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Quick Response Code:

Website: www.ijhonline.org
DOI: 10.4103/ijh.ijh_45_21

A study on significance and correlation of red cell distribution width with severity of clinical illness in COVID-19 patients

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Abstract:

BACKGROUND: Global pandemic COVID-19 is an acute respiratory illness with a high rate of hospitalization and death rate. Red cell distribution width coefficient of variation (RDW-CV), a routine component of complete blood count (CBC) automatically generated by most hematology analyzers is a useful predictor of clinical outcomes in critically ill patients and in those with infection and sepsis. RDW will provide information for early risk stratification of COVID-19 patients, thereby enabling timely intervention for reducing morbidity and mortality. In such a massive pandemic, early stratification of cases based on routinely available biomarkers can be of great help inefficient utilization of critical care and laboratory assets.

MATERIALS AND METHODS: We retrospectively studied the significance and correlation of RDW (CV) (admission) with the severity of clinical illness in 800 confirmed cases of COVID-19 between August 2020 and October 2020 at our hospital. Demographic and clinical details were obtained from medical records; data pertaining to CBC were retrieved through electronic records of our fully automated hematology analyzer (NihonKoden 5 part auto analyzer Model-MEK-7300K). Statistical workup was done and results were analyzed.

RESULTS: Of 800 patients, 60% were male. RDW (CV) >14.5 (elevated) seen in 52% males and 47% females. Elevated RDW was noted in 43.6% (300/688) nonsevere illnesses (mild and moderate), 82% (92/112) in the severe illness group. The mean RDW (CV) for mild, moderate, and severe cases was found to be 14.21 ± 0.61 , 15.32 ± 0.67 , and 16.34 ± 1.64 , respectively. The number of survivors was 704 (88%). The number of people who died was 96 (12%). Elevated RDW was seen in 74% (71/96) who died and 45% (321/704) of people who survived. To determine the efficacy of RDW (CV) in identifying the severity of disease, a ROC curve was used in which a cutoff value of 13.65 is obtained with a sensitivity of 97.3% and specificity of 85%.

CONCLUSION: Higher RDW (CV) was found to have a significant association with clinical severity and mortality prediction. Hence, it can be considered as one of the important hematological parameters in the workup to efficiently stratify the patients at the earliest in COVID-19.

Keywords:

COVID-19, disease severity, mortality prediction, red cell distribution width coefficient of variation

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Submission: 16-12-2021

Revised: 31-12-2021

Accepted: 11-01-2022

Published: 09-06-2022

Introduction

“Corona” in Latin meaning crown are viruses belonging to *coronaviridae*

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family having single-stranded RNA genome surrounded by a helical capsid, lipoprotein envelope and having spicules of glycoprotein together giving them the crown appearance.^[1]

Wuhan city China reported to WHO a cluster of pneumonia cases of unknown

How to cite this article: SakthiKannamma M, Srinivasamurthy BC, Sinhasan SP, Bhat RV. A study on significance and correlation of red cell distribution width with severity of clinical illness in COVID-19 patients. *Iraqi J Hematol* 2022;11:25-31.

etiology by December 2019 whose causative agent has been identified as Coronavirus. This novel virus subsequently spread all over the world when the WHO declared this a pandemic and public health emergency of international concern on March 11, 2020.^[2]

In Pondicherry, the first case was reported on March 26, 2020. As of September 28, 2020, there were nearly 26,685 total cases with 5014 being active and 21,156 recovered and 515 dead.

Infection caused by coronavirus may range from asymptomatic to critical illness. About 40% manifest with mild disease, 40% with moderate disease, 15% develop severe disease, and only 5% manifest with critical illness and complications such as ARDS, thromboembolism, and acute kidney injury.^[3,4]

Red cell distribution width (RDW) being a simple parameter which reflects the heterogeneity of erythrocyte volume (anisocytosis) is automatically calculated in all basic and advanced hematological analyzer along with routinely included complete blood count (CBC) and this is reported either as absolute/percent value without any additional cost. An abnormal increase in it shows a profound imbalance of erythrocyte hemostasis, thereby causing abnormal red blood cell (RBC) survival due to ineffective erythropoiesis. RDW being a reliable measure of anisocytosis being recently emerged as a valuable parameter for predicting morbidity and mortality throughout a wide spectrum of human diseases.^[5,6] Various meta-analysis and systematic reviews were done to evaluate the prognostic value of RDW and concluded that RDW being an inflammatory associated marker was found to be an independent prognostic marker for predicting overall mortality in various cancer of the lung, prostate, and chronic lymphocytic leukemia (CLL) where high RDW was associated with poor outcome.^[7] Studies have also ventured the use of RDW as a prognostic marker in neonatal sepsis where elevated baseline RDW during the initial 4 days was found to have a significant correlation with mortality.^[8] Studies have been proposed to stress the role of RDW in various diseases such as diabetic nephropathy, acute pancreatitis, Hodgkin's lymphoma, and upper gastrointestinal bleeding.^[9]

The purpose of this study is to analyze the RDW in COVID-19 confirmed cases as categorized into those with mild disease, moderate disease, and severe disease. Our results could be helpful in expanding the use of RDW in COVID-positive patients as a biomarker.

Materials and Methods

The study was conducted in the department of pathology. After obtaining clearance from the Institute

Ethics committee, records of reverse-transcription polymerase chain reaction confirmed COVID-19 patients who fulfilled the inclusion criteria were retrieved from the medical records department. Patients aged below 18 years, nutrient-deficient anemia, pregnant women, and those patients with incomplete hematological data (patients lacking routinely performed CBC and differential count) were excluded from the study.

The patients are categorized as mild, moderate, and severe. According to Ministry of Health and Family Welfare (India) guidelines, COVID-19 is clinically classified as (1) Mild-uncomplicated upper respiratory tract symptoms such as malaise, fever, sore throat without any evidence of hypoxia, (2) moderate pneumonia with no signs of severe disease and clinical features of dyspnea or hypoxia with respiratory rate $\geq 24/\text{min}$, SpO₂ of range 90%–94%, (3) severe – severe pneumonia with clinical signs of pneumonia with a respiratory rate of $\geq 30/\text{min}$ and SpO₂ $< 90\%$ in room air.^[10] Baseline clinical data such as age, sex, epidemiological details, clinical features, duration of symptoms, and course of stay in hospital were collected from the case sheets. Data regarding CBC parameters such as RBC, white blood cell (WBC), and platelet counts, Hb concentration, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet distribution width (PDW), and RDW–CV and RDW standard deviation (SD) were obtained using automated hematology five-part analyzer (Nihon Koden 5 part auto analyzer Model-MEK – 7300K, Serial No: 02335). The Reference interval for RDW coefficient of variation (CV) was kept at 11.6%–14.5%.^[11–14] Categorization based on age, gender, and severity of the disease was done.

Data regarding age, sex, epidemiological details of the patient, clinical features, and hematological findings were collected. Data entry was done using MS EXCEL and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 16. Numerical variables are represented in mean $\pm$ SD and categorical variables are represented in percentage and proportions. The Chi-square test and independent “t”-test were used for the comparison of categorical and numerical values, respectively. $P < 0.05$ is considered statistically significant. Receiver operating characteristic (ROC) curve analysis was done to find out the cutoff value.

Results

Out of 800 study population, about 60% were male and 40% were female. Among the population, the percentage of males more than 60 years is 61.2% and % of females more than 60 years is 38.8%. The mean age with SD was found to be 49.7 ± 15.97 . When comparing the severity, the percentage of the study population

who manifested with mild illness was 65.4% (523/800) and those who manifested with moderate illness were 20.6% (165/800) and those who manifested with severe illness were 14% (112/800). Elevated RDW was noted in 43.6% (300/688) nonsevere illnesses (mild and moderate), 82% (92/112) in the severe illness group.

Of the 800 patients, the percentage of survivors was 88% (704/800) and the percentage of dead was 12% (96/800). Among them, elevated RDW (CV) was found to be 74% (71/96) in dead and 45% (321/704) among survivors. Mean RDW (CV) among dead was found to be 15.6 ± 1.51 and that among survivors was found to be 14.62 ± 1.03 . The age-wise distribution of the study population with percentage is shown in Figure 1. Baseline characters of the patients including age, gender, RDW, and other significant laboratory test parameters in association with the severity of clinical illness are presented in Table 1. The following variables were significantly associated with severity ($P \leq 0.05$). It includes Hb (g/dl), MCV (fl), MCH (pg), MCHC (g/dl), Packed Cell Volume (PCV) (%), RDW-CV(%), RDW-SD (%), WBC count/cu mm, neutrophil %, lymphocyte %, MPV (fl), and outcome. No significant difference observed between the groups in terms of age, gender, RBC count, and platelet value. A significant difference between the three groups is observed in terms of hemoglobin (g/dl) with $P \leq 0.001$ and the median hemoglobin being highest in the mild group. Significant difference between the three groups is observed in terms of MCV, MCH, MCHC with $P \leq 0.001$, and the median value of all the three variables being highest in the mild group.

A significant difference between the three groups is observed in RDW-CV ($P \leq 0.001$) with a median RDW-CV (%) being the highest in the patients who manifested with severe illness. The same observation is noted with RDW-SD values too. The percentage of neutrophils was significantly higher in patients who manifested with severe illness than compared to those with mild and moderate illness. The percentage of lymphocytes was significantly lower in patients with severe illness than compared to those with mild and moderate illness. A significant difference between the three groups is noted in terms of outcome where the percentage of people who survived being the highest in those with mild illness. In Figure 2, the association between outcome and age with the worst outcome (death) being the highest in 71–80 year age group and good outcome (survival) being the highest in 51–60 year age group. The association between severity and outcome is summarized in Figure 3. The association of variables with reference to RDW-CV values is shown in Table 2. The study population was divided into two

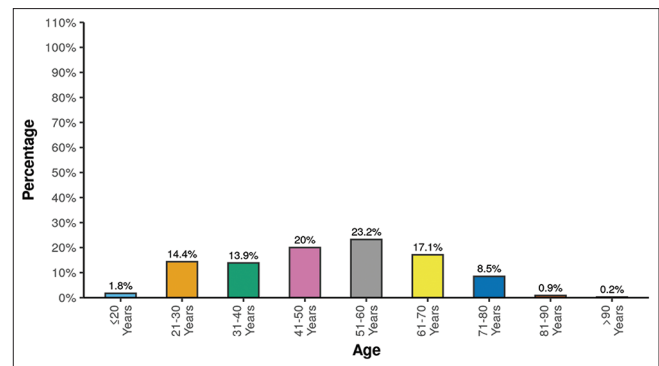


Figure 1: The age-wise distribution of study population with percentage

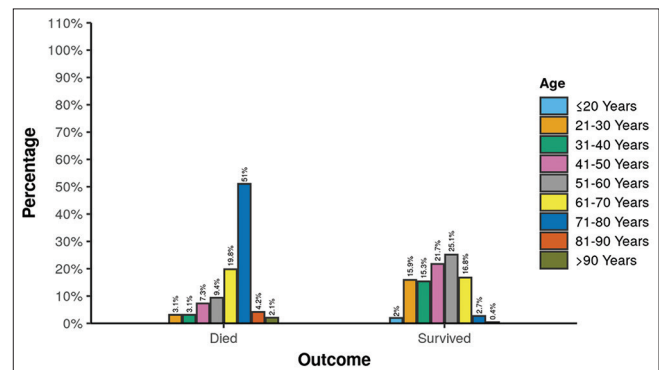


Figure 2: The association between outcome and Age

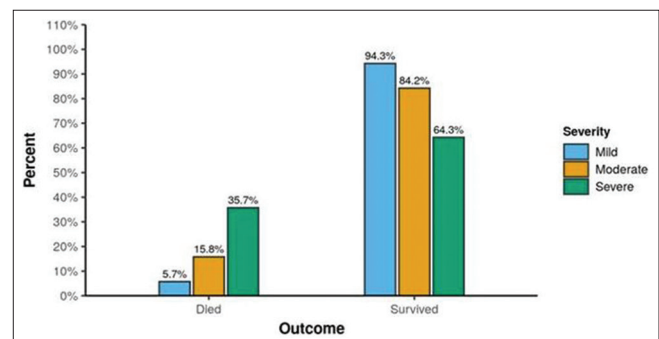


Figure 3: The association between severity and outcome

groups with one group having RDW values $\leq 14.5\%$ and the other group with RDW >14.5 . The statistical significance between the two groups is noted in terms of age, hemoglobin, MCV, MCH, MCHC, PCV, RDW-SD, and MPV ($P < 0.05$). A comparison of the severity of illness with RDW values is presented in Table 3. When comparing the severity of illness with these two groups, the percentage of population with mild illness having RDW-CV $\leq 14.5\%$ is about 90% whereas those with RDW-CV $>14.5\%$ is only 39.2%. Similarly, in people with moderate illness, the RDW-CV ≤ 14.5 is 4.7% while those with RDW-CV >14.5 is 37.2%. Similarly, when we do the comparison in people with severe illness those whose RDW-CV ≤ 14.5 is only 5% while it is 23.4% in those with RDW-CV $>14.5\%$. The ROC curve was used

Table 1: Showing the association between severity of disease and Hematological parameters

Parameters	Severity			P
	Mild (n=523)	Moderate (n=165)	Severe (n=112)	
Age (years)	49.34±15.43	50.64±16.64	49.78±17.44	0.661 ^a
Age (years), n (%)				
≤20	7 (1.3)	6 (3.6)	1 (0.9)	0.132 ^b
21–30	70 (13.4)	24 (14.5)	21 (18.8)	
31–40	81 (15.5)	18 (10.9)	12 (10.7)	
41–50	111 (21.2)	27 (16.4)	22 (19.6)	
51–60	116 (22.2)	44 (26.7)	26 (23.2)	
61–70	95 (18.2)	28 (17.0)	14 (12.5)	
71–80	36 (6.9)	16 (9.7)	16 (14.3)	
81–90	6 (1.1)	1 (0.6)	0	
>90	1 (0.2)	1 (0.6)	0	
Gender, n (%)				
Male	324 (62.0)	88 (53.3)	65 (58.0)	0.135 ^b
Female	199 (38.0)	77 (46.7)	47 (42.0)	
Hemoglobin (g/dL)***	13.32±1.49	12.89±1.45	12.76±1.52	<0.001 ^a
RBC count (million/cu.mm)	4.61±0.51	4.57±0.50	4.61±0.62	0.727 ^a
MCV (fL)***	87.31±4.59	85.43±6.88	84.77±7.84	<0.001 ^c
MCH (pg)***	28.86±3.04	28.06±2.77	27.77±3.34	<0.001 ^a
MCHC (g/dL)***	32.91±0.76	32.75±0.86	32.64±1.16	0.019 ^a
PCV (%)***	40.44±4.32	39.33±4.35	39.09±4.45	<0.001 ^a
RDW-CV (%)***	14.21±0.61	15.32±0.67	16.35±1.64	<0.001 ^a
RDW-SD (%)***	49.61±3.28	52.38±4.49	55.31±7.03	<0.001 ^a
TLC (/cu.mm)***	8160.23±3341.71	9267.27±3926.72	10,845.54±5084.92	<0.001 ^a
Platelet count (×1000/cu.mm)	211.47±71.70	210.78±86.07	202.38±83.84	0.486 ^a
Neutrophils (%)***	68.19±13.90	71.81±15.38	77.55±14.04	<0.001 ^a
Lymphocytes (%)***	25.70±12.48	22.01±13.65	17.12±12.05	<0.001 ^a
MPV (fL)***	7.30±0.64	7.52±0.69	7.52±0.69	<0.001 ^a
PDW (%)	18.35±0.74	18.47±0.76	18.50±0.92	0.056 ^c
Outcome, n (%)***				
Died	30 (5.7)	26 (15.8)	40 (35.7)	<0.001 ^b
Survived	493 (94.3)	139 (84.2)	72 (64.3)	

***Significant at $P < 0.05$, ^aKruskal–Wallis test, ^bChi-squared test, ^cOne-way ANOVA. MCV=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, PDW=Platelet distribution width, RDW-CV=Red cell distribution width co-efficient of variation, RDW-SD=Red cell distribution width standard deviation, MCHC=Mean hemoglobin concentration, RBC=Red blood cell, TLC=Total leukocyte count, MPV=Mean platelet volume, PCV=Packed cell volume

to determine the efficacy of RDW -CV in identifying the disease severity in COVID-19 patients. The cutoff value obtained was 13.65 with a sensitivity of 97.3% and specificity of 85% [Figure 4].

Discussion

For decades, hematological parameters have helped in the prognostication of many diseases. The RDW is one of the routinely obtained hematological parameters which measures the variation in red cell volume that can help in correlating severity of clinical illness in COVID-19 patients.^[15] The cytokine storm in COVID-19 infection dysregulates hematopoiesis and red cell clearance. Among many pro-inflammatory mediators, tumor necrosis factor- α and interleukin-1 impairs red cell production and old red cells with decreased MCV circulate due to impaired clearance of red cells in the spleen. The increase in RDW is directly proportional to the proinflammatory mediators in COVID-19 infection.^[16-19]

The RDW-CV, included in a validated prognostic nomogram developed by Gong *et al.* concluded that it can be a very good prognostic predictor of adverse outcomes in both severe COVID infection and sepsis.^[18] A large-scale online pooled analysis of three studies comprising of 11,445 COVID-19 patients revealed high RDW-CV values in severe covid illness in comparison to mild disease. The severe illness patients had a 0.69% higher absolute RDW-CV value than the mild disease patients.^[20] A prospective multicentric study by Karampitsakos *et al.* revealed that the patients with baseline RDW $< 14.5\%$ ($n = 156$, 80.8%) had less progressive disease compared to patients with baseline RDW $\geq 14.5\%$ ($n = 41$, 19.2%). The study further substantiated the reproducibility and validity of RDW in predicting the severity of the COVID-19 disease as concluded by Foy *et al.* study.^[6,11] In our study, a cutoff value of 13.65 was obtained with a sensitivity of 97.3% and specificity of 85% in predicting the outcome of the disease. A study by Lux *et al.* on the classification of

Table 2: Showing the association of Hematological variables with reference to RDW-CV values

Variables	Mean±SD		P	Total (n=800), mean±SD
	RDW-CV ≤ 14.5 (n=408)	RDW-CV > 14.5 (n=392)		
Gender, n (%)				
Female	136 (33.3)	187 (47.7)	0.000*	323 (40.4)
Male	272 (66.7)	205 (52.3)		477 (59.6)
Age	50.87±14.80	48.42±17.03	0.030	49.67±15.97
Hemoglobin	13.38±1.39	12.916±1.58	0.000	13.15±1.50
RBC	4.598±0.49	4.604±0.55	0.860	4.60±0.522
MCV	87.49±4.36	85.603±6.79	0.000	86.57±5.75
MCH	28.927±1.67	28.147±3.98	0.000	28.55±3.06
MCHC	33.055±0.74	32.621±0.91	0.000	32.84±0.86
PCV	40.461±4.08	39.56±4.62	0.004	40.02±4.37
RDW-SD	48.702±2.64	53.352±5.22	0.000	50.98±4.72
WBC	8567.402±3938.5	8969.64±3784.40	0.141	8764.50±3866.63
PLT	212.049±75.94	207.98±77.30	0.453	210.06±76.59
N	70.105±14.65	70.39±14.54	0.783	70.25±14.59
L	24.113±13.28	23.344±12.75	0.404	23.74±13.02
MPV	7.326±0.60	7.429±0.73	0.029	7.38±0.66
PDW	18.403±0.76	18.382±0.79	0.698	18.40±0.77

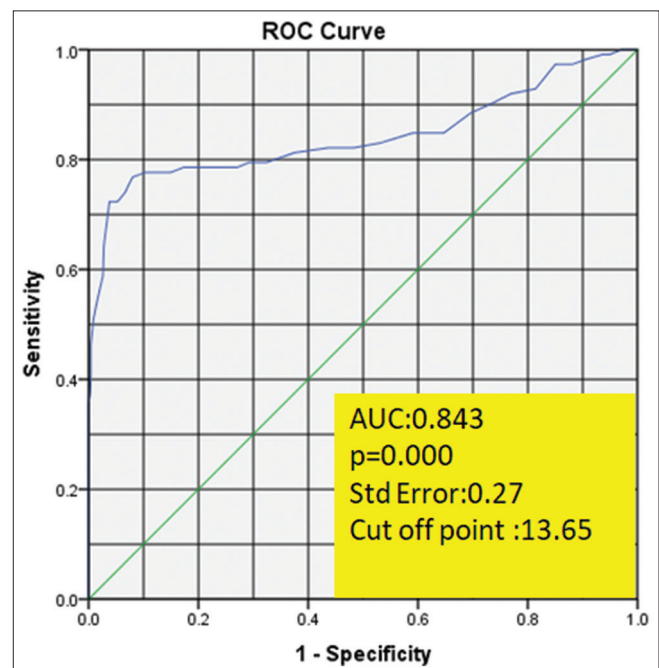
*Chi-square test was used to find the statistical association between the RDWCV and gender. *t*-test was used to find the statistical significant difference between RDWCV and the study variable which are continuous type data, and follows normal distribution (by normality test). MCV=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, MCHC=Mean hemoglobin concentration, RDW-SD=Red cell distribution width standard deviation, MPV=Mean platelet volume, PDW=Platelet distribution width, WBC=White blood count, PLT=Platelet count, SD=Standard deviation

Table 3: Showing the association between Severity of Disease and RDW-CV values

Severity	RDW-CV ≤ 14.5 (n=408)	RDW-CV > 14.5 (n=392)
Mild	90% (369/408)	39.2% (154/392)
Moderate	4.7% (19/408)	37.2% (146/392)
Severe	4.9% (20/408)	23.4% (92/392)

RDW-CV: Red cell distribution width co-efficient of variation

Covid-19 in intensive care patients studied 150 intensive care unit (ICU) patients who were prognosticated into four groups as type A, B, C, and D. Type A category has an extremely poor prognosis with a mean RDW-CV value of 13.4 (12.8–14.1) while that of category type D category had favorable prognosis with mean RDW of 12.2 (11.8–12.7).^[21] A study by Wu *et al.* on clinical characters and immune injury mechanism in COVID 19 patients studied around 71 COVID-positive cases and found out that neutrophil count and total WBC counts were significantly elevated in severe cases of Covid infection when compared to that of mild and moderate cases while the lymphocyte percentage was found to be low comparatively. This study also analyzed that both mild and severe cases had normal levels of RBC, HGB, mean RBC volume (MCV), mean hemoglobin content (MCH), and mean hemoglobin concentration (MCHC) and no much significant difference was observed between them. While some of the parameters exhibited a tendency to decrease in severe patients during the course of admission which was attributed to dietary abnormality postinfection. MPV was found to be high in severe cases when compared to of mild but within normal limits. These results were consistent with the results of our study.^[22] A study by Wang *et al.* to identify severe

**Figure 4: The receiver operator curve analysis graph**

from moderate cases of COVID-19 using hematological parameters concluded that out of 45 patients examined 35 belong to the moderate group and 10 belong to the severe group. This study concluded that with the progression of disease (increase in severity of disease) the WBC count, neutrophil count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), RDW-CV, and red cell volume distribution width- (RDW-SD) parameters were significantly higher in a severe group than those in the

moderate group ($P < 0.05$); meanwhile, Lymphocyte count, Eosinophil count, RBC count, hemoglobin (HGB), and HCT) parameters in the severe group were significantly lower than those in the moderate group ($P < 0.05$). ROC curve analysis was done for NLR, PLR, RDW-SD values, and RDW-CV values. It was found out from the study that parameters such as NLR and RDW-SD when combined had the best diagnostic efficiency (area under the curve [AUC] = 0.938), and when the cutoff value was 1.046, the sensitivity and the specificity were 90.0% and 84.7%, respectively. They further analyzed that the combined parameter of NLR & RDW-CV (AUC = 0.923) had a cut-off value of 0.62, the sensitivity and the specificity for distinguishing severe type from moderate cases were 90% and 82.4%, respectively.^[23] A study by MandanaPouladzadeh *et al.* from Ahvaz Jundisapur university of medical sciences on validation of RDW as a COVID-19 severity screening tool prospectively studied 331 COVID-19 patients as categorized into severe and nonsevere and concluded with the following results. The mean levels of WBC, RDW-CV, RDW-SD, PDW, MCHC, and erythrocyte sedimentation rate were found to be significantly higher in people with severe illness. The percentage of neutrophils was found to be higher in severe illness while that of lymphocyte percentage was found to be lower. This situation was vice versa in the case of people with mild and moderate illnesses. The mean values of RBC, Hb, and Hct were significantly lower in severe patients. ROC curve analysis was done in this study for RDW-SD values to identify the severity of disease in COVID-19 and also to predict the probability of death in COVID-19. The cutoff value obtained to identify the disease severity was found to be 43fl with the specificity of 90.1% and sensitivity of 62.2% and the cutoff point to predict death probability was found to be 47fl with specificity 91.4 and sensitivity of 47.5%.^[24] Our study results were compared with a study from Apollo hospitals by MamtaSoni *et al.* on the significance of RDW in predicting mortality which analyzed around 622 COVID-positive cases where the no of survivors was 522 and dead were 97. When compared with our study, we had 704 survivors and 96 dead people. The percentage of the dead with elevated RDW was 53%, while in our study, it was 74%. The percentage of survivors with elevated RDW was 43% in their study and we too had similar results. The ROC curve analysis was done to find out the cutoff value and they arrived at a value of 14.9% as cutoff value, while in our study, we arrived at a value of 13.65 as a cut-off value.^[11] Table 4 shows a comparison between the two studies. A prospective and observational study by Lorento *et al.* on the association between RDW and mortality of COVID-19 patients analyzed patients from 8 ICU of six hospitals of Canary islands. These patients were categorized into survivors and nonsurvivors and RDW was monitored from admission till 30 days. Following findings were observed from this study, first,

Table 4: The comparison of our study with a study from Apollo hospital

Category	Apollo hospital (Chennai)	Our study
Cases	622	800
Survivors	522	704
Dead	97	96
Percentage of male	72.2	60
Elevated RDW in dead (%)	53	74
Elevated RDW in survivors (%)	43	45
ROC cut off (%)	14.9	13.65

RDW=Red cell distribution width, ROC=Receiver operating characteristics

nonsurviving patients had higher RDW at admission and a significant association between high RDW and mortality was observed, and most importantly, the mortality predictive value of RDW was found to be similar to other scores such as APACHE-II and SOFA.^[25-27]

Conclusion

Higher RDW(CV) taken at the time of admission was found to have a significant association with clinical severity and mortality prediction. Hence, it can be considered in the workup to efficiently stratify patients at the earliest in COVID-19.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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