VOLUME 03 ISSUE 01 (2024)

AMERICAN JOURNAL OF LIFE SCIENCE AND INNOVATION (AJLSI)

ISSN: 2833-1397 (ONLINE)

PUBLISHED BY
E-PALLI PUBLISHERS, DELAWARE, USA

American Journal of Life Science and Innovation (AJLSI)

Volume 3 Issue 1, Year 2024
ISSN: 2833-1397 (Online)
DOI: https://doi.org/10.54536/ajlsi.v3i1.2441
https://journals.e-palli.com/home/index.php/ajlsi

Predictive Value of RDW/PLT for Progression of COVID-19 Pneumonia: A Potential Biomarker for Disease Severity

Kang Huang[1], Salwa M. Imran[2], Wafa Mohammad,[3] Pengfei Liu[4], Yali Chao[5], Suming Zhang[5*]

Article Information

Received: February 02, 2024

Accepted: March 15, 2024

Published: March 19, 2024

Keywords

COVID-19, Pneumonia, Disease Progression, Biomarker, Clinical Decision-Making

ABSTRACT

Identifying reliable predictors for COVID-19 pneumonia progression is crucial for effective patient management. The purpose of this study is to evaluate the Red Cell Distribution Width to Platelet Ratio (RDW/PLT) as a potential predictive biomarker for the development of moderate to severe COVID-19 pneumonia. Conducting a retrospective analysis from August 2021 to March 2023, we categorized patients with moderate COVID-19 pneumonia at admission into different severity groups. The objective was to explore clinical and laboratory variables associated with disease progression. Fifty-three patients initially diagnosed with moderate COVID-19 were studied, of which 17 progressed to severe disease. Univariate logistic regression analyzed various factors, including age, PLT, RDW-SD, RDW/PLT, AST, ALB, CRP, and IL-6, evaluating their correlation ($P < 0.05$) with higher odds ratios of a poor prognosis. To ascertain these factors' predictive power, Receiver Operating Characteristic (ROC) curve analysis was used. Univariate logistic regression highlighted several factors associated with increased odds ratios for poor prognosis. Notably, RDW/PLT exhibited the highest predictive value (AUC: 0.925, 95% CI 0.858–0.991) among single parameters in predicting the risk of COVID-19 progression. This study underscores the potential of RDW/PLT as an accessible and cost-effective biomarker for determining COVID-19 pneumonia severity. The findings support its utility in risk stratification and clinical decision-making, offering valuable insights for effective patient management strategies.

INTRODUCTION

Global health has been greatly impacted by the COVID-19 pandemic, which has resulted in widespread illness and mortality (Cases, 2020; Fernandes *et al.*, 2021). The persistent difficulties caused by the COVID-19 pandemic highlight the vital need for strong prognostic markers that can enable early identification of patients at risk of severe disease progression; the search for trustworthy indicators to predict disease severity and progression in COVID-19 patients remains a crucial focus as the scientific community steps up efforts to unravel the complex pathophysiology of SARS-CoV-2 infection (Chen *et al.*, 2020; Sharma *et al.*, 2020; Sun *et al.*, 2020).

Within the cohort of COVID-19 patients initially presenting with moderate symptoms, a subset exhibited an alarming deterioration, progressing towards severe disease. Notably, an intriguing pattern emerged upon meticulous analysis: those experiencing the severe progression manifested elevated levels of RDW/PLT. This observation serves as the fulcrum for exploring the predictive value of RDW/PLT in predicting COVID-19 severity.

RDW/PLT, amalgamating Red Cell Distribution Width (RDW) and Platelet Count (PLT) measurements, represents a composite metric derived from routine complete blood counts (Pulgar-Sánchez *et al.*, 2021). The RDW captures the heterogeneity in red blood cell sizes, often indicative of underlying physiological perturbations, while PLT reflects the platelet count critical for hemostasis and immune response regulation (Ullah *et al.*, 2020; Wynants *et al.*, 2020). These parameters, individually recognized for their diagnostic utility across various medical conditions, converge in RDW/PLT, offering a potentially novel prognostic avenue for COVID-19.

The exploration of RDW/PLT as a predictive biomarker holds significant implications for clinical practice. Should its predictive potential be validated, RDW/PLT could emerge as a non-invasive, cost-effective, and readily available tool for risk stratification among COVID-19 patients. Its role in the early identification of individuals prone to rapid disease progression may revolutionize clinical decision-making, enabling timely interventions and tailored therapeutic strategies aimed at averting severe complications (Albahri *et al.*, 2020; Borghesi *et al.*, 2020; Tian *et al.*, 2020; Ullah *et al.*, 2020). Moreover, the integration of RDW/PLT into prognostic models may streamline resource allocation within healthcare systems, optimizing the allocation of limited resources toward high-risk patient cohorts.

This research endeavor transcends mere association establishment by delving into the temporal dynamics and clinical correlations of RDW/PLT alterations concerning COVID-19 progression. Understanding whether changes in RDW/PLT precede the onset of severe symptoms or coincide with disease exacerbation remains a pivotal

[1] Department of Emergency Intensive Care Unit, Affiliated Hospital of Xuzhou Medical University, Jiangsu, China
[2] Xuzhou Medical University, Jiangsu, China
[3] King Abdulaziz University Hospital, Jeddah, Saudi Arabia
[4] Shandong First Medical University, Shandong, China &Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Jiangsu, China
[5] Department of Intensive Care Unit, Affiliated Hospital of Xuzhou Medical University, Jiangsu, China
[*] Corresponding author's e-mail: SumingZhang18@outlook.com

aspect to unravel for effective predictive utility. The nuances of RDW/PLT kinetics throughout the disease course may provide critical insights into the trajectory of COVID-19 and guide intervention strategies.

Additionally, investigating demographic variations and potential associations with comorbidities concerning RDW/PLT elevations in COVID-19 patients presents an intriguing avenue. Determining whether specific patient subgroups exhibit distinct RDW/PLT profiles could facilitate personalized risk assessment, tailored monitoring protocols, and targeted interventions. This pursuit aligns with the broader goal of precision medicine, aiming to tailor treatments based on individual patient characteristics and disease progression patterns.

This study aims to scrutinize the Red Cell Distribution Width to Platelet Ratio (RDW/PLT) as a potential harbinger of the progression of COVID-19 pneumonia from moderate to severe stages. Amid the diverse clinical manifestations and trajectories observed in COVID-19 cases, identifying specific markers that herald a transition to severe illness holds paramount importance in clinical management and resource allocation. This study endeavors to bridge an essential knowledge gap in understanding COVID-19 prognosis by exploring RDW/PLT as a potential predictive biomarker. Beyond establishing its association with disease progression, the comprehensive investigation aims to lay the groundwork for its potential clinical utility, stressing the necessity for robust validation and integration of RDW/PLT into existing prognostic frameworks.

LITERATURE REVIEW

COVID-19 Pathophysiology and Prognostic Markers

The clinical spectrum of COVID-19, which is caused by SARS-CoV-2, is varied and ranges from mild respiratory symptoms to severe pneumonia and multi-organ dysfunction. Finding trustworthy prognostic markers requires an understanding of the complex pathophysiological mechanisms guiding the course of the disease (Huang *et al*., 2020; Zhang *et al*., 2020). Research into markers that reflect this dysregulation has been prompted by emerging evidence that points to a dysregulated immune response and an elevated inflammatory cascade as indicators of severe disease (Levi *et al*., 2020; Tay *et al*., 2020).

Red Cell Distribution Width (RDW) and Platelet Count (PLT) in Disease Evaluation

RDW, traditionally a marker of red blood cell size heterogeneity, has garnered attention beyond its conventional utility. It has been linked to systemic inflammation and adverse outcomes in various pathological conditions (Lippi & Mattiuzzi, 2020; Patel *et al*., 2015). In the context of COVID-19, elevated RDW levels have been observed and correlated with disease severity, possibly reflecting underlying inflammatory processes and physiological stress (Foy *et al*., 2020a; Lippi & Plebani, 2020). Similarly, alterations in platelet count (PLT) have been implicated in COVID-19 pathogenesis, with thrombocytopenia often associated with severe disease and adverse clinical outcomes (Althaus *et al*., 2021; Xu *et al*., 2020).

RDW/PLT Ratio as a Potential Biomarker

The integration of RDW and PLT into the RDW/PLT ratio represents a composite marker that may hold significant prognostic value in COVID-19. Previous studies across various medical conditions have demonstrated the potential of RDW/PLT as a prognostic indicator, reflecting systemic inflammation and disease severity (Zhou *et al*., 2020; Zorlu *et al*., 2012). Applying this ratio specifically in COVID-19 patients presents a novel approach to anticipate disease progression and severity.

Clinical Studies Investigating RDW/PLT in COVID-19

RDW/PLT's function in COVID-19 prognosis has been specifically examined in recent clinical studies. As an illustration of its potential as a predictive marker for disease severity, a study by Wang *et al*., 2020 found that severe COVID-19 cases had noticeably higher RDW/PLT ratios than moderate cases (Wang *et al*., 2022). Similarly, in a retrospective analysis, Kilercik *et al*., 2021 found that in COVID-19 patients admitted to intensive care units, high RDW/PLT ratios were associated with unfavorable outcomes and severe disease (Kilercik *et al*., 2021).

Mechanistic Insights and Future Directions

Elucidating the mechanistic underpinnings of the association between elevated RDW/PLT ratios and COVID-19 severity remains a critical area for exploration. Factors such as the inflammatory milieu, endothelial dysfunction, and potential interactions between platelets and red blood cells might contribute to alterations in RDW/PLT ratios (Henry, Aggarwal, *et al*., 2020; Lippi & Favaloro, 2020). Future research endeavors should focus on unravelling these mechanisms and conducting prospective trials to validate RDW/PLT as a robust prognostic marker in COVID-19.

MATERIALS AND METHODS

Study Participants

Retrospective review of patient medical records from August 1, 2021, to March 1, 2023, at the Third People's Hospital of Yangzhou and the Affiliated Hospital of Xuzhou Medical University was part of the study. Included were patients who had been diagnosed with COVID-19 and initially classified as having a moderate illness. According to the World Health Organization's interim guidelines, confirmation of COVID-19 depended on positive results from high-throughput sequencing or real-time reverse transcription-polymerase chain reaction (RT-PCR) assays of nasal and pharyngeal swab specimens. Following admission, patients were observed for at least 14 days to determine whether severe pneumonia had developed.

Ethical Approval

The Affiliated Hospital of Xuzhou Medical University's Ethics Committee approved the study protocol (Protocol ID: XYFY2022-KL034-01).

Data Collection

Standardized data collection forms were used to gather information from electronic medical records about the following: demographics (age, gender), comorbidities (diabetes, hypertension, coronary heart disease), and laboratory parameters (such as White Blood Cell - WBC, Lymphocyte - LY, Eosinophil Cell - EOS, Platelet - PLT, Mean Platelet Volume - MPV, Red Cell Distribution Width - RDW, Red Cell Distribution Width to Platelet Count Ratio - RDW/PLT, Aspartate Aminotransferase - ALT, Alanine Aminotransferase - ALT, Albumin - ALB, Creatinine - CREA, C-reactive protein - CRP, and Interleukin-6 - IL-6).

Patients were categorized into the progressive group (17 cases) and the stable group (36 cases) based on the development of severe illness within 3 days post-sample collection. Patients already categorized as severe at admission were excluded from statistical analyses.

Clinical Classification of COVID-19 Pneumonia

Based on the severity of their illness, patients with COVID-19 pneumonia were divided into various clinical groups in this study. A decrease in oxygen saturation, aberrant chest imaging, or the manifestation of COVID-19 symptoms without dyspnea were among the characteristics that classified the condition as mild. People who showed signs of a lower respiratory disease but were still able to maintain a sufficient oxygen saturation (SpO2) of ≥94% on room air at sea level were classified as having a moderate illness. Individuals classified as having a severe illness included those with heart rates under 94%, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) ratios less than 300 mm Hg, elevated respiratory rates greater than 30 breaths per minute, or lung infiltrates greater than 50%. These categorizations were crucial in distinguishing and describing the different levels of severity among the COVID-19 pneumonia cases in this investigation.

Statistical Analysis

All statistical analysis was performed on SPSS 26.0 and GraphPad Prism 8.0. The formats for descriptive statistics are mean ± SD, median (IQR), and n (%). The Chi-square test or Fisher's exact test were used to analyze categorical variables, and the student's t-test or Mann-Whitney U-test were used to analyze continuous variables. If the two-sided P value was less than 0.05, it was considered statistically significant. Using single-variable logistic regression based on the likelihood ratio, risk factors were found, and these risk components were then combined to create a forest plot. The area under the curve (AUC) was used to evaluate discrimination performance.

RESULTS

Patient Characteristics and Group Classification

The rigorous application of inclusion criteria yielded a cohort of 64 individuals diagnosed with COVID-19. Following careful screening, 11 patients were excluded due to severe/critical COVID-19 status at admission or being below 18 years of age, resulting in a final study population of 53 patients. Among these, a subgroup of 17 patients experienced a distressing progression to severe pneumonia during their hospital stay, prompting a comparative evaluation to discern distinguishing clinical features, as shown in Figure 1.

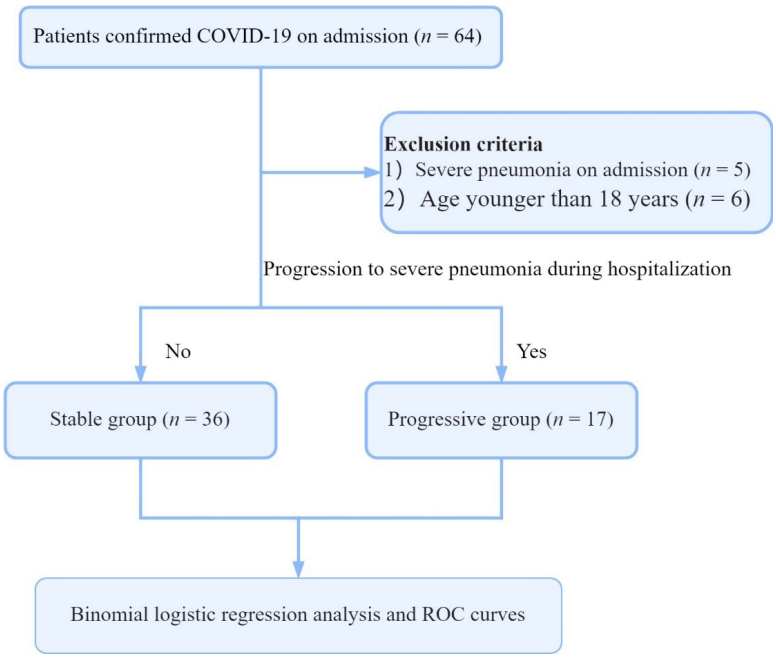

Figure 1: The flow diagram shows the study population enrollment

Comparison between Stable and Progressive Patients

A thorough comparison of the clinical and demographic traits of patients who developed severe COVID-19 and those who kept their condition stable is shown in Table 1. Interestingly, the mean age of patients in the progressive group was 7.88 years ± 14.66 years, which was significantly higher than the mean age of patients in the stable group (58.97 years ± 18.94) (P = 0.021). Moreover, individuals with underlying coronary heart disease were notably more prevalent within the progressive group (41.2%) than in the stable group (2.8%) (P = 0.001).

Notably, various laboratory parameters manifested pronounced differences between the groups, with significantly higher levels of RDW-SD, RDW/PLT, AST, CREA, CRP, and IL-6 observed in the progressive cohort (all P < 0.05).

Table 1: Characteristics between the stable and progressive patients

Characteristic	Stable group	Progressive group	P
Gender, n (%)			
Male	15 (41.7%)	11 (64.7%)	0.117
Female	21 (58.3%)	6 (35.3%)	
Age, years	58.97 ± 18.94	70.88 ± 14.66	0.021
Times of vaccination			
0	19 (52.8%)	8 (47.1%)	0.832
1	6 (16.7%)	4 (23.5%)	
2	11 (30.6)	5 (29.4)	
Comorbidities, n (%)			
Diabetes	4 (11.1%)	4 (23.5%)	0.443
Hypertension	12 (33.3%)	5 (29.4%)	0.775
Coronary heart disease	1 (2.8%)	7 (41.2%)	0.001
Laboratory findings			
WBC (×109/L)	4.57 ± 1.56	4.61 ± 1.81	0.929
LY (×109/L)	1.18 ± 0.53	0.89 ± 0.36	0.051
EOS (×109/L)	0.01 (0.00-0.08)	0.00(0.00-0.00)	0.003
PLT (×109 /L)	146.50 (124.25-193.25)	92.00 (66.50-106.5)	0.000
MPV (fL)	11.59 ± 1.13	11.98 ± 1.08	0.240
RDW-SD	40.58 ± 2.35	42.98 ± 2.15	0.001
RDW/PLT (×10-2)	27.25 (20.43-33.60)	46.80 (38.95-64.95)	0.000
AST (U/L)	21.50 (18.50-34.00)	50.20 (29.80-88.40)	0.000
ALT (U/L)	25.89 ± 21.85	38.25 ± 21.39	0.059
ALB (g/L)	44.11 ± 3.37	38.91 ± 3.81	0.000
CREA (umol/L)	68.50 (61.00-88.00)	90.00 (64-113)	0.038
CRP (mg/ L)	22.92 (9.43-33.07)	58.00 (39.35-91.70)	0.000
IL-6 (pg/ml)	21.85 (13.75-32.85)	81.50 (39.35-115.30)	0.000

Predictors of Progression from Moderate to Severe COVID-19

Univariate logistic regression analysis illuminated several potential predictors of disease progression, unveiling age, PLT, RDW-SD, RDW/PLT, AST, ALB, CRP, and IL-6 as significantly associated with the transition to severe COVID-19 pneumonia, as shown in Table 2.

The construction of a forest plot, which is shown in

Table 2: Univariate logistic regression analysis independent high-risk factors for severity of COVID-19 patients

Variables	OR (95%CI)	P value
Age	1.05 (1.00-1.09)	0.029
EO	0.00 (0.00-455.76)	0.349
PLT	0.94 (0.90-0.97)	<0.001
RDW-SD	1.05 (1.02-1.08)	0.004
RDW/PLT	1.21 (1.08-1.36)	<0.001
AST	1.04 (1.02-1.07)	0.002

ALB	0.68 (0.54-0.84)	<0.001
CREA	1.02 (1.00-1.04)	0.052
CRP	1.06 (1.03-1.10)	<0.001
IL-6	1.07 (1.03-1.12)	<0.001

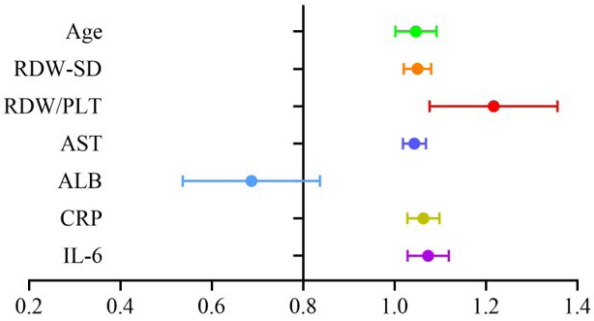

Figure 2: Forest plot

Figure 2, further underscored the prominence of RDW/PLT, IL-6, CRP, RDW-SD, age, and AST as prominent predictors in delineating disease severity.

Predictive Value of RDW/PLT

Intriguingly, receiver operating characteristic (ROC) curve analysis highlighted the remarkable predictive capacity of RDW/PLT in forecasting the risk of progression in COVID-19 patients. With an impressive area under the curve (AUC) of 0.925 (95% CI 0.858–0.991), RDW/PLT emerged as the most robust single parameter. Utilizing a cut-off value of 0.355, RDW/PLT showcased a high sensitivity of 94.12% and specificity of 80.56% in predicting the risk of progression, which is shown in Figure 3.

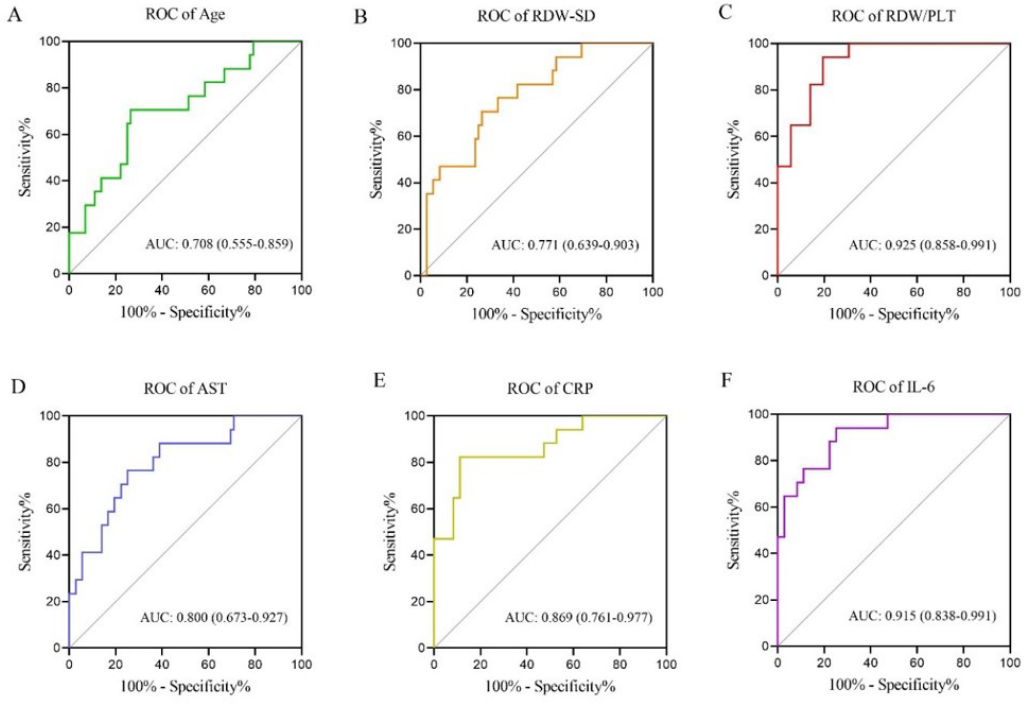

Figure 3: ROC curve for the prediction of developing severe COVID-19 pneumonia

Interpretation and Implications

These findings underscore the clinical relevance of specific hematological and demographic markers in predicting the trajectory of COVID-19 pneumonia. Notably, the identification of RDW/PLT as a robust predictor of disease progression signifies its potential utility as an early prognostic marker, allowing for prompt interventions and focused clinical management.

DISCUSSION

According to the study's findings, the Red Cell Distribution Width to Platelet Ratio (RDW/PLT) may prove to be a useful biomarker for determining when COVID-19 pneumonia will progress from a moderate to a severe stage (Alballa & Al-Turaiki, 2021; Ghahramani *et al.*, 2020; Yamada *et al.*, 2020). Since elevated RDW/PLT values have been associated with disease progression,

physicians may be able to use them as a preemptive measure to identify patients who are more likely to develop severe illness in the future (Alnor *et al*., 2020; Gong *et al*., 2021). Early detection could result in targeted therapy, attentive observation, and intervention strategies that could enhance patient outcomes (Bonetti *et al*., 2020). The study's findings indicate that the Red Cell Distribution Width to Platelet Ratio (RDW/PLT) may be a valuable biomarker for predicting how COVID-19 will progress. Numerous studies have reported a relationship between RDW and disease severity for a range of medical conditions, including cancer, pulmonary disorders, and cardiovascular diseases (Foy *et al*., 2020b). RDW is a measure of the heterogeneity in red blood cell size that is caused by oxidative stress, inflammatory reactions, and decreased erythropoiesis. Within the framework of COVID-19, the noted increase in RDW could be linked to the inflammatory reaction and subsequent cytokine storm, which could lead to modifications in red blood cell properties (Liu *et al*., 2020; Pongpirul *et al*., 2020). Furthermore, the correlation between RDW/PLT and the severity of the COVID-19 virus is consistent with decreased platelet counts, which are frequently observed in cases of severe viral infections (Ponti *et al*., 2020).

This study's findings align with previous investigations highlighting the role of RDW and platelet count as markers of systemic inflammation and hematological abnormalities (C. Wang *et al*., 2020). Elevated RDW has consistently been linked to adverse outcomes in diverse medical conditions, including cardiovascular and respiratory disorders (Yuan *et al*., 2020). Similarly, alterations in platelet count have been associated with inflammatory responses and endothelial dysfunction (Li *et al*., 2020). This study contributes by emphasizing the utility of the composite RDW/PLT ratio as a potential biomarker, specifically within the context of COVID-19 pneumonia (Ballaz *et al*., 2021).

A plausible underlying mechanism for the observed association involves the systemic inflammation and oxidative stress triggered by SARS-CoV-2 infection (Shiri *et al*., 2021). The virus-induced inflammatory response might lead to hematological changes, affecting red cell distribution and platelet activation (Khosravi *et al*., 2021). The RDW/PLT ratio could capture these underlying pathophysiological processes, serving as an indicator of disease severity (X. Wang *et al*., 2020). Furthermore, leveraging the RDW/PLT ratio as a predictive tool may contribute to personalized approaches to managing COVID-19.

Table 1 and Table 2 in the current study elucidate demographic, clinical, and laboratory characteristics associated with the progression of COVID-19 pneumonia. Similar analyses in previous studies have often highlighted age, comorbidities, and specific laboratory parameters, such as inflammatory markers (e.g., CRP, IL-6), as crucial predictors of disease severity (Tjendra *et al*., 2020). However, the current study emphasizes the RDW/PLT ratio, which might have been less extensively in prior literature for COVID-19 severity prediction.

Figure 2, displaying a forest plot of predictors, echoes findings from previous studies, often revealing multiple factors associated with disease severity. Previous studies have reported diverse predictors, ranging from inflammatory markers to specific clinical parameters, consistently emphasizing the multifactorial nature of disease progression (Krintus *et al*., 2014).

Figure 3 exhibits ROC curve analysis, demonstrating the predictive performance of individual parameters for severe COVID-19 pneumonia. Prior research often presents ROC analyses assessing the diagnostic or predictive accuracy of various markers, with AUC values serving as indicators of predictive strength. In comparison to previous studies, the current study highlights the RDW/PLT ratio as a potential strong predictor for disease progression (Cai *et al*., 2019).

The study highlights the potential of this readily available and cost-effective measure to aid risk classification and guide clinical decision-making (Henry, De Oliveira, *et al*., 2020). However, validation of these findings, exploring underlying mechanisms, and assessing the RDW/PLT ratio's value in larger patient cohorts necessitate further investigation. The prospective application of the RDW/PLT ratio in clinical practice holds promise for enhancing patient outcomes in COVID-19 pneumonia.

CONCLUSION

This study concludes that elevated RDW/PLT values are linked to the advancement of illness, indicating the practicality of utilizing this readily available parameter in clinical settings. Identifying patients at higher risk of developing severe illness early on could facilitate timely interventions, enhanced surveillance, and more effective allocation of healthcare resources. It provides initial evidence supporting the potential of the RDW/PLT ratio as a prognostic biomarker in predicting the progression of COVID-19 pneumonia from moderate to severe stages.

STRENGTHS AND LIMITATIONS

The strength of this study is that it investigates RDW/PLT as a potential predictor for COVID-19 pneumonia progression using robust statistical analyses. Clear inclusion criteria and focus on moderate COVID-19 cases enhance specificity.

The limitations are retrospective design and small, single-center sample size, which may introduce biases and limit generalizability. Unaccounted confounding factors and the need for prospective validation in larger cohorts pose limitations.

Acknowledgements

Conception and design of the study: Suming Zhang. Acquisition of data: Suming Zhang, Pengfei Liu, Salwa Mohammad Imran. Analysis and interpretation of data: Suming Zhang. Drafting the article: Salwa Mohammad Imran, Wafa Mohammad. Revising it critically for

important intellectual content: Suming Zhang, Salwa Mohammad Imran. Final approval of the version to be submitted: All authors contributed to the final version. Suming Zhang takes responsibility for the paper as a whole.

Funding

This work was supported by the Wu Jieping Medical Foundation's special fund for clinical research under Grant (320.6750.2021-08-3) and the Xuzhou Youth Science and Technology Talent Project under Grant (KC2204).

Declaration of Interest

The authors report that there are no competing interests to declare.

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