

Association of Monocyte Distribution Width with the Need for Respiratory Support in Hospitalized COVID-19 Patients

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Received on: 27 February 2023; Accepted on: 04 April 2023; Published on: 29 April 2023

ABSTRACT

Background: The monocyte distribution width (MDW), a novel inflammatory biomarker reflecting morphological changes in response to inflammation, has been shown to be useful in identifying COVID-19 infection or predicting death. However, data on the association with predicting the need for respiratory support are still limited. The aim of this study was to determine the association of MDW with the need for respiratory support in patients with SARS-CoV-2 infection.

Patients and methods: This is a single-center retrospective cohort study. Consecutive hospitalized COVID-19 adult patients who presented at the outpatient department (OPD) or emergency department (ED) between May and August 2021 were enrolled. Respiratory support was defined as any one of the following: conventional oxygen therapy, high-flow oxygen nasal cannula, noninvasive, or invasive mechanical ventilation. The performance of MDW was measured using the area under the receiver operating characteristic (AuROC) curve.

Results: Of the 250 enrolled patients, 122 (48.8%) patients received respiratory support. The mean MDW was significantly higher in the respiratory support group: 27.2 ± 4.6 vs 23.6 ± 4.1 ($p < 0.001$). The MDW ≥ 25 had the best AuROC characteristics of 0.70 (95% CI: 0.65–0.76).

Conclusions: The MDW is a potential biomarker that may aid in identifying individuals at risk of requiring oxygen support in COVID-19 and can be easily implemented in clinical practice.

Keywords: COVID-19, High-flow nasal cannula, Mechanical ventilation, Mortality, Monocyte distribution width, Respiratory support.

Indian Journal of Critical Care Medicine (2023): 10.5005/jp-journals-10071-24447

HIGHLIGHTS

The monocyte distribution width (MDW), a novel biomarker, might help identify individuals at risk of requiring oxygen support during COVID-19. We found that a MDW value of ≥ 25 has significantly associated with the need for respiratory support. Monocyte distribution width can be easily implemented in routine clinical practice.

INTRODUCTION

There has been growing interest in many biomarkers and their value in predicting COVID-19 severity and death.^{1,2} High levels of blood biomarkers and inflammatory cytokines (e.g., C-reactive protein (CRP) and interleukin-6 (IL-6)) are associated with disease severity and mortality. In response to SARS-CoV-2 infection, neutrophils and monocytes are recruited first, followed by cytokines that characterize the innate and adaptive immune responses. The monocyte distribution width (MDW) is a novel biomarker, as the activated monocytes increase in size during the inflammatory processes. The MDW is used as a biomarker for sepsis identification and prognostication.^{3,4} More recently, it is used to predict poor outcomes in COVID-19.^{5,6}

A MDW value of more than or equal to 20.1 was helpful to detect SARS-CoV-2 infection in confirmed COVID-19 patients,⁷ and a higher value (MDW 28.8) was associated with intensive care unit (ICU) admission.⁸ The difference between the first and last MDW < 1 correlated with unfavorable outcomes.⁹

Given the ease at which the MDW can be measured in a full blood count, a routine hospital investigation, and its low cost, it has

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How to cite this article: Daorattanachai K, Hirunrut C, Pirompnich P, Weschawalit S, Srivilaithon W. Association of Monocyte Distribution Width with the Need for Respiratory Support in Hospitalized COVID-19 Patients. *Indian J Crit Care Med* 2023;27(5):352–357.

Ethical approval: The trial was approved by the Human Research Ethics Committee of the Faculty of Medicine of Thammasat University (ID MTU-EC-EM-0-262/64). Because this study is an observational study from retrospectively collected data, the process of obtaining written informed consent was waived.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Source of support: This study is funded by the Research group in Emergency Medicine and Emergency Critical Care of the Faculty of Medicine of Thammasat University.

Conflict of interest: None

the potential to be used as a biomarker in clinical practice, especially in COVID-19 patients with potentially greater severity of symptoms, who presented to the outpatient department (OPD) or emergency department (ED). Data on the correlation between MDW and the need for respiratory support in COVID-19 patients are scarce. We, therefore, set out to investigate this relationship in patients with COVID-19 infection who need hospitalization.

PATIENTS AND METHODS

Study Design

This single-center, retrospective cohort study was conducted at Thammasat University Hospital (TUH), a tertiary care referral hospital for COVID-19 patients in the northern region of Bangkok and central Thailand. Approval from Thammasat University Ethics Committee was obtained (ID MTU-EC-EM-0-262/64). We followed the Strengthening the Reporting of Observational Studies in Epidemiology statement recommendations.

Participants

The OPD or ED patients who were 18 years or older and were at risk of getting SARS-CoV-2 virus or have suspicious symptoms of COVID-19 infection were screened. The symptoms included fever, respiratory symptoms, loss of smell or taste, alter mentation, gastrointestinal symptom, or radiological sign of viral pneumonia. All eligible patients were immediately tested for SARS-CoV-2 virus with rapid, antigen-detecting point-of-care test and had undergone RT-PCR testing in the same visit. The prevalence of COVID-19 infection in the TUH is about 15%.¹⁰ Patients with confirmed COVID-19 infection with RT-PCR and who were admitted to the TUH between 1st May and 31st August 2021 were enrolled. Patients who received treatment from other hospitals prior to admission and were referred patients were excluded. Patients were admitted to three levels of care: the ICU, intermediate ICU, and the infectious disease ward, according to their severity.

Data Sources and Collection

All of the data were retrieved from the electronic medical record. Demographic data, including age, comorbidities, initial Sequential Organ Failure Assessment (SOFA) score, and vital signs, were collected. Laboratory parameters, including complete blood count (CBC) with MDW, creatinine, lactate, C-reactive protein, D-dimer, procalcitonin, cardiac troponin, and lactate dehydrogenase (LDH), were also recorded.

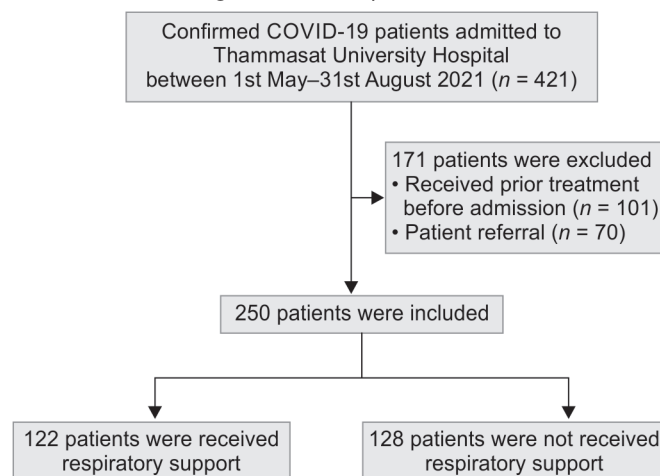
Severe COVID-19 patients were defined as patients with clinical signs of pneumonia (respiratory rate >30 breaths/minute, severe respiratory distress, or oxygen saturation <90% on room air). Critical COVID-19 patients were defined as the presence of acute respiratory distress syndrome (ARDS) or respiratory failure requiring ventilation, sepsis, or septic shock.¹¹

Respiratory support interventions were defined as any one of the following: conventional oxygen therapy, high-flow oxygen nasal cannula (HFNC), noninvasive ventilation (NIV), and invasive mechanical ventilation (IMV). Disease complications and outcomes, death or survived, were gathered. The CBC profiles were measured by Unicel DxH 900 (Beckman coulter, Inc., CA, USA) from EDTA venous samples.

Sample-size Estimation

We first performed a pilot study, gathering the data on 44 patients admitted to TUH in March 2021. Of those, 21/33 (63%) patients with

Flowchart 1: Flow diagram of the study



a MDW > 20 and 2/11(18.1%) patients with MDW ≤ 20 received respiratory support. A two-sample comparison of these proportions (63 vs 18%) was used to calculate the sample size with 90% power and 5% alpha error (two-sided test). The estimated sample size was 28 patients per MDW group.

Statistical Analysis

Descriptive data were summarized as mean and standard deviation (SD), median and interquartile range (IQR), or percentage, as appropriate. All variables were compared between patients who received respiratory support and those who did not. The unpaired *t*-test and exact probability test were used for continuous and categorical variables, respectively. The area under the receiver-operating characteristic curve (AuROC) was used to assess the performance of the MDW for predicting the need for respiratory support. The cutoff value of MDW was determined using the sensitivity, specificity, and positive likelihood ratio. Multivariable logistic regression analysis was used to evaluate the independent effect of MDW on respiratory support needs. A *p*-value less than 0.05 was statistically significant. We used STATA program version 14 (StataCorp, College Station, TX) for data analysis.

RESULTS

Participants

From 1st May to 31st August 2021, 421 confirmed COVID-19 patients were identified and were hospitalized. Of these, 170 patients were excluded due to prior treatment from other hospitals (101 patients) and referral patients (70 patients) (Flowchart 1). Of the 250 patients, who were eligible for the study, 122 patients received respiratory support, while 128 patients did not. Among these 250 patients, 50 (20%), 95 (38%), and 105 (42%) patients were admitted to ICU, intermediate ICU, and cohort infectious disease ward, respectively.

Descriptive Data

The patients who required respiratory support were significantly older (57.1 vs 46.6 years, *p* < 0.001), had chronic kidney disease (83.3% vs 16.7%, *p* < 0.008), and had higher SOFA scores on admission (3.4 vs 0.6, *p* < 0.001) when compared with those without respiratory support. Severe and critical COVID-19 infections received more respiratory support. Clinical characteristics and demographic data are summarized in Table 1.

Table 1: Patient baseline characteristics

Characteristic	Respiratory support (N = 122) n (%)	Nonrespiratory support (N = 128) n (%)	p-value
Male	76 (62.3)	70 (54.7)	0.171
Age, mean (±SD) (years)	57.1 (±16.8)	46.6 (±16.5)	<0.001
BMI ≥25 (kg/m ²)	87 (71.3)	88 (68.6)	0.721
Comorbidity			
Hypertension	52 (46.7)	39 (30.5)	0.036
Diabetes mellitus	31 (25.4)	22 (17.2)	0.178
Obesity (BMI ≥30)	37 (30.3)	31 (24.2)	0.380
Dyslipidemia	24 (19.7)	28 (21.9)	0.716
Chronic kidney diseases	10 (8.2)	2 (1.6)	0.008
Pulmonary diseases	7 (5.7)	3 (2.3)	0.164
Vital signs			
Body temperature, mean (±SD) (°C)	37.6 (0.9)	37.4 (0.9)	0.098
Respiratory rate, mean (±SD) (/min)	23.0 (4.5)	20.6 (2.9)	<0.001
Mean arterial pressure, mean (±SD) (mm Hg)	98.5 (13.1)	96.8 (13.5)	0.324
Pulse rate, mean (±SD) (beat per min)	95.1 (15.5)	92.0 (13.9)	0.099
Oxygen saturation, mean (±SD) (%)	92.8 (7.6)	97.1 (2.2)	<0.001
SOFA score at admission, mean (±SD)	3.4 (2.6)	0.6 (1.2)	<0.001
Classification of COVID-19			
Mild	4 (3.2)	127 (99.2)	<0.001
Severe	76 (62.3)	1 (0.8)	
Critical	42 (34.4)	0 (0)	

BMI, body mass index; SOFA, sequential organ failure assessment

The MDW and CRP values were significantly higher in the respiratory support group (27.2 ± 4.6 vs 23.6 ± 4.1 , $p < 0.001$ and 78.2 vs 25.5 , $p < 0.001$, respectively). Among all CBC parameters, neutrophil count, lymphocyte count, platelets, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were significantly different between the two groups, as were the mean ferritin and procalcitonin levels. By contrast, serum lactate, D-dimer, and IL-6 were not different between the two groups ($p = 0.062$ and $p = 0.676$, respectively). Additional laboratory parameters are presented in [Table 2](#).

Outcome Data

Half of the patients (122/250, 48.8%) received respiratory support that consisted mostly HFNC (113/122, 92.6%), followed by IMV (41/122, 33.6%), oxygen mask with a bag (20/122, 16.4%), and NIV (17/122, 13.9%). The 128 patients in the nonrespiratory support group might or might not receive conventional oxygen cannula according to their needs. Vasopressors and renal replacement therapy were also significantly higher in the respiratory support group: 25/122 (20.5%) vs 1/128 (0.7%), $p < 0.001$ and 9/122 (7.4%) vs 1/128 (0.7%), $p = 0.008$. The patients who required respiratory support had a lower survival rate (74.8% vs 100%, $p < 0.001$). A longer mean length of hospital stay was also found in the respiratory support group (17.5 vs 7.8 days, $p < 0.001$). The treatments and results are shown in [Table 3](#).

Compared with the nonrespiratory support group, the respiratory support group had significantly higher complication rates. Hospital-acquired pneumonia, ARDS, sepsis, septic shock, acute kidney injury, and cardiac arrest were more frequent in the respiratory support group ([Table 4](#)).

The AuROC was 0.70 [95% confidence interval (CI): 0.64–0.76, sensitivity 71.9, specificity 68.2, and positive likelihood ratio 2.26] ([Table 5](#)). By a multivariable logistic regression analysis, the independent factors associated with the need for respiratory support were MDW ≥ 25 and increasing age ([Table 6](#)). After adjusting with age, the MDW ≥ 25 was statistically significantly associated with the need for respiratory support (ORs 5.19, 95% CI: 2.96–9.11, $p < 0.001$).

DISCUSSION

In this study, we have shown that an increase in the MDW was associated with more severe disease, the need for respiratory support, and death. SARS-CoV-2 infection ranges in severity from asymptomatic to mild flu-like symptoms to severe respiratory failure and multi-organ failure. Severe disease is related to the cytokine storm that develops in the second phase of the illness as the viral load is declining. Several studies have addressed the usefulness of biomarkers for predicting disease severity and outcomes of COVID-19 infection like CRP, thrombocytopenia, procalcitonin, D-dimer, and LDH.^{1,2}

When host cells are infected by viruses, the innate immune system is activated to eliminate them, and interferon plays an important role. Macrophages are one source of type-I interferon, and NK cells are primed to be activated by type-I interferon, which produces interferon-gamma (type-II interferon) to prime macrophages. In a hyperactive state, macrophages grow larger, and their ability to phagocytose and present antigens increases. During the inflammatory process, monocytes are attracted away

Table 2: Initial laboratory parameters at presentation

Laboratory	Respiratory support (N = 122)		Nonrespiratory support (N = 128)		p-value
	Mean	±SD	Mean	±SD	
Complete blood count and coagulogram					
Initial monocyte distributive width (unit)	27.2	4.6	23.6	4.1	<0.001
Hemoglobin (g/dL)	13.8	1.8	13.4	1.8	0.110
White blood cell count (median, IQR) (10 ³ /μL)	6.5	4.9, 8.5	6	4.7, 7.6	0.215
Neutrophil count (median, IQR) (cells/mm ³)	4617	3120, 6873	3469	2562, 4900	<0.001
Lymphocyte count (median, IQR) (cells/mm ³)	999	666, 1470	1540	1196, 1890	<0.001
Platelets (10 ³ /μL)	202.1	82.8	237.9	88.8	<0.001
Neutrophil-to-lymphocyte ratio (median, IQR)	4.42	2.54, 7.94	2.22	1.42, 3.58	<0.001
Platelets-to-lymphocyte ratio (median, IQR)	184.6	113.8, 291.9	139.7	103.2, 195.9	0.001
Blood chemistry					
Creatinine (median, IQR) (mg/dL)	1.01	0.7, 1.3	0.85	0.69, 1.04	0.002
Lactate (median, IQR) (mmol/L) (n = 91)	2.9	1.8, 3.8	2.3	1.64, 2.6	0.062
CRP (median, IQR) (mg/dL) (n = 180)	78.21	42.3, 87.52	25.5	8.42, 68.35	<0.001
Interleukin-6 (median, IQR) (pg/mL) (n = 24)	19.8	13.4, 45.82	27.48	4.77, 50.19	0.676
D-dimer (median, IQR) (ng/mL) (n = 96)	666	395, 1980	672	365, 1101	0.511
Ferritin (median, IQR) (ng/mL) (n = 9)	881	430, 1124	27.5	12, 43	0.040
Procalcitonin (median, IQR) (μg/L) (n = 125)	0.17	0.09, 0.37	0.11	0.07, 0.22	0.019
Cardiac troponin (median, IQR) (ng/mL) (n = 24)	0.04	0.009, 0.165	0.01	0.004, 0.095	0.260
NT-proBNP (median, IQR) (pg/mL) (n = 16)	1724	572, 3766	20	39, 201	0.080
LDH (median, IQR) (U) (n = 60)	420	293, 554	353	233, 437	0.022

CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Table 3: Treatment and outcomes

Treatment	N (%)		p-value
	Respiratory support (N = 122)	Nonrespiratory support (N = 128)	
Received respiratory support* (N = 122)			
Oxygen mask with bag		20 (16.4)	
High-flow nasal cannula		113 (92.6)	
Noninvasive ventilation		17 (13.9)	
Mechanical ventilation		41 (33.6)	
Treatment			
	Respiratory support (N = 122)	Nonrespiratory support (N = 128)	p-value
	n (%)	n (%)	
Vasopressor requirement	25 (20.5)	1 (0.7)	<0.001
Renal replacement therapy	9 (7.4)	1 (0.7)	0.008
Results			
7-day mortality	5 (4.1)	0 (0)	0.025
14-day mortality	20 (16.4)	0 (0)	<0.001
28-day mortality	26 (21.3)	0 (0)	<0.001
Length of stay mean (±SD) (day)	17.5 (10.1)	7.8 (4.9)	<0.001
Survival to discharge	90 (74.8)	128 (100)	<0.001

*Some patients need more than one method of respiratory support

from the circulation,^{12,13} and when activated, their size increases.¹⁴ This change in size and MDW can be measured in new-generation hematologic analyzers. Monocyte distribution width has been used as a marker for the early detection of sepsis and a predictor of prognosis.^{3,4} It is also raised in SARS-CoV-2 infection and is associated with poor outcomes.⁹

Many biomarkers were discovered in COVID-19 patients to predict outcomes and guiding treatment. C-reactive protein is a predictor for disease severity and poor outcomes.^{2,15} A previous study in India found that nonsurvivors COVID-19 patients had a significantly higher CRP level ($p < 0.001$),¹⁶ Riva et al. reported a significant positive correlation between MDW and inflammatory

Table 4: Complications

Complication	Respiratory support (N = 122)	Nonrespiratory support (N = 128)	p-value
	n (%)	n (%)	
Hypotension	32 (26.2)	1 (0.7)	<0.001
Arrhythmia	22 (18)	3 (2.3)	<0.001
Cardiac arrest	32 (26.2)	0 (0)	<0.001
Acute respiratory distress syndrome (ARDS)	40 (32.8)	1 (0.7)	<0.001
Hospital-acquired pneumonia	54 (44.3)	4 (3.1)	<0.001
Sepsis	49 (40.2)	1 (0.7)	<0.001
Septic shock	28 (23)	0 (0)	<0.001
Acute kidney injury	41 (33.6)	7 (5.5)	<0.001
Gastrointestinal bleeding	10 (8.2)	1 (0.7)	0.004
Received blood transfusion	11 (9.0)	0 (0)	<0.001
Pulmonary embolism	4 (3.3)	0 (0)	0.053
Transaminitis	24 (19.7)	14 (10.9)	0.048

Table 5: Cut point of the MDW in COVID-19 patients with respiratory support requirement

Cut point	AuROC	Sensitivity, % (95% CI)	Specificity, % (95% CI)	LR+	LR-
(≥20)	0.572	96.7 (91.8–99.1)	17.8 (11.7–25.5)	1.18	0.19
(≥21)	0.618	95.9 (90.6–98.6)	27.9 (20.4–36.5)	1.33	0.15
(≥22)	0.645	94.2 (88.4–97.6)	34.9 (26.7–43.8)	1.45	0.17
(≥23)	0.674	86.8 (79.4–92.2)	48.1 (39.2–57.0)	1.67	0.28
(≥24)	0.671	76.9 (68.3–84.0)	57.4 (48.4–66.0)	1.80	0.40
(≥25)	0.700	71.9 (63.0–79.7)	68.2 (59.4–76.1)	2.26	0.41
(≥26)	0.657	56.2 (46.9–65.2)	75.2 (66.8–82.4)	2.27	0.58
(≥27)	0.630	46.3 (37.2–55.6)	79.8 (71.9–86.4)	2.30	0.67
(≥28)	0.582	28.9 (21.0–37.9)	87.6 (80.6–92.7)	2.33	0.81
(≥29)	0.581	24.0 (16.7–32.6)	92.2 (86.2–96.2)	3.09	0.82
(≥30)	0.564	19.0 (12.4–27.1)	93.8 (88.1–97.3)	3.07	0.86

AuROC, area under the receiver operating characteristic curve; 95% CI, 95% confidence interval; LR+, likelihood ratio of positive; LR-, likelihood ratio of negative

Table 6: Logistic regression of MDW ≥ 25 for respiratory support

Respiratory support	Odd ratio	95% CI	p-value
MDW ≥ 25	5.19	2.96–9.11	<0.001
Age	1.03	1.02–1.05	<0.001

markers such as CRP, fibrinogen, and ferritin in COVID-19 patients.⁵ Alsuwaidi revealed that high MDW value (>24.6) had a strong correlation with poor-prognosis COVID-19 biomarkers.⁶ Similar to previous studies, CRP was elevated in patients with SARS-CoV-2 infection and statistically significantly higher in the respiratory support group. Among all CBC parameters, neutrophil count, lymphocyte count, platelets, NLR, and PLR are significantly higher in the respiratory support group. Neutrophil-to-lymphocyte ratio and PLR are combined hematologic biomarkers elevated in COVID-19 patients¹⁷ and associated with severe COVID-19.¹⁸

We identified a MDW value of 25 as the best cutoff value associated with the need for respiratory support for a sensitivity of 72% and specificity of 68%. This finding is consistent with that of Kim et al. who showed that a MDW of 25.8 at admission predicted

the need for HFNC or IMV in COVID-19 patients.¹⁹ However, this MDW cutoff demonstrated a fair predictive discrimination for 28-day mortality (AuROC 0.64), which differed from the study of Riva et al., who found that a MDW cutoff 26.4 was associated with a fatal outcome with an AuROC of 0.76 (95% CI: 0.66–0.87), and a sensitivity of 0.75 and specificity of 0.70.⁵

Crouser et al. determined that a MDW > 20 distinguished sepsis from other conditions in high-risk emergency patients,²⁰ while a MDW ≥ 20 favored a diagnosis of COVID-19 over other respiratory tract infections and influenza with AuROCs of 0.70 and 0.63 for COVID-19 and influenza, respectively.²¹ In another study, the same cutoff showed an outstanding diagnostic performance for predicting SARS-CoV-2 infection with an AuROC of 0.91, sensitivity 98%, specificity 65%, positive predictive value 51.9%, and negative predictive value 98.6%.⁸ Previous studies have shown that a MDW ≥ 21 was the best threshold for predicting hospital stay longer than 14 days (OR 5.67, 95% CI: 1.19–27.10),²² and a MDW > 28 was significantly associated with ICU admission.⁸

We also found that increasing age and MDW ≥ 25 were significantly associated with the need for respiratory support. Grasselli et al. revealed that a 10-year increase in age was associated with an increased risk of mortality of 75% (HR 1.75, 95% CI: 1.60–1.92).²³ Another study in India also found that age was significantly higher in patients with respiratory failure (P/F ratio less than 300, $p = 0.023$).²⁴ Respiratory rate has also been identified as an independent predictor for a fivefold increase in mortality (OR 4.90, 95% CI: 1.08–22.24).

Our study had several limitations. First, this was a retrospective study from one single center in a middle-income country, so its generalizability is limited. We did not exclude other causes of increased MDW, e.g., hematologic malignancy. Nonetheless, this study sheds light on a potential biomarker that may aid in identifying individuals at risk of requiring oxygen support. Further studies are warranted to explore the clinical utility of MDW in predicting clinical outcomes.

CONCLUSION

In conclusion, we have shown that the MDW is a potential biomarker that may aid in identifying individuals at risk of requiring oxygen support in COVID-19. Measuring MDW is inexpensive, reported as part of a routine CBC, and easily implemented. Further studies

are warranted to explore the clinical utility of MDW in predicting clinical outcomes.

AUTHOR'S CONTRIBUTIONS

KD, WS, and SW were responsible for conceptualization and methodology. KD and CH were responsible for data curation and investigation. KD, SW, and WS were responsible for formal analysis. KD and WS were responsible for supervision, validation, and review and editing. KD, SW, WS, CH, and PP were responsible for original draft preparation. All authors contributed to data interpretation and discussion and approved the published version of the paper.

ACKNOWLEDGMENT

The authors greatly appreciate all the members of the Thammasat University Hospital for their efforts and devotion during the crisis of COVID-19. This study is part of the project from the Research Group in Emergency Medicine and Emergency Critical Care of the Faculty of Medicine of Thammasat University.

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