33 / 47	6,550 (500-21,100)	0.37 (0.01-13.64)	18.9 (15.0-27.2)
Moderate I (N=52)	77.5 (15-90)	30 / 22	9,350 (2,100-17,900)	3.96 (0.46-31.46)	20.0 (16.4-28.2)
Moderate II (N=9)	79 (35-91)	4 / 5	6,500 (3,700-13,800)	9.21 (0.46-22.55)	21.2 (16.5-25.0)
Non-respiratory infection (N=19)	64 (13-87)	7 / 12	8,400 (3,800-18,100)	5.01 (0.03-23.15)	23.0 (16.6-30.2)
Viral infection (N=1) (generalized herpes zoster)	81	0 / 1	3,100	1.84	27.7
After Treatment for COVID-19 (N=11) [median time from onset to testing: 43 days (11 to 140 days)]	68 (24-75)	7 / 4	5,500 (2,600-9,000)	0.09 (0.02-0.7)	18.1 (16.6-21.7)
Contacted with COVID-19 patients (N=1)	21	1 / 0	6,100	0.01	16.2
Non-infectious disease (N=59)	72 (17-96)	26 / 33	5,400 (3,200-12,800)	0.11 (0.01-6.5)	18.0 (13.6-21.7)

Data are expressed as median(range)

Abbreviation: WBC: white blood cell, CRP: C-reactive protein, MDW: Monocyte Distribution Width

Table 3 Relationship between MDW and other clinical parameters Multiple regression analysis

Factors	95% Confidence Interval		*P* Value
	Lower	Upper	
Age	-0.0159	0.0211	NS
Gender	-0.6675	0.8627	NS
COVID-19	3.3219	5.3098	<0.001
Severity	-0.3102	1.1857	NS
WBC	-0.0001	0.0001	NS
CRP	0.1373	0.3081	<0.001

Abbreviation: WBC: white blood cell, CRP: C-reactive protein, MDW: Monocyte Distribution Width

Figures

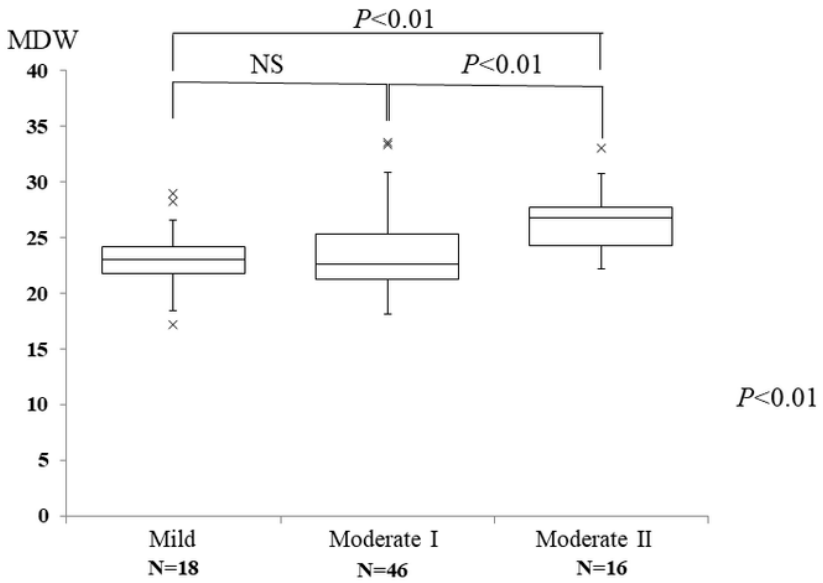

Figure 1

Figure 1

Relationship between MDW and severity in COVID-19 patients

Data are expressed as median and interquartile range(box). × shows boxplot outliers.

Abbreviation: MDW: Monocyte Distribution Width

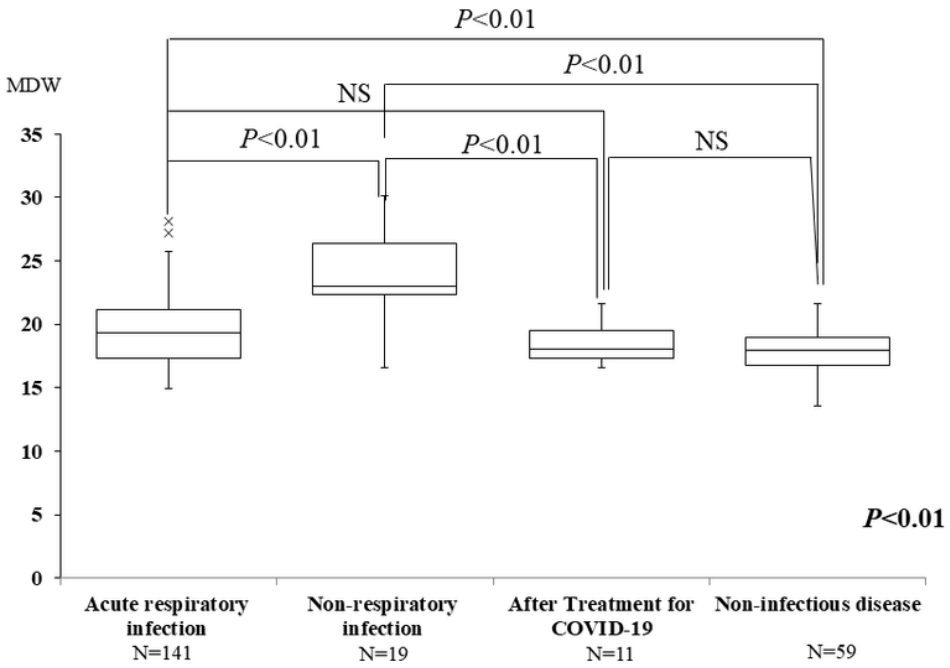

Figure 2

Figure 2

Comparison of MDW in Non-COVID-19 patients

Data are expressed as median and interquartile range(box). × shows boxplot outliers.

Abbreviation: MDW: Monocyte Distribution Width

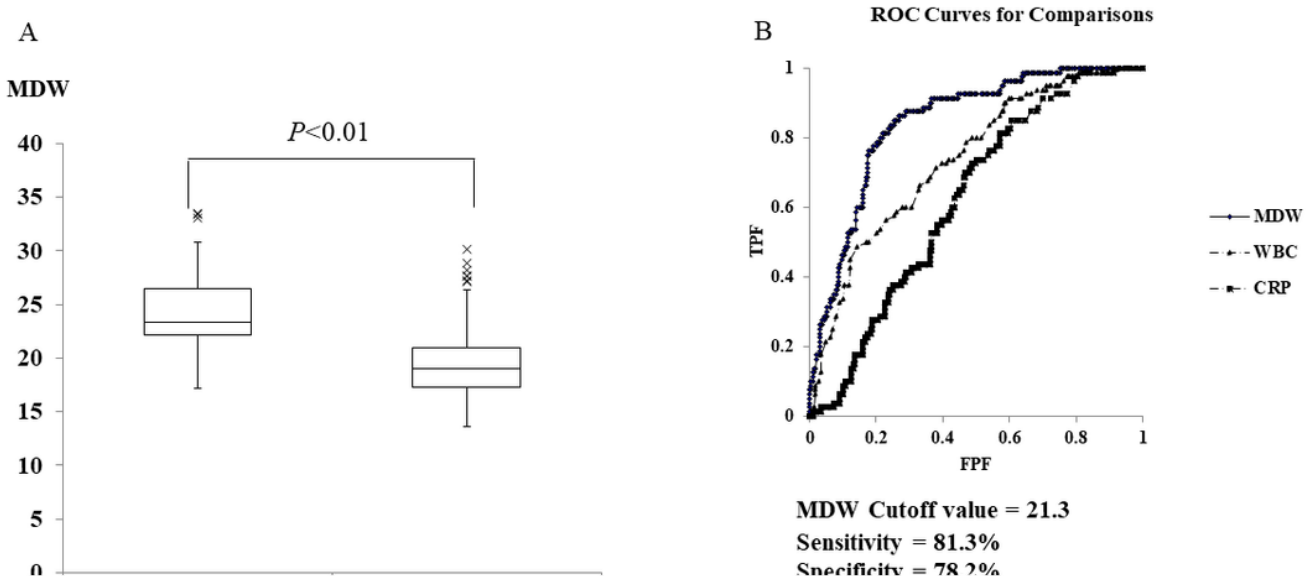

Figure 3

A, B. Results of ROC analysis

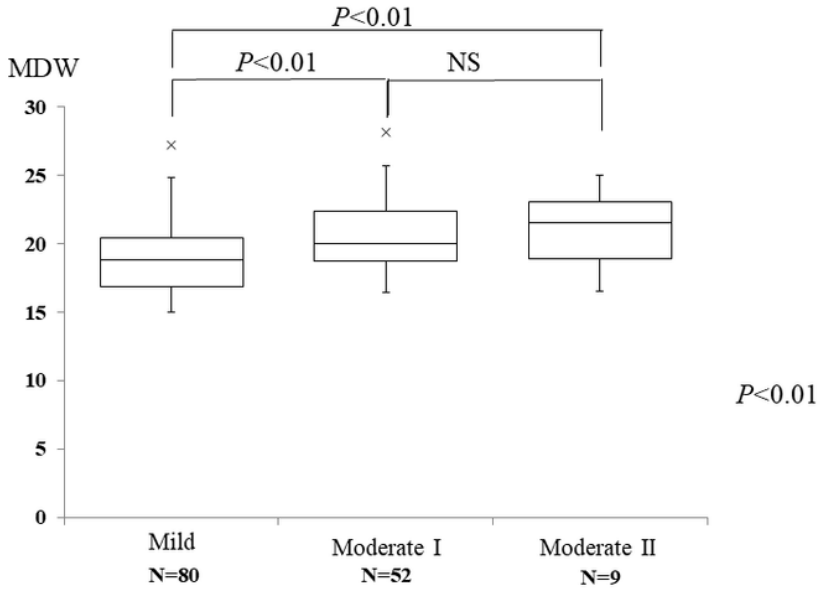

Figure 4

Figure 4

Relationship between MDW and severity in Non-COVID-19 patients with acute respiratory infection

Data are expressed as median and interquartile range(box). × shows boxplot outliers.

Abbreviation: MDW: Monocyte Distribution Width

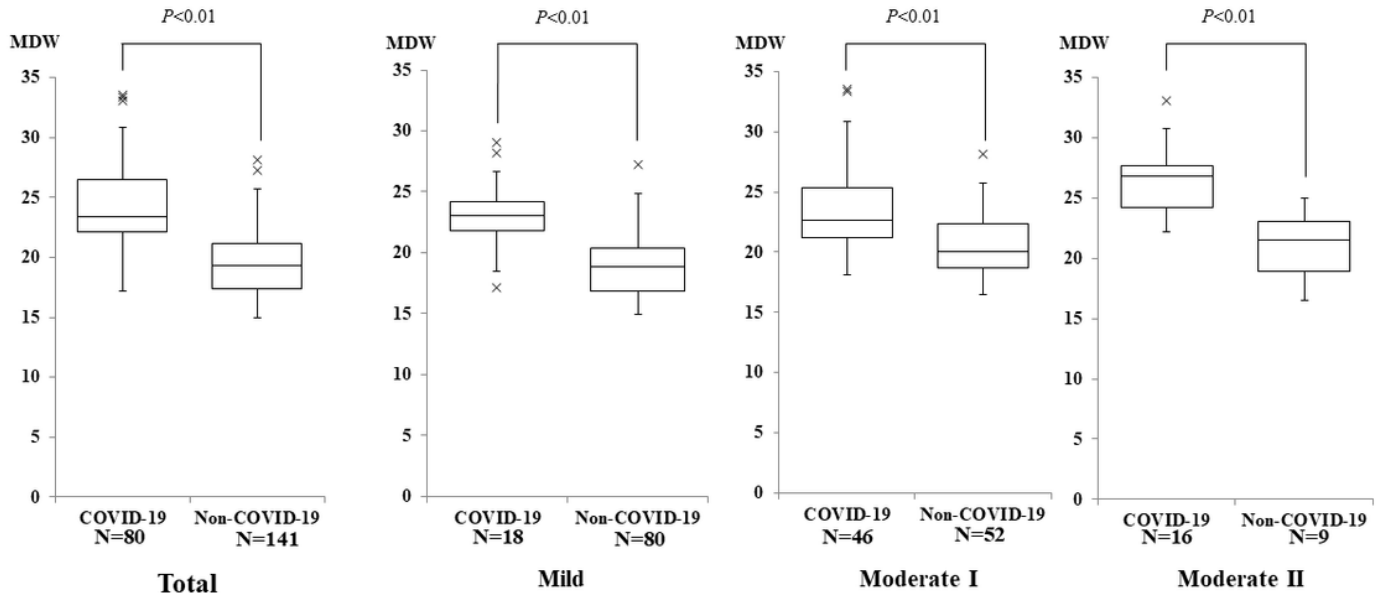

Figure 5

Figure 5

Comparison of MDW by severity between COVID-19 patients and Non-COVID-19 patients with acute respiratory infection

Data are expressed as median and interquartile range(box). × shows boxplot outliers.

Abbreviation: MDW: Monocyte Distribution Width