Section: General Medicine

Original Research Article

ANALYTICAL CROSS-SECTIONAL STUDY TO DETERMINE THE ROLE OF RED CELL DISTRIBUTION WIDTH AS A PREDICTOR OF SEVERITY AMONG COVID 19 PATIENTS

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Abstract

Background: Patients with coronavirus disease (COVID-19) have been shown to have higher lymphopenia, thrombocytopenia, and overall leukopenia upon hospital admission. Additionally, higher morbidity and death rates in COVID-19 patients with leukopenia have been linked to higher red blood cell distribution width (RDW) throughout the hospital stay. This study aimed to determine the role of red cell distribution width as a predictor of severity among covid 19 patients. **Materials and Methods:** This analytical cross-sectional study was conducted on 100 patients with covid 19 confirmed by RT-PCR at the Govt Stanley Medical College and Hospital, Chennai, between April 2021 and March 2022. Blood pressure, SpO2, respiratory rate, and physical examinations were performed upon admission. Routine investigations were performed upon admission, including a complete blood count. The correlation between red cell distribution width (RDW-CV) and disease severity was analysed. **Result:** The mean age was 38.5 years (SD=15.2), ranging between 18 and 96 years. Most patients were males (n=65, 65%). A statistically significant relationship was found between RDW-CV values on admission and the severity of COVID-19. There was a statistically significant relationship between COVID severity and NLR. Higher RDW and NLR values were associated with more severe disease. **Conclusion:** Among patients with COVID-19, RDW, as a simple, routinely measured, inexpensive laboratory parameter, was independently associated with disease severity. An RDW >14.5% could be the optimal cut-off for discriminating critical COVID-19 infections.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by severe respiratory coronavirus-2 (SARS-CoV-2), is a respiratory illness responsible for a global pandemic that has led to millions of deaths and widespread economic damage. To better mitigate the effects of coronavirus and improve medical outcomes, it is imperative to identify demographic, clinical, and laboratory factors that predict the clinical deterioration and prognosis of patients affected by this virus. Blood tests are affordable, minimally invasive, and fast prognostic indicators that have proven useful in assessing disease progression. RDW is a routine blood measure taken as part of a complete blood count, and it quantifies anisocytosis by displaying the variation in RBC volume. The RDW measures the size variance between the RBCs. It is postulated that pro-inflammatory states lead to insufficient and delayed erythropoiesis with structural and functional alterations in RBCs and increased production and turnover of platelets and leucocytes.[1]

In 2020, multiple studies demonstrated that RDW is a powerful prognostic indicator for hospitalised COVID-19 patients. Brody et al. demonstrated that hospitalised COVID-19 patients with an RDW value above the upper limit of normal have a greater risk of morbidity and mortality than those with normal RDW values. If RDW can act as a predictive measure to understand potential disease progression at the time of diagnosis of COVID-19, this would allow for risk stratification and resource allocation to observe and treat patients with a greater risk for more severe disease courses.[2]

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Aim

This study aimed to determine the role of red cell distribution width as a predictor of severity among covid 19 patients.

MATERIALS AND METHODS

This analytical cross-sectional study was conducted on 100 patients with covid 19 confirmed by RT-PCR at the Govt Stanley Medical College and Hospital, Chennai, between April 2021 and March 2022. The study received approval from the institutional ethics committee before its initiation.

Inclusion Criteria

According to WHO guidelines, patients were diagnosed with mild, moderate, and severe COVID-19. For mild disease, patients with symptoms of COVID without signs of pneumonia or hypoxaemia. Patients with moderate disease had cough, shortness of breath, and saturation of >90% in room air. Patients with cough, shortness of breath with respiratory rate >30/min, or saturation <90% in room air were included for severe disease.

Exclusion Criteria

Patients aged < 18 years, anaemic patients (Hb < 10 g%), and postoperative patients or those with a recent history of blood loss were excluded.

As per the inclusion criteria, all eligible patients were subjected to basic clinical assessment and routine investigations, including complete blood count, and inflammatory markers such as CRP and ferritin were measured and assessed based on the WHO criteria regarding disease severity. The correlations between red cell distribution width (RDW-CV), NLR, and disease severity were analysed. The cut-off values for RDW-CV were 14.5 and 3.89, and CRP was 10 mg/L mg/L, which were considered elevated.

After obtaining informed written consent from the patients, a history of fever, cough, breathlessness, and other comorbidities was obtained. Oxygen saturation, blood pressure, respiratory rate, other vital signs, and general and systemic examinations were performed on admission. Blood samples were obtained for complete blood count, routine investigations, inflammatory markers, and chest radiography or chest CT.

Patients were categorised as mild, moderate, or severe based on clinical examination. Oxygen saturation, need for o2 supplementation, noninvasive ventilation, invasive ventilation, inflammatory markers, comorbidities, and complications of COVID-19 such as ARDS, Sepsis, and Thromboembolic manifestations were closely monitored. The red cell distribution width was examined for all patients, and the mean red cell width was calculated for each severity category.

Statistical Analysis: All data were collected using structured questionnaires, and data analysis was performed using IBM SPSS v23. Frequency and percentage analyses were also performed. A chi-square test analysis was performed, and the p-value was set at 0.05.

RESULTS

The mean age was 38.5 years (SD=15.2), ranging between 18 and 96 years. Most patients were males (n=65, 65%). Most patients had mild disease (n=49), 23% had severe disease, and 28% had moderate disease severity. Diabetes mellitus was present in 30%, hypertension was present in 22%, and coronary artery disease was present in 13% of the patients. 2% had an old cerebrovascular accident, chronic obstructive lung disease was present in 7%, and chronic liver disease was present in 5% of the patients [Table 1].

CRP was elevated in 28%, RDW-CV in 20%, and NLR in 14% of the patients. D-dimer levels were elevated in 24% and 18% of the patients. Of the 100 patients, 25% did not receive any vaccination, 60% had received two doses, and 15% had received a single dose. 43% did not require oxygen support, 8% needed HFNO, and 19% needed CPAP. 28% needed non-breathing masks, and 2% needed mechanical ventilation [Table 2].

The relationship between the red cell distribution width coefficient of variation and severity showed that higher RDW-CV was associated with increased disease severity, which was statistically significant (p=0.007). The relationship between NLR and disease severity showed that a higher NLR was significantly associated with increased disease severity (p<0.001).

The relationship between CRP level and severity showed that higher CRP level was associated with increased disease severity, which was statistically significant (p<<0.001). The relationship between diabetes mellitus and severity showed that DM was significantly associated with high severity (p=0.006). The relationship between hypertension and severity showed that HTN was significantly associated with high severity (p<0.001). The relationship between CAD and severity showed that CAD was significantly associated with high severity (p<0.001). The relationship between CKD and severity showed that CKD was associated with high severity, which was not statistically significant (p=0.125). The relationship between CLD and severity was not statistically significant (p=0.322). The relationship between COPD and severity was not statistically significant (p=0.116) [Table 3].

The relationship between the red cell distribution width coefficient of variation and CRP showed that higher RDW-CV was associated with higher CRP (p=0.002). The relationship between NLR and CRP level showed that a higher NLR was significantly associated with higher CRP levels (p=0.001).

The red cell distribution width-coefficient variation and mechanical ventilation showed a positive correlation. A high RDW was associated with increased mechanical ventilation use, and the relationship between NLR and mechanical

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ventilation showed a positive correlation. A high NLR was significantly associated with increased mechanical ventilation ($p<0.001$).

The relationship between the red cell distribution width coefficient of variation and sex did not show any statistical significance, and the relationship between NLR and sex did not show any statistical significance [Table 4].

Table 1: Demographic data of the study

		Frequency (%)
Age (Mean± SD)		39.02±15.2852
Gender	Female	35(35%)
	Male	65(65%)
Severity	Mild	49(49%)
	Moderate	28(49%)
	Severe	23(23%)
Diabetes mellitus	Absent	70(70%)
	Present	30(30%)
Hypertension	Absent	78(78%)
	Present	22(22%)
Coronary artery disease	Absent	87(87%)
	Present	13(13%)
Chronic kidney disease	Absent	95(95%)
	Present	5(5%)
Old cerebrovascular accident	Absent	98(98%)
	Present	2(2%)
Chronic obstructive lung disease	Absent	93(93%)
	Present	7(7%)
Chronic liver disease	Absent	95(95%)
	Present	5(5%)

Table 2: Distribution of biochemical parameters, vaccine, oxygen support, and complications

		Frequency (%)
CRP	High	28(28%)
	Normal	72(72%
RDW-CV	High	20(20%)
	Normal	80(80%)
NLR	High	14(14%0
	Normal	86(86%)
D-dimer	High	24(24%)
	Normal	76(76%)
Ferritin	High	18(18%)
	Normal	82(82%)
Vaccinated (number of doses)	0	25(25%)
	1	15(15%)
	2	60(60%)
Oxygen support	NRM	28(2%)
	HFNO	8(8%)
	CPAP	19(19%)
	No support	43(43%)
	Mechanical ventilator	2(2%)
Complications	ARDS	18(18%)
	DKA	24(24%)
	Septic shock	15(15%)
	MI/Stroke	3(3%)
	AKI	24(24%)

Table 3: Relationship of biochemical parameters between severity

		Severity			P value
		Mild	Moderate	Severe	
RDW-CV	High	4	7	9	0.007
	Normal	45	21	14	
Neutrophil-to-lymphocyte ratio	High	1	3	10	<0.001
	Normal	48	25	13	
C-reactive protein	High	6	9	13	<0.001
	Normal	43	19	10	
Diabetes mellitus	Absent	39	21	10	0.006
	Present	10	7	13	
Hypertension	Present	3	6	13	<0.001
	Absent	46	22	10	
Coronary artery disease	Present	2	2	9	<0.001
	Absent	47	26	14	

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Chronic kidney disease	Absent	48	27	20	0.125
	Present	1	1	3	
Chronic liver disease	Absent	46	28	21	0.322
	Present	3	0	2	
Chronic obstructive pulmonary disease	Absent	43	27	23	0.116
	Present	6	1	0	

Table 4: Relationship of biochemical parameters between CRP, mechanical ventilation, and sex

		CRP		P value
		High	**Normal**	
RDW-CV	High	11	9	0.002
	Normal	17	63	
NLR	High	9	5	0.001
	Normal	19	67	
		Mechanical Ventilation		P value
		Yes	No	
RDW-CV	High	11	9	<0.001
	Normal	10	70	
NLR	High	9	5	<0.001
	Non-severe	12	74	
CRP	Elevated	12	16	<0.001
	Normal	9	63	
		Sex		P value
		Female	Male	
RDW-CV	High	5	15	0.294
	Normal	30	50	
NLR	High	3	11	0.251
	Non-severe	32	54	

DISCUSSION

Since the COVID-19 outbreak began in December 2019, many reports have been published on haematological parameters in patients with COVID-19. Few studies have investigated the role of haematological parameters in predicting the prognosis of patients. RDW quantifies the heterogeneity of circulating RBCs and has been used to differentiate between the causes of anaemia.[3]

In previous studies, RDW was a robust predictor of mortality in critically ill or ICU patients. About COVID-19, the significance of RDW in predicting adverse outcomes remains. Our study further verified a significant association between RDW and the severity of disease with COVID-19, whereas haemoglobin was not an independent predictor when included in the model.[4]

The RDW is a simple, widely available, and inexpensive test. However, these data may have significant clinical implications for determining potentially critical diseases in patients with COVID-19 during this pandemic.[5]

Currently, there is no consensus on the optimal cut-off for RDW. Several studies defined RDW ≥14.5% as abnormally elevated RDW and demonstrated good predictive performance for unfavourable clinical outcomes (Foy BH et al.). However, various studies found that cut-off values might vary, ranging from 12.85% to 14.35%.[6]

Our study showed that RDW could be a good predictor of critical illness in patients with COVID-19, as higher RDW values are significantly associated with disease severity and other parameters such as NLR and ferritin. Our study also showed that higher RDW values are significantly associated with complications of COVID disease.[7]

Although the pathophysiological mechanism underlying the strong association between RDW and severity remains unclear, several explanations may explain this phenomenon. Increased RDW values may reflect overall inflammatory status, oxidative stress, or arterial underfilling. Accumulating evidence from various studies suggests that patients with severe COVID-19 may have a hyperinflammatory state with a cytokine storm. Cytokine release during systemic inflammation impairs bone marrow function and iron metabolism. These cytokines also suppress erythrocyte maturation, accentuated by sepsis, allowing newer and larger erythrocytes to enter the circulation, associated with increased RDW. The role of oxidative stress during COVID-19 infection has not been fully elucidated, but free radicals have been shown to protect against invading microorganisms. Reactive oxygen species, such as peroxynitrite, nitric oxide (NO), and superoxide, have been associated with endothelial damage (Pouladzadeh M et al.). Pathological findings in COVID-19 patients support the presence of endothelial cell damage and endothelium, possibly due to direct viral infection and diffuse endothelial inflammation. Oxidative stress can also directly damage red blood cells and decrease survival, leading to anisocytosis and increased RDW. Thus, higher RDW may reflect severe oxidative stress.[8]

Finally, a high RDW was associated with activating the renin-angiotensin-aldosterone system (RAAS). Angiotensin-converting enzyme 2 (ACE 2), an enzyme that counters RAAS activation physiologically, is the receptor for SARS-CoV-2

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(Wang Z-H et al.). This virus not only enters through ACE2, but it also downregulates ACE2 expression such that the enzyme is unable to exert protective effects in organs. It has been postulated that unabated angiotensin 2 activity is responsible for organ damage in COVID-19 patients. Therefore, these factors may explain the higher RDW level in COVID patients with critical illness. Further studies are required to clarify the underlying mechanisms.[9]

Our study also showed a significant relationship between RDW and the need for oxygenation in COVID patients. The oxygen and mechanical ventilation requirements were higher in patients with elevated RDW values. There was no significant correlation between sex and RDW. Complications such as ARDS, DKA, AKI, and septic shock were more common in patients with a higher RDW.

CONCLUSION

Among patients with COVID-19, RDW, as a simple, routinely measured, inexpensive laboratory parameter, was independently associated with disease severity. An RDW >14.5% could be the optimal cut-off for discriminating critical COVID-19 infections. This might be useful in clinical practice to identify patients more prone to developing severe disease and its complications in the early stages, and early medical intervention can be provided, leading to better outcomes.

Limitations

The major limitation of this study was that the disease outcomes were not studied. Inflammatory markers and RDW were assessed only at admission; no follow-up analyses were performed. Other highly specific inflammatory markers, such as IL-6, which have a proven role in severity assessment, were not assessed. However, the sample size of this study was relatively small. Not all age groups have been studied equally, and the effects of vaccination have not been studied.

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