Received: 15 January 2021 | Revised: 16 February 2021 | Accepted: 13 March 2021

DOI: 10.1111/ijlh.13526

LETTER TO THE EDITOR

ISLH International Journal of Laboratory Hematology WILEY

Significance of RDW in predicting mortality in COVID-19—An analysis of 622 cases

Dear Editors,

Red cell distribution width-coefficient of variation (RDW—CV) is a routine component of the complete blood count, automatically generated by most hematology analyzers at no extra cost. RDW is a quantitative estimation of the heterogeneity of volume of red blood cells (RBCs), commonly known as anisocytosis. Elevated RDW can result from an increase in RBC volume variance and/or a reduction in mean corpuscular volume (MCV).[1]

There is significant evidence to suggest that inflammatory responses play a critical role in COVID-19.[2] A possible association can exist between a high RDW and inflammation.[3] Inflammatory responses negatively impact RBC production and turnover.[3,4] Many of the pro-inflammatory cytokines up-regulated in COVID-19 such as tumor necrosis factor-α and interleukin-1 can cause reduction in erythropoietin production.[2] Further, SARS-CoV-2 infection can cause both direct injury to the peripheral circulating RBCs or erythroblasts in bone marrow and an indirect injury to RBCs due to hemolytic anemia or intravascular coagulopathy, and disturbances in iron metabolism.[5-7] Overall, the predominant cause of elevation of RDW in COVID-19 is indicated to be the increased number of older RBCs in the circulation due to delayed clearance.[1,3] This is because older RBCs have a reduced volume resulting in a reduced MCV.

RDW is a useful predictor of the clinical outcomes in critically ill patients and in patients with infection and sepsis.[4,8] RDW may provide information for early risk stratification of COVID-19 patients and enable timely interventions to reduce mortality and morbidity. Although certain markers such as D-dimer and eosinophils have been evaluated as prognostic indicators in COVID-19 infection,[9,10] only a few studies have explored the role of RDW in predicting prognosis. In a pandemic, early risk stratification based on a biomarker, which is routinely available with existing tests, without any extra cost can help efficient utilization of both critical care and laboratory resources, particularly in resource-constrained environments. Thus, we aimed to evaluate the role of RDW as a prognostic indicator in COVID-19-infected patients.

For our study, data on patient demography, laboratory investigations, and clinical details of confirmed COVID-19 cases admitted between June 04, 2020, and September 11, 2020, at Apollo Hospitals, Chennai, India, were retrieved through electronic records and analyzed.

As per World Health Organization guidelines, patients with a positive result of the nucleic acid test for SARS-CoV-2 by RT-PCR were considered as confirmed COVID-19 cases. Adult patients (≥18 years) who had a definite outcome (discharge or death) during the course of admission were included in the study. Patients still under admission were excluded from the study.

The complete blood count was performed on fully automated hematology analysers (Coulter DXH 900 and Siemens Healthineers ADVIA 2120i). Reference interval for RDW-CV at our center is 11.6%-14.5%. Any value above 14.5% was considered as elevated.

The data were analyzed for a total of 772 patients, of which 150 negative samples were kept as reference for normal distribution. On-admission values were available for 622 COVID-19 patients. RDW values before the definite outcome were available for 366 patients.

Statistical workup included calculation of mean and standard deviations, Pearson's chi-square test or Fisher's exact test, independent sample *t* test, paired *t* test, Receiver Operating Characteristics (ROC) analysis to find the area under the curve (AUC) and Youden Index (J) method to obtain optimal cutoff point for RDW, Kaplan-Meier Survival analysis, and Cox regression model to calculate the hazard ratio (HR) for RDW, D-dimer, age, and co-morbidities. All analyses were performed by using the R-software version 4.0.3 for windows. A two-sided *P*-value of <.05 was considered as statistically significant.

Baseline characteristics of the patients, including age, gender, other significant test parameters, and RDW values, are presented in Table 1. The mean (SD) age of the patients was 59.31 (14) years, and 37.6% of the patients were aged ≥65 years. Of the 622 COVID-19 patients, 72.2% were males.

Elevated RDW on admission was detected in 36.8% (229/622) of COVID-19 patients and 9.3% (14/150) of the COVID-19-negative patients ($P < .01$). Mean (range) of RDW on admission was 14.6% (12.00-31.60) and 13.7% (12.2-17.8) in COVID-19-positive and COVID-19-negative patients, respectively ($P < .01$).

Of the 622 patients whose samples were studied, there were 525 survivors and 97 nonsurvivors. Elevated RDW was found in 53% (51 of 97) of the nonsurvivors and 43% (178 of 525) of the survivors ($P < .001$). Mean (range) RDW on admission was 15.45% (13-32) in nonsurvivors and 14.49% (12-26) in survivors ($P \leq .001$).

Kaplan-Meier survival analysis stratified by RDW indicated that the survival probability significantly worsened in the elevated RDW group ($P = .008$) (Figure S1).

Of the 97 patients with a fatal outcome, 53% (51/97) had an elevated RDW on admission and 47% (46/97) had a normal RDW ($P < .001$).

TABLE 1 Baseline characteristics of 622 patients with COVID-19

Variable		RDW ≤ 14.5 (N = 393)	RDW > 14.5 (N = 229)	Total (N = 622)	*P*-value	Mortality	Mortality *P*-value
Age	Mean (SD)	58.58 (13.83)	60.55 (14.23)	59.31 (14.00)	.0920	-	-
Age n (%)	<65	256 (65.1%)	132 (57.6%)	388 (62.4%)	.0757	45 (11.60%)	<.001
	≥65	137 (34.9%)	97 (42.4%)	234 (37.6%)		52 (22.22%)	
Gender	Female	80 (20.4%)	93 (40.6%)	173 (27.8%)	<.001	24 (13.87%)	.5378
	Male	313 (79.6%)	136 (59.4%)	449 (72.2%)		73 (16.26%)	
Mortality	Death	46 (11.7%)	51 (22.3%)	97 (15.6%)	<0.001		

Variable		RDW ≤ 14.5 (N = 393)	RDW > 14.5 (N = 229)	Total (N = 622)	*P*- value
Hemoglobin (g/dl)	Mean (SD)	13.32 (1.72)	11.46 (2.32)	12.64 (2.16)	<.001
Total WBC ($10^3/mm^3$)		9.46 (6.51)	10.07 (6.22)	9.69 (6.41)	.2457
NLR (%)		10.61 (11.08)	11.03 (12.76)	10.77 (11.72)	.6735
D-Dimer (μg/ml)		2.76 (8.91)	6.58 (20.08)	4.16 (14.20)	.0068

Abbreviations: N, number of subjects in treatment; SD, Standard Deviation.

TABLE 2 Mortality hazard ratios (HRs) using cox proportional hazards regression modeling

Parameter	Hazard ratio	95% Confidence Interval (Lower limit-Upper limit)	*P*-value
Age	1.45	(0.96-2.20)	.0790
Gender	1.23	(0.80-2.10)	.2920
RDW (Admission)	1.84	(1.20-2.81)	.0050
D-Dimer (Admission)	1.30	(0.78-2.16))	.3240
Comorbidities	0.97	(0.57-1.66)	.9150

Cox proportional hazards regression model showed that RDW > 14.5% was an independent predictor of mortality, beyond age, gender, D-dimer level, and comorbidities (Table 2).

RDW values before discharge or death were available for 280 survivors and 86 nonsurvivors. In these patients, elevated RDW was found in 81.4% (70 of 86) of the nonsurvivors and 41.8% (117 of 280) of the survivors ($P < .001$). Mean (range) RDW before death was 16.52% (13-30), while it was 14.87% (12-24) before discharge ($P < .05$).

Out of the 86 nonsurvivors, elevated RDW was found in 70 patients (81.4%), whereas 16 (18.6%) patients had a normal RDW ($P < .001$).

Since the time of presentation of a patient to the hospital varies, it cannot be ascertained whether the baseline elevation of RDW is due to COVID-19 pathophysiology or an underlying condition. Thus, RDW levels a few days after admission may establish a better correlation with the clinical outcomes than those at admission. Trend of RDW was found to be significantly different during the course of admission in survivors and nonsurvivors. Over the course of admission, an increasing RDW was observed in 66.3% of the nonsurvivors, whereas no increase was observed in majority (67.1%) of the survivors (Table 3).

TABLE 3 RDW trends over the course of admission in survivors and nonsurvivors

Patients	RDW			*P*-value
	No change N = 214	Increase N = 128	Decrease N = 24	
Survivors % (n)	67.1 (188)	25.4 (71)	7.5 (21)	<.001
Nonsurvivors % (n)	30.2 (26)	66.3(57)	3.5 (3)	

Comparison of the mean RDW at admission and before discharge or death showed an increase ($P < .01$) in both survivors and nonsurvivors. However, the mean increase in RDW in the nonsurvivors group was nearly 4 times than that in the survivors group (1.2 and 0.31, respectively).

In this study, we also attempted to establish a cutoff value of RDW for predicting mortality in COVID-19 patients. The optimum cutoff value for RDW for predicting mortality calculated by using the ROC curve was 14.90%, with a sensitivity of 77.32% and a specificity of 65.0%. C-index was 0.738.

The results of our study are similar to other evaluations of the association of elevated RDW with mortality. In a cohort study that included 1641 patients with COVID-19, RDW was associated with increased mortality risk in Cox proportional hazards modeling adjusted for various parameters including age and D-dimer (HR of 2.01 for an RDW >14.5% versus ≤14.5%).[3] Similar to the finding in our study, an increase in RDW over the period of hospitalization was associated with increased mortality.[3] In another study of 294 hospitalized COVID-19 patients, RDW was associated with increased mortality (Odds Ratio = 4.5; 95% CI 1.4-14.3) after adjustment for covariates such as age, anemia, and co-morbidities.[11] However, in one smaller study that included 70 COVID-19 patients, although RDW was found to be higher, there was no significant association with mortality.[12]

Our study has some limitations. As ours was a single-center, retrospective study, it could have resulted in a selection bias. A larger, multicentric study may be required to confirm the findings. As there was no follow-up, post-discharge clinical status could not be ascertained. It is acknowledged that a prediction model for outcomes in COVID-19 patients will include a combination of clinical and laboratory parameters.

In conclusion, RDW can be considered during the workup for COVID-19 patients as it helps in early risk stratification for efficient and effective utilization of available resources especially in limited resources settings.

FUNDING INFORMATION

There are no funding sources to declare.

CONFLICT OF INTEREST

The author has no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. *Am J Hematol*. 2015;90(5):422-428. https://doi.org/10.1002/ajh.23982
2. Zeng F, Huang Y, Guo Y, et al. Association of inflammatory markers with the severity of COVID-19: A meta-analysis. *Int J Infect Dis*. 2020;96:467-474. https://doi.org/10.1016/j.ijid.2020.05.055
3. Foy BH, Carlson JCT, Reinertsen E, et al. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 Infection. *JAMA Netw Open*. 2020;3(9):e2022058. https://doi.org/10.1001/jamanetworkopen.2020.22058
4. Zhang Z, Xu X, Ni H, Deng H. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. *J Thorac Dis*. 2013;5(6):730-736. https://doi.org/10.3978/j.issn.2072-1439.2013.11.14
5. Henry BM, Benoit JL, Benoit S, et al. Red blood cell distribution width (RDW) predicts COVID-19 severity: a prospective, observational study from the Cincinnati SARS-CoV-2 emergency department cohort. *Diagnostics*. 2020;10(9):618. https://doi.org/10.3390/diagnostics10090618
6. Lazarian G, Quinquenel A, Bellal M, et al. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol*. 2020;190(1):29-31. https://doi.org/10.1111/bjh.16794
7. Thomas T, Stefanoni D, Dzieciatkowska M, et al. Evidence of structural protein damage and membrane lipid remodeling in red blood cells from COVID-19 patients. *J Proteome Res*. 2020;19(11):4455-4469. https://doi.org/10.1021/acs.jproteome.0c00606
8. Uffen JW, Oomen P, de Regt M, et al. The prognostic value of red blood cell distribution width in patients with suspected infection in the emergency department. *BMC Emerg Med*. 2019;19:76. https://doi.org/10.1186/s12873-019-0293-7
9. Soni M, Gopalakrishnan R, Vaishya R, Prabu P. D-dimer level is a useful predictor for mortality in patients with COVID-19: analysis of 483 cases. *Diabetes Metab Syndr*. 2020;14(6):2245-2249. https://doi.org/10.1016/j.dsx.2020.11.007
10. Soni M. Evaluation of eosinopenia as a diagnostic and prognostic indicator in COVID-19 infection. *Int J Lab Hematol*. 2020;1–5. http://doi.org/10.1111/ijlh.13425
11. Ramachandran P, Gajendran M, Perisetti A, et al. Red blood cell distribution width (RDW) in Hospitalized COVID-19 Patients. *medRxiv*. 2020.06.29.20143081. https://doi.org/10.1101/2020.06.29.20143081
12. Sharma D, Dayama A, Banerjee S, Bhandhari S, Chatterjee A, Chatterjee D. To study the role of absolute lymphocyte count and RDW in COVID 19 patients and their association with appearance of symptoms and severity. *J Assoc Physicians India*. 2020;68(8):39-42.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.