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Efficacy of monocyte distribution width in predicting critical illness in patients with COVID-19 pneumonia: a retrospective cohort study

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Abstract

Background Identifying patients at a risk of severe COVID-19 is crucial for prompt intervention and mortality risk mitigation. The monocyte distribution width (MDW) is an effective accurate predictor of sepsis in emergency settings, facilitating timely patient management. However, few reliable laboratory parameters are available for predicting the severity and prognosis of COVID-19. Thus, this study was conducted to investigate whether MDW can accurately predict the severity and progression of COVID-19 pneumonia.

Methods This retrospective cohort study included patients with COVID-19 pneumonia who had been admitted to our hospital between January 1, 2022, and September 31, 2022. The primary outcome was the development of critical illness, which was assessed in terms of intensive care unit (ICU) admission, need for mechanical ventilation (MV), or mortality. The secondary outcomes were durations of ICU stay, MV, and hospital stay. Multivariate logistic regression was performed to estimate the risks of critical illness and mortality.

Results Data from 878 patients with COVID-19 were analyzed. Of these, 258 (29.4%) developed critical illness. The high-MDW group (MDW > 22) showed a higher rate of critical illness (155/452, 34.29%) compared to the low-MDW group (103/426, 24.18%). Mortality was also higher in the high-MDW group (95/452, 21.02%) than in the low-MDW group (37/426, 8.69%). Patients with MDW > 22 exhibited a significantly higher risk of developing critical illness (adjusted odds ratio [aOR]: 1.48; 95% confidence interval [CI]: 1.08–2.04) and mortality (aOR: 2.46; 95% CI: 1.63–3.74) compared to those with MDW ≤ 22.

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Conclusion Our findings suggest that an elevated MDW value at presentation may serve as a promising predictor of severe outcomes in patients with COVID-19 pneumonia. This underscores the need for further research to validate the utility of MDW in predicting critical illness among patients with viral pneumonia.

Keywords Monocyte distribution width, COVID-19, Pneumonia, Infection severity, Critical illness

Introduction

The initial outbreak of COVID-19 affected over half a billion individuals worldwide, causing more than 6 million deaths and posing a considerable burden on global health-care systems [1]. Consequently, researchers have increasingly focused on understanding and predicting the severity of COVID-19. Patients with COVID-19 who experience hyperinflammation are at increased risk of severe outcomes, such as death, severe respiratory distress necessitating mechanical ventilation (MV), and intensive care unit (ICU) admission. Regular blood tests and continuous laboratory evaluations are essential for identifying the hyperinflammatory state associated with COVID-19 [2–4]. However, a definitive laboratory biomarker that can consistently predict disease severity in patients with COVID-19 remains to be identified [5].

Monocytes are activated and undergo morphological changes during the immune response [6]. In cases of severe infection, immune dysregulation occurs, characterized by a combination of a heightened proinflammatory state and immunosuppression due to an overwhelmed immune response [7]. This immune dysregulation results in increased morphological and size heterogeneity of monocytes, thereby leading to an elevated Monocyte Distribution Width (MDW) [8]. MDW has emerged as a key hematological indicator for the early detection of systemic infections such as sepsis. MDW, which indicates infection severity, can predict potential complications such as septic shock and organ failure [9–12]. Moreover, MDW can be used to monitor treatment efficacy and differentiate between bacterial and viral infections [12].

In severe COVID-19 cases, we hypothesize that a similar pattern of immune dysregulation occurs. This would suggest that MDW, reflecting the increased heterogeneity in monocyte morphology and size, could serve as a useful predictor for identifying patients at risk of developing critical illness. Previous studies had recognized MDW as a preliminary indicator of severe COVID-19 [13–15]. However, little studies have focused on the application of MDW in detecting severe COVID-19 in Asian populations. Furthermore, the MDW threshold for clinical outcome prediction remains to be established. Therefore, we conducted this study to investigate the predictive value of MDW on critical illness in patients with COVID-19 pneumonia.

Methods

Study design and setting

This retrospective cohort study was conducted at China Medical University Hospital, Taichung, Taiwan. Between January 2020 and December 2022, 8,872,955 confirmed cases of COVID-19 and 15,253 COVID-19-related fatalities were recorded in the study region [16]. SARS-CoV-2 infection management protocols issued by the Taiwan Centers for Disease Control recommend admission to specialized care units for patients exhibiting moderate to severe symptoms, those with critical illness, those exhibiting pneumonia signs on X-ray, those requiring supplemental oxygen ($SpO_2 < 94\%$). This recommendation is specifically for patients with risk factors that may exacerbate the disease and aims to ensure appropriate care in facilities equipped to meet patients' medical needs.

Study cohort

This study included patients who had received a diagnosis of COVID-19 (made through reverse transcription polymerase chain reaction) at China Medical University Hospital between January 1, 2022, and September 30, 2022. We included only patients with COVID-19 pneumonia who required hospitalization and either supplemental oxygen or remdesivir treatment (administered to those with room air SpO2 < 94% or requiring oxygen support [17]). We excluded patients not requiring hospitalization, those admitted for reasons unrelated to COVID-19, those lacking risk factors for severe COVID-19, those aged < 20 years, and those with incomplete medical records. Each patient was monitored for 30 days or until discharge or death, whichever occurred first.

Study variables and data collection

We retrospectively collected relevant data from the patients' electronic medical records by using a standardized data extraction template. Thus, we gathered information on their basic demographic details such as age and sex as well as of preexisting conditions associated with an increased risk of severe COVID-19, including age, cancer, chronic kidney disease, cardiovascular disease, diabetes mellitus, chronic lung diseases, chronic liver disease, obesity ($BMI \geq 30\ kg/m^2$), cancer, organ transplantation status and use of immunosuppressive medications [18–20]. In addition, we recorded each patient's COVID-19 vaccination status and use of oral antiviral drugs before hospitalization. Inflammatory biomarkers, including MDW, C-reactive protein (CRP),

white blood cell count (WBC), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) upon presentation at the ED were accessed and recorded.

Outcome measurement

The primary outcome was development of critical illness, defined by a composite of ICU admission, need for MV, or death [21–23]. The secondary outcomes included mortality, the durations of ICU stay, MV, and hospital stay. These variables were monitored from either hospital or ICU admission until discharge or death.

Statistical analysis

All statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a two-tailed p-value of < 0.05.

Patients were stratified into two groups by critical illness. Demographic characteristics are presented using descriptive statistics. Categorical variables are presented in terms of numbers and percentages, whereas continuous variables are presented in terms of mean ± standard deviation values. Nonparametric variables are presented in terms of median values with interquartile ranges.

Bivariate analysis was performed to identify predictors of critical illness in patients with COVID-19. The chi-square and Student *t* tests were used to analyze categorical and continuous variables, respectively. The Mann–Whitney U test was used for nonparametric variables.

Variables there were significantly associated with the development of critical illness and risk factors for critical COVID-19 illness that identified in previous studies were further analyzed in multivariate analysis [24, 25] Co-morbidities that could be risk factors of developing COVID-19 critical illness were categorized based on organ systems according to risk factors described above. The number of risk factors for each patient was calculated based on the number of affected systems and categorized into three groups: 1,2 and ≥3. Since age was already included as a variable in the model, it was not counted again as a separate risk factor in this calculation. Multivariate logistic regression models with adjustment for potential confounders, including age, number of risk factors for critical illness, white blood count, and vaccination status was performed to evaluate the predictive value of MDW on critical illness after COVID-19. As inflammatory biomarkers such as NLR, CRP, and PLR, were highly collinear with MDW and theoretically do not influence the result of MDW, we conducted multiple models with replaced MDW with other indicators with adjustment for the same covariates. Receiver operating curve analysis was performed (supplementary Figure S1), and the Youden J statistic was used to determine the optimal cutoff value for MDW in predicting critical illness. To address potential bias arising from the exclusion of a substantial number of patients due to missing MDW values, we performed multiple imputations for MDW and other relevant indicators. Subsequently, we conducted multivariate logistic regression models using the same covariates as in the primary analysis to serve as a sensitivity test.

Results

Among the 16,667 COVID-19 patients identified between January 1 and September 31, 2022, a final cohort of 878 hospitalized patients with available Monocyte Distribution Width (MDW) values was included in the study. Patients were excluded if they lacked hospital admission, initial MDW values, or severe risk factors, were admitted for conditions other than COVID-19, were under 20 years of age, or had missing data (Fig. 1). The cohort had a mean age of 69.92 ± 16.18 years, and consisted of 523 males (59.57%) and 355 females (40.43%). Of these, 258 patients (29.38%) were classified as critical cases, and 620 (70.62%) as non-critical cases. Among the critical cases, 167 patients (19.02%) required ICU care, 158 (18.00%) required mechanical ventilation, and 132 (15.03%) experienced mortality.

Table 1 presents a comparison between patients with and without critical illness due to COVID-19. There was no significant difference in age or sex distribution between the critical and non-critical groups. However, a higher proportion of patients with critical illness had three or more risk factors (59/258, 21.71%) compared to non-critical patients (20/620, 3.23%). Additionally, non-critical patients were more likely to have received two or more vaccine doses (370/620, 59.68%) than those with critical illness (110/258, 42.64%). The use of oral antiviral drugs was also more common in the non-critical group (320/620, 51.61%) compared to the critical group (61/258, 23.64%). Laboratory findings revealed that critical illness was associated with elevated levels of CRP, MDW, WBC, and NLR.

Based on the Youden J statistics, patients were stratified into high-MDW (MDW > 22) and low-MDW (MDW ≤ 22) groups. In the high-MDW group ($n = 452$), 155(34.29%) patients developed critical illness, compared to 103 (24.18%) in the low-MDW group ($n = 426$; $p = 0.001$). Mortality was also higher in the high-MDW group, with 95 deaths (21.02%) compared to 37 deaths (8.69%) in the low-MDW group ($p < 0.001$). Although not statistically significant, the high-MDW group also had a higher rate of mechanical ventilation use (94/452, 20.80%) compared to the low-MDW group (64/426, 15.02%; $p = 0.064$). Trends toward higher ICU admission rates, longer ICU stay, and longer days of MV support were also observed in the high-MDW group (Table 2).

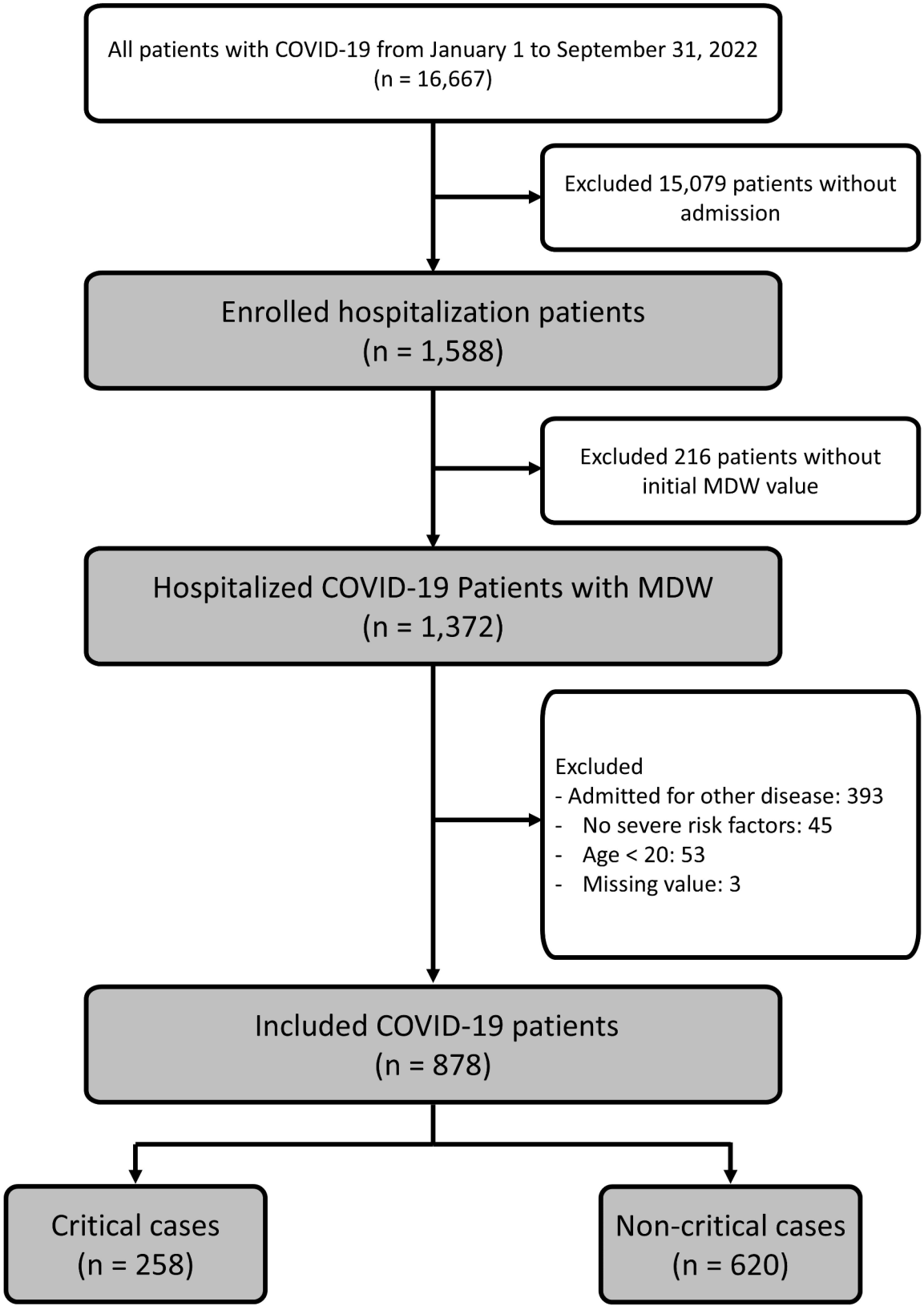

Fig. 1 Patient enrollment flowchart

Table 1 Demography and clinical characteristics of COVID-19 patients

Variables	Critical disease		
	No (*n* = 620)	Yes (*n* = 258)	*p* value
Age	69.54 ± 16.27	70.85 ± 15.96	0.274
Male sex	366(59.03)	157(60.85)	0.616
Body mass index			0.239
< 30	567(91.45)	242(93.80)	
≥ 30	53(8.55)	16(6.20)	
Diabetes mellitus	223(35.97)	100(38.76)	0.434
Cardiovascular disease	104(16.77)	38(14.73)	0.453
Chronic kidney disease	124(20.00)	68(26.36)	0.037
Chronic lung disease	39(6.29)	13(5.04)	0.474
Chronic liver disease	36(5.81)	20(7.75)	0.282
Cancer	158(25.48)	88(34.11)	0.009
Organ transplantation	15(2.42)	7(2.71)	0.799
Immunosuppressant	13(2.10)	3(1.16)	0.419
Number of risk factors			0.026
1	360(58.06)	134(51.94)	
2	171(27.58)	68(26.36)	
≥ 3	89(14.35)	56(21.71)	
Vaccination			< 0.001
Nonvaccinated	193(31.13)	124(48.06)	
1 dose	57(9.19)	24(9.30)	
≥ 2 doses	370(59.68)	110(42.64)	
Antiviral drug	320(51.61)	61(23.64)	< 0.001
WBC, 10^3/μL	8.69 ± 12.14	11.39 ± 6.86	< 0.001
MDW	22.49 ± 4.84	23.70 ± 5.49	0.002
CRP, mg/dL	4.78 ± 6.36	7.54 ± 7.73	< 0.001
Neutrophil-to-lymphocyte ratio	9.42 ± 12.12	16.46 ± 17.21	< 0.001
Platelet-to-lymphocyte ratio	2.91 ± 2.67	3.40 ± 3.83	0.064

Abbreviations: CRP, C-reactive protein; MDW, monocyte distribution width; WBC, white blood count

Table 2 Comparison of prognosis for COVID-19 patients with high and low-MDW

Variables	MDW ≤ 22 (*n* = 426)	MDW > 22 (*n* = 452)	*p* value
Critical case	103(24.18)	155(34.29)	0.001
Mortality	37(8.69)	95(21.02)	< 0.001
ICU	73(17.14)	94(20.80)	0.167
Mechanical ventilator	64(15.02)	94(20.80)	0.026
Duration of ICU, median (IQR)	11.0(6.0–21.0)	13.0(6.0–24.0)	0.209
MV duration, median (IQR)	8.0(2.0–18.0)	10.0(5.0–24.0)	0.064
Length of hospital stay, median (IQR)	19.0(10.0–35.0)	18.0(10.0–33.0)	0.241

Abbreviations: ICU, intensive care unit; MV, mechanical ventilation; MDW, monocyte distribution width

Multivariate logistic regression analysis revealed that patients with an MDW > 22 had a 1.48-fold higher likelihood of developing critical illness (adjusted OR: 1.48; 95% CI: 1.08–2.04; $p = 0.016$). Additionally, the number of risk factors was a significant predictor; patients with three or more risk factors exhibited a 2.01-fold increased risk compared to those with only one risk factor (adjusted OR: 2.01; 95% CI: 1.32–3.06; $p < 0.001$). Conversely, vaccination demonstrated a protective effect, as individuals who received two or more doses had a significantly reduced risk of critical illness (adjusted OR: 0.56; 95% CI: 0.40–0.77; $p = 0.012$). When MDW was replaced by other inflammatory markers in the analysis, CRP (OR: 1.04; 95% CI: 1.01–1.06; $p = 0.004$), NLR (OR: 1.03; 95% CI: 1.02–1.04; $p < 0.001$), and PLR (OR: 1.05; 95% CI: 1.01–1.10; $p = 0.042$) all demonstrated significant associations with disease severity (Table 3). A sensitivity test using multiple imputation for missing laboratory biomarkers, rather than excluding patients lacking MDW, was conducted and presented in Supplementary Table S1. The results were consistent with those of the primary analysis.

Table 3 Multivariate logistic regression for critical COVID-19 illness

Variables	Adjusted OR	95% CI		*p* value
MDW > 22	1.48	1.08	2.04	0.016
Age	1.00	0.99	1.01	0.834
Number of risk factor				
1	Reference			
2	1.23	0.85	1.78	0.448
≥ 3	2.01	1.32	3.06	< 0.001
Vaccine				
0	Reference			
1	0.77	0.44	1.34	0.913
≥ 2	0.56	0.40	0.77	0.012
White blood count	1.04	1.01	1.07	0.006
Replacing MDW with other inflammatory biomarkers of interesting				
MDW	1.02	1.01	1.06	0.046
Neutrophil-to-lymphocyte ratio	1.03	1.02	1.04	< 0.001
C-Reactive protein	1.04	1.01	1.06	0.004
Platelet-to-lymphocyte ratio	1.05	1.01	1.10	0.042

Abbreviations: MDW, monocyte distribution width

In COVID-19-related mortality, MDW > 22 also emerged as a predictor, with an adjusted OR of 2.46 (95% CI: 1.63–3.74; $p < 0.001$). Patients with three or more risk factors had an increased risk of mortality (adjusted OR: 1.76; 95% CI: 1.08–2.89; $p = 0.024$). Conversely, vaccination with two or more doses was associated with a reduced mortality risk (adjusted OR: 0.60; 95% CI: 0.40–0.90; $p = 0.014$). When MDW was replaced with other biomarkers, CRP and NLR continued to demonstrate predictive value for mortality. In contrast, PLR did not show significant predictive associations (Table 4). The sensitivity test using multiple imputation for laboratory biomarkers, presented in Table S2, yielded similar results.

Table 4 Multivariate logistic regression for mortality COVID-19 illness

Variables	Adjusted OR	95% CI		*p* value
MDW > 22	2.46	1.63	3.74	< 0.001
Age	1.01	0.99	1.03	0.057
Number of risk factor				
1	Reference			
2	1.40	0.89	2.18	0.149
≥ 3	1.76	1.08	2.89	0.024
Vaccine				
0	Reference			
1	0.79	0.40	1.57	0.494
≥ 2	0.60	0.40	0.90	0.014
White blood count	1.02	0.99	1.04	0.138
Replacing MDW with other inflammatory biomarkers of interesting				
MDW	1.09	1.05	1.14	< 0.001
Neutrophil-to-lymphocyte ratio	1.03	1.02	1.04	< 0.001
C-Reactive protein	1.05	1.02	1.07	< 0.001
Platelet-to-lymphocyte ratio	1.03	0.98	1.09	0.243

Abbreviations: MDW, monocyte distribution width

Discussion

This study demonstrates that a high MDW at admission is associated with an increased risk of critical illness and mortality in COVID-19 patients. Specifically, patients in the high-MDW group (MDW > 22) had a 48% higher risk of critical outcomes (aOR: 1.48, 95% CI: 1.08–2.04) compared to those in the low-MDW group. These findings suggest that MDW could serve as a promising early marker of disease severity, aiding clinicians in identifying high-risk COVID-19 patients who may benefit from intensive monitoring and early intervention. Furthermore, our study found that patients who had received two or more doses of the COVID-19 vaccine, as well as those treated with antiviral agents, had a significantly reduced risk of critical illness. This underscores the protective effects of vaccination and antiviral therapy in this population.

MDW has demonstrated potential in diagnosing sepsis and inflammatory conditions due to its automated, rapid data collection compared to traditional markers like CRP and procalcitonin [8, 26]. While no universally accepted cutoff exists, studies have linked higher MDW levels with severe COVID-19 outcomes. For instance, Ognibene et al. reported elevated MDW in ICU patients (28.3 ± 5.3 vs. 25.4 ± 3.6; $p < 0.05$) with a sensitivity of 98% at a cutoff of 20 [9], while Alsuwaidi et al. found MDW ≥ 24.68 predicted poor prognosis [15]. Similarly, Giovanni et al. identified MDW ≥ 26.4 as predictive of fatal outcomes (AUC: 0.76) [26], and Hossain et al. correlated MDW ≥ 23.5 with respiratory failure (AUC: 0.68) [14]. Sharma et al. reported MDW ≥ 25.4 as indicative of poor outcomes in COVID-19 [27]. In our study, MDW > 22 was significantly associated with critical illness and a 48% higher risk of severe outcomes, providing valuable insights in Asian population.

Several studies have investigated the relationship between inflammatory markers and COVID-19 severity. Commonly studied markers, including CRP, WBC counts, NLR, and PLR, have consistently shown significant associations with disease severity and mortality [28–31]. For instance, Karimi et al. demonstrated that elevated CRP and WBC counts were predictive of severe outcomes in COVID-19 patients, with NLR emerging as a particularly robust marker of disease severity and survival outcomes [32]. Similarly, Jemaa et al. highlighted the prognostic value of NLR and CRP, indicating a strong correlation with mortality and critical disease progression [33]. Furthermore, Yang et al. found that a combination of inflammatory indices, such as NLR and PLR, effectively distinguished severe from non-severe COVID-19 cases and predicted patient outcomes [34]. These findings align closely with the results of our study, which confirmed the strong predictive value of inflammatory markers in determining COVID-19 severity and outcomes. Such evidence underscores the utility of these markers as accessible and practical tools for risk stratification in clinical settings.

Evolving COVID-19 treatment protocols, such as the increased use of corticosteroids, have been shown to significantly impact outcomes and predictive markers, as highlighted by Mayerhöfer et al. [35]. These variations in management practices over the course of the pandemic could influence the reliability of prognostic indicators. However, our study was conducted during a period of protocol consistency at our institution, minimizing variability in treatment effects. This stability allowed for a clearer evaluation of MDW as an independent predictor of disease severity in critical COVID-19 care.

The present study has some limitations. First, we focused solely on patients admitted to a single hospital for COVID-19, which might have introduced selection bias, as our cohort primarily represents patients with severe diseases. This bias may limit the applicability of our findings to broader populations, particularly those with mild or asymptomatic infection. Second, we deliberately excluded pediatric patients and patients hospitalized for reasons unrelated to COVID-19, which precluded investigation into how different age groups and underlying health conditions influence disease progression and biomarker efficacy. Third, we did not analyze long-term outcomes, such as rehospitalization or long COVID. Additionally, the lack of available SAPS3 or APACHE II scoring data limits the contextual interpretation of MDW as an independent predictor in our study. During the study period, resource constraints, including shortages of personnel and hospital space, posed significant challenges. While every effort was made to provide

optimal care for all patients, it is not possible to fully evaluate how these limitations might have influenced the study outcomes. Moreover, secondary infections were not recorded or considered as potential factors in our analysis, which may represent an additional limitation. Furthermore, not all complete blood count analyzers can produce the result of MDW, which could also limit the utility of MDW among COVID-19 patients. Finally, our data were exclusively derived from Asian populations, so our findings may not be directly extrapolated to other ethnic groups. Further studies in diverse demographic and geographic settings are needed to enhance the generalizability of our findings, with extended follow-up to identify long-term health outcomes and expand the patient demographic to clarify the effects of COVID-19 across populations.

Conclusion

Our findings suggest that MDW may serve as a promising prognostic biomarker for developing critical illness in patients with COVID-19. This highlights the potential utility of assessing MDW at admission for early identification of patients at higher risk of severe outcomes. Further research is warranted to establish a more precise cutoff for MDW and to explore its integration with other laboratory and clinical parameters in the management of patients with viral pneumonia.

Abbreviations

MV	Mechanical ventilation
ICU	Intensive care unit
MDW	Monocyte distribution width
CRP	C-reactive protein
WBC	White blood count
NLR	Neutrophil-to-lymphocyte ratio
PLR	Platelet-to-lymphocyte ratio aOR: adjusted odds ratio
CI	Confidence interval

Supplementary Information

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Supplementary Material 1

Author contributions

CHL and CHC contributed equally to the work. CHL: data curation, writing the original draft, review, and editing. CHC: conceptualization, investigation, data curation, formal analysis, funding acquisition, and editing. YWC: writing, review, and editing. FWH: methodology, formal analysis, and project administration. SYW: project administration, review, and editing. HMS: review and editing, Resources, Methodology, Conceptualization, Project administration, and Funding acquisition. PRH: review and editing, supervision, Funding acquisition. All authors have read and approved the final manuscript.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was reviewed and approved by the Research Ethics Committee, China Medical University & Hospital, Taichung, Taiwan (CMUH REC No.: CMUH111-REC1-173). The need for informed consent from study participants was waived by the Research Ethics Committee, China Medical University & Hospital, Taichung, Taiwan due to the retrospective nature of the study and the use of de-identified data, ensuring participant anonymity and confidentiality. All procedures were executed in accordance with ethical standards outlined in the Helsinki Declaration of 1975.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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