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Utility of hematological parameters as predictors of mortality in COVID-19 patients.

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ABSTRACT

Red Cell Distribution Width (RDW-CV %), Neutrophil lymphocyte ratio (NLR), and Platelet lymphocyte ratio (PLR) were proposed as prognostic biomarkers for COVID-19 patients, but limited research exists with varying results[1]. Further investigation is needed,particularly in India.

Aim

To determine the association of Red Cell Distribution Width, Neutrophil Lymphocyte Ratio, Platelet Lymphocyte Ratio, and Hematocrit values with COVID-19 mortality risk.To establish cut-off values for predicting mortality.

Settings and Design

Retrospective study conducted in Pondicherry including 100 non-survivors and 100 age-matched survivors hospitalized between April 20th, 2021, and June 30th, 2021.

Methods and Material

Demographic details, survival status, clinical and laboratory data were obtained from discharge summaries and laboratory records.

Inclusion criteria

Inpatients (≥ 18 years old) who were diagnosed as SARS-CoV-2 nucleic acid-positive by real-time polymerase chain reaction and hospitalized in our institute between April 20th 2021 and June 30th 2021 were included in this study.

Exclusion criteria

Patients who were discharged against medical advice during the study period were excluded. The initial (admission values) of Hematocrit, RDW-CV %, NLR and PLR values were determined for each patient. The peak values of RDW-CV %, NLR and PLR and minimum (nadir) value for Hematocrit values were also determined and compared between survivors and non-survivors.

Statistical analysis used

Statistical analysis included Chi square/Fisher's exact test,univariate and multivariate binary logistic regression analyses and ROC analysis.

ResultsRDW-CV % and NLR (initial values) showed a significant association with mortality (relative risk of 1.584 and 1.127, respectively). RDW-CV %, NLR, and PLR (peak values) were significantly associated with mortality with relative risks of 1.731, 1.106, and 0.998, respectively. The ROC analysis indicated RDW-CV % value of 14.1, NLR of 10.94, and PLR of 387 as mortality predictors.

Conclusions: Red Cell Distribution Width (RDW-CV %), NLR and PLR are useful predictors of COVID-19 mortality. PLR is a weaker prognosticator compared to RDW-CV % and NLR[1].Serial Monitoring of these parameters can play role in deciding Intensive Care admission and treatment protocol for patients.

Key-words: COVID-19, Hematological Tests, Blood Cell Count, mortality.

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INTRODUCTION

Hypothesis

Elevated RDW-CV, NLR and PLR can be considered independent biomarkers for predicting adverse clinical outcomes in COVID-19 patients.The second wave of COVID-19 has had severe consequences globally and posed several challenges for resource limited countries like India. There have been successive waves of sub-variants since June 2021. Lab parameters like D-dimer and CRP are helpful in predicting progression and the risk of mortality. Cost-effective hematological parameters would be more helpful in developing nations. The prognostic significance of Red cell distribution width (RDW), Neutrophil lymphocyte ratio (NLR) and Platelet lymphocyte ratio (PLR) has been evaluated in a few studies[1].RDW and NLR have shown promising results. Elevated baseline RDW levels were independently associated with worse clinical outcomes in hospitalized patients with COVID-19[1].NLR and PLR are inflammatory biomarkers. High NLR levels were found to be associated with severe COVID-19 and mortality.[2] Combination of NLR and RDW parameters has also been found to be clinically useful.[3] Studies have also shown alterations of PLR and hematocrit in COVID-19,[4,5] but the prognostic significance of PLR and hematocrit in COVID-19 is not clear.[4]The previous studies have yielded conflicting results possibly due to factors like age and comorbidities. Age matched controls is a strength of this study as previous studies have shown that advanced age is also associated with poor clinical outcomes in COVID-19 patients. Multivariate logistic regression and receiver operating characteristic (ROC) analysis were used to evaluate the association and efficacy of these parameters for predicting COVID-19 mortality. Multicentric studies should conducted to validate the clinical applicability of these parameters especially in India.

METHODS

The present study is a retrospective hospital-based study of patients admitted for COVID-19. Inpatients (≥ 18 years old) who were diagnosed as SARS-CoV-2 nucleic acid-positive by real-time polymerase chain reaction and hospitalized between April 20th 2021 and June 30th 2021 were included in this study. Patients who were discharged against medical advice during the study period were excluded. Patients were categorized as survivors and non-survivors.100 non-survivors and 100 survivors were included in the Retrospective study. Consecutive non-survivors who died during hospitalization were included. The survivors were inpatients who were treated in the same period and survived to discharge. Age-matched survivors were used for comparison with non-survivors.

- **Data collection procedure:** Demographic details, clinical data, disease severity and survival status were collected from the patient's medical chart/discharge summary. This included age, sex, period of hospital stay in isolation ward /ICU, comorbidities and other pertinent information during the course of admission. Laboratory data was recorded from the analyzers and lab reports. Complete blood count and differential count values were recorded from the automated hematology analyzers and medical records. Results of other relevant investigations were also obtained retrospectively from medical records and the Hospital Information Software (HIS). Automated hematology analyzers Sysmex-XN1000 (Sysmex Corporation, Kobe, Japan) and Horiba Pentra DF Nexus (Horiba Medical, Montpellier, France) were used for complete blood counts in the study period. Internal quality controls were run routinely for the CBC and differential count in our laboratory.

- **Study variables:** The data of CBC parameters evaluated on hospital admission and on different days after admission was gathered. This included hemoglobin, hematocrit, RDW-CV%, Platelet count, white blood cell (WBC) count, differential and absolute counts. Neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were calculated.

- **Statistical analysis**: The clinical and laboratory data were collected and entered into a Microsoft Excel file. The patients were segregated into two groups (survivors and non-survivors) based on the survival status. The NLR, PLR, RDW-

CV and Hematocrit were compared between the two groups. The NLR, PLR, RDW-CV and Hematocrit values at admission as well as maximum (peak) value during the course of admission were considered for each patient. Quantitative variables were described using mean± standard deviation (SD). Student's t-test was used to assess the significance of differences observed between continuous variables. Chi square/Fishers exact test was used to assess the relationship between categorical variables. Univariate and multivariate binary logistic regression analyses were used to identify the association of NLR, PLR, RDW-CV and Hematocrit with mortality. Variables which are significant at ≤ 0.1 in simple regression were considered for multiple logistic regression analysis.

The efficacy of the parameters for predicting mortality was assessed using the area under the curve (AUC) generated by a receiver operating characteristic (ROC) analysis. The cutoff value and corresponding sensitivity and specificity were estimated. The ROC plots the true positive rate (sensitivity) against the false-positive rate (1-specificity). A perfectly accurate test would yield a ROC of 1.0 and a ROC of 0.5 indicates a predictive efficacy no better than chance. A p-value <0.05 was considered statistically significant for all tests. Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Our study included 100 non-survivors and 100 age-matched survivors. The mean age of the survivors and non- survivors was 60.99 years and 60.49 years respectively. The difference in the mean age was not statistically significant (p value-0.827.) Of a total of 200 patients, 136 (68%) were males. 136 (68%) patients had comorbidities like hypertension, diabetes, chronic kidney disease, coronary artery disease, COPD, and others. Non-survivors were more frequently associated with hypertension, diabetes and chronic kidney disease. The differences between survivors and non-survivors are displayed in Table 1

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Table 1:Clinical characteristics of COVID-19 patients

Characteristics	Clinical Outcome Survivors (100)	Non- survivors (100)	P value
Male Sex	70 70.0%	66 66.0%	0.544
Diabetes mellitus	36 36.0%	56 56.0%	0.005
Hypertension	34 34.0%	52 52.0%	0.010
Coronary artery disease	9 9.0 %	7 7.0 %	0.602
Chronic kidney disease	2 2.0%	10 10.0%	0.017
Presence of co-morbidities	57 57.0%	79 79.0%	0.001

The initial (admission values) and peak Hematocrit, RDW-CV %, NLR and PLR values were determined for each patient as mentioned previously. The minimum (nadir) value during the course of admission for Hematocrit value was also determined for each patient. The mean of the initial and peak values varied significantly between survivors and non- survivors as shown in Table 2. The initial (admission values) RDW-CV (%), NLR and PLR were significantly higher in non- survivors and hematocrit was significantly lower in survivors.

The peak values of RDW-CV (%), NLR and PLR obtained during the course of admission were also significantly higher in non-survivors. The mean minimum value for hematocrit was significantly lower (p value <0.001) in non-

survivors (34.27%) compared to survivors (38.05%)

Table 2:Laboratory parameters by clinical outcome

Characteristics	Clinical outcome		P value
	Survivors (100)	Non- survivors (100)	
Admission values			
Hematocrit	39.3±4.7	37.1±6.3	0.005
RDW-CV (%)	13.6±1.2	14.9±2.7	<0.001
NLR	6.1±5.2	10.1±10.3	0.001
PLR	229.51±138.10	295.47±223.44	0.013
Peak values obtained during the course of admission			
RDW-CV (%)	13.8±1.3	15.5±2.7	<0.001
NLR	10.4±13.5	32.8±24.0	<0.001
PLR	344.13±349.70	609.03±411.83	<0.001

Data expressed as Mean± SD

The association between Hematocrit, RDW-CV % NLR, PLR (initial values) and mortality was estimated by binary logistic regression. The RR and 95% CI of Hematocrit, RDW-CV %, NLR and PLR are shown in Table 3. Hematocrit, RDW-CV % NLR, PLR was significantly associated with mortality in univariate analysis. RDW-CV % and NLR were significantly associated with mortality with relative risk of 1.584 and 1.127 respectively in multivariate analysis.

The association between Hematocrit, RDW-CV % NLR, PLR (peak values) and Hematocrit (minimum value) mortality was also estimated by binary logistic regression. RDW-CV % NLR, PLR (peak values) and Hematocrit (minimum value) were significantly associated with mortality in univariate analysis. RDW-CV %, NLR and PLR (peak values) were significantly associated with mortality with relative risk of 1.731 (95 % CI of 1.286-2.330; p value <0.001), 1.106 (95 % CI of 1.060-1.154; p value <0.001) and 0.998 (95 % CI of 0.996-1.000; p value-0.037) respectively in multivariate analysis. Hematocrit (minimal values) was not significantly associated with mortality (p value 0.592).

Table 3:Association between Hematocrit,RDW-CV %NLR,PLR and mortality estimated by binary logistic regression

Variable	Univariate			Multivariate		
	RR	95% CI	P value	RR	95% CI	P value
Comorbidities	0.352	0.189-0.657	0.001	0.455	0.226- 0.915	0.027
Hematocrit	0.929	0.881-0.979	0.006	0.962	0.904- 1.023	0.217
RDW-CV %	1.612	1.280-2.031	<0.001	1.584	1.230- 2.040	<0.001
NLR	1.081	1.028-1.136	0.002	1.127	1.034- 1.229	0.006
PLR	1.002	1.000-1.004	0.017	0.998	0.995- 1.001	0.194

Figures 1 and 2 show the receiver operating characteristic curves of initial and peak RDW-CV %, NLR, PLR and hematocrit values. The appropriate cut-off and AUC values with sensitivity and specificity are shown in table

4.Hypothesis: Elevated RDW-CV, NLR and PLR can be considered independent biomarkers for predicting adverse clinical outcomes in COVID-19 patients

Table 4:Area Under the Curve and critical values for RDW-CV%, NLR and PLR

Parameter	AUC	SE	95 % CI	P value	Cut-off value	Sensitivity (%)	Specificity (%)
Initial RDW-CV%	0.671	0.038	0.597-0.746	< 0.001	13.7	65	60
Peak RDW-CV%	0.754	0.034	0.687-0.82NLR	< 0.001	14.1	79	65
Initial NLR	0.644	0.039	0.569-0.720	< 0.001	6.0	57	64
Peak NLR	0.843	0.028	0.789-0.897	< 0.001	10.94	78	74
Initial PLR	0.580	0.040	0.501-0.659	0.050	170.0	70	43
Peak PLR	0.727	0.036	0.657-0.798	< 0.001	387.4	65	88

Abbreviation SE: Standard Error AUC: Area Under the Curve

Fig 1. Receiver operating characteristic curves of initial values of RDW-CV %, NLR, PLR and hematocrit in predicting mortality in COVID-19 patients.

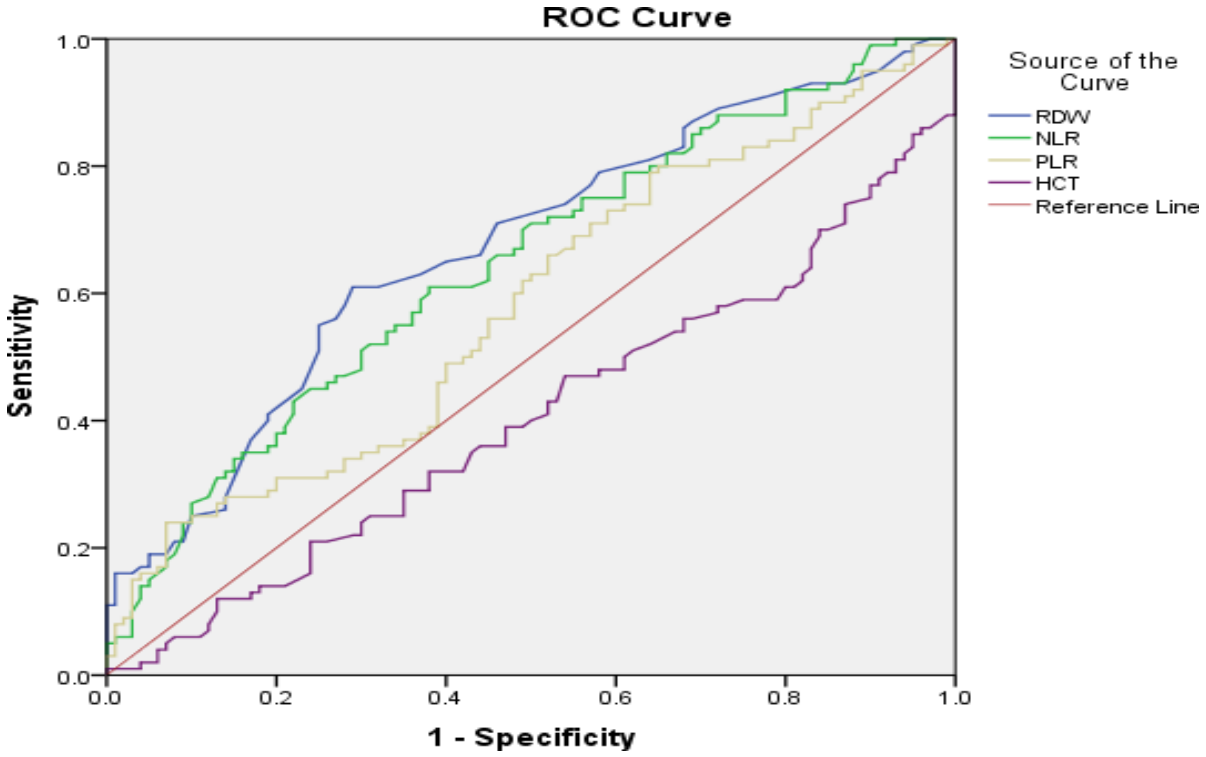
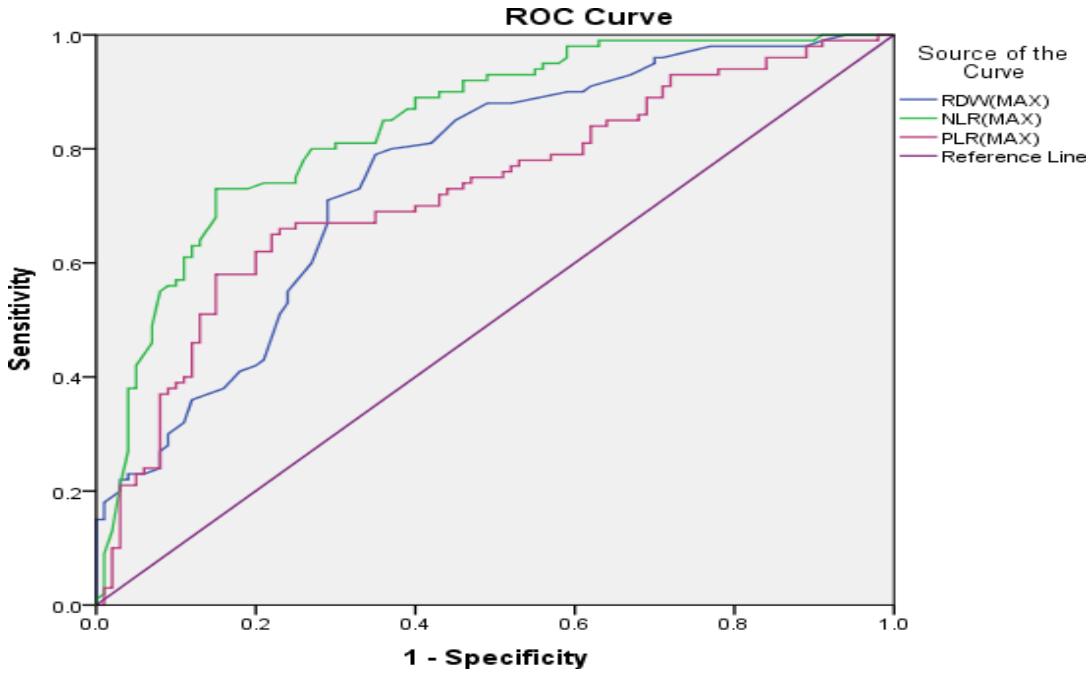


Fig 2. Receiver operating characteristic curves of peak values of RDW-CV %, NLR, PLR and hematocrit in predicting mortality in COVID-19 patients.



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DISCUSSION

RDW quantifies the variation in the size of circulating red blood cells. Elevated RDW is associated with an increased risk for mortality from heart disease, pulmonary disease, sepsis, influenza, and cancer. RDW is a promising marker that can provide general risk stratification that may be useful for a new disease like COVID-19.[9,10]NLR and PLR are inflammatory biomarkers with well-known prognostic value and independently correlate with mortality in the general population and in diseases like sepsis, pneumonia, cancer, etc.[11,12] Various studies have assessed the utility of RDW and inflammatory biomarkers in COVID-19.[13-35]Majority of these studies have investigated the differences with respect to severity. Tables 5 and 6 compare the mean /median NLR, PLR and RDW-CV% in survivors and non- survivors and AUC values with optimal cut-offs in various studies. The variation in the results could be due to sample size, selection of patient population for the study, age, ethnicity, different stages of the disease and presence of comorbidities. Age adjusted survivors were used in the current study to minimize bias resulting from baseline clinical characteristics of the patients.

Table 5. Comparison of AUC, sensitivity and specificity for RDW in predicting mortality

Place of study	No. of survivors	No. of non-survivors	Type of RDW	Mean ± SD / Median (range) RDW values survivors	Mean ± SD / Median (range) RDW values non-survivors	Optimal Cut off Value	AUC [Sensitivity, Specificity]
Canary Islands Spain[20]	118	25	Initial	13.3 (12.5 - 14.5)	14.1 (13.3 - 16.1)	13.0	0.71 [88,45]
Madrid, Spain[21]	1090	279	Initial	14.0±1.4	15.2±2.1	NE	NE
Davangere, India[22]	75	25	Initial	13.9± 2.2	14.8±3.0	15.0	0.708 [92,47]
Guanajata, Mexico[30]	149	174	Initial	13 (12.3-13.7)	13.6 (12.94-14.4)	13.30	0.655 [62.1,65.4]
			Discharge	12.9 (12.2-13.5)	14.6 (12.67 - 15.6)	13.70	0.830 [75.8,78.8]
Present study	100	100	Initial	13.6±1.2	14.9±2.7	13.7	0.671 [65,60]
			Peak	13.8±1.3	15.5±2.7	14.1	0.754 [79,65]

NLR values are significantly higher in non-survivors in various studies (Table 6). Our AUC values for NLR are similar to a previous Indian study.[13]There is also a minimal variation with respect to the optimal cut-off values in various studies. Baseline and elevated NLR were associated with increased risk of in-hospital mortality in our study. Regolo et al found NLR tobe an independent predictor of mortality in COVID-19 patients. The AUC of NLR (0.772) was also better than PLR (0.570) similar to our study. NLR showed a larger AUC, with specificity of 71.9% and sensitivity of 72.9%, compared to CRP which showed lower sensitivity (60.2%) but slightly higher specificity (72.3%) and a AUC of 0.676.[34] In the study by Citu et al[7], binary logistic regression identified elevated NLR (aOR = 4.14), as independent factors for mortality with an optimal cut-off of 9.1. PLR was not significantly associated with mortality.Tatum e t al found NLR to be an independent predictor for risk of mortality in SARS-CoV-2 patients and a prognostic factor for endotracheal intubation upon hospital admission.[19] NLR is a better tool than the absolute lymphocytes and neutrophil counts and reflects the inflammatory response to COVID-19.It is very helpful in forecasting mortality.

Both thrombocytopenia and lymphopenia are associated with poor outcomes in SARS-COV-2 infection. Studies mentioned in table 6 show higher PLR values in non-survivors. However,the

diagnostic utility of PLR in predicting mortality is less compared to NLR. In the study by Simon et al,[8] Our study showed that PLR was associated with mortality only in the univariate analysis, but not in the multivariate analysis.

The best PLR value for predicting mortality in COVID-19 was 356.6. López-Escobar et al also found that PLR was associated with mortality only in the univariate analysis, but not in the multivariate analysis. However, Ortega-Rojas[23] found PLR to be significantly associated with mortality. PLR could not predict the death of patients with COVID-19 (AUC: 0.601, 95% CI 0.414–0.788, p = 0.251) in the study by Wang et al.[27] In our study baseline PLR was not significantly associated with mortality whereas peak PLR value was significantly associated with mortality. Our PLR results were comparable to the study from Chennai, South India.[13] Compared to NLR; PLR seems to be a weak prognosticator. RDW was associated with increased risk of in-hospital mortality (aOR, 4.6; 95%CI, 1.5-14.6)and septic shock (aOR, 4.6; 95%CI, 1.4-15.1) in a previous study.[6] A multicentric study found elevated RDW (>14.5%) to be associated with an increased mortality risk in patients of all ages.[1] The mortality rate was 11% in patients with normal RDW and 31% in those with an elevated RDW. The RR for the entire cohort in the study was 2.73. Kaufman et al [35] also found increased RDW to be a significant predictor of mortality [crude odds ratio (OR) 1.717, 95% confidence interval (CI) 1.462–2.017], independent of clinical confounders, co-morbidities and established prognostic markers of COVID-19 (adjusted OR of 1.368, 95% CI 1.126–1.662). Ourstudy also found both baseline and peak RDW- CV % values to be associated with increased risk of in-hospital mortality. Elevated RDW-CV % values in mortality could be due to impaired red homeostasis. Inflammatory cytokines can induce RBC destruction, alterations in iron metabolism and down regulation of erythropoietin receptor. This could be aggravated by nutritional deficiency-related anemia. Hematocrit was significantly lower in non-survivors. Our findings were similar to previous studies.[30,31] This reduction in hematocrit could be related to suppression by the virus or destruction of RBCs or the presence of comorbidities. Release of inflammatory cytokines like IL-4 and IL-10 can inhibit erythropoiesis. However, hematocrit was not a significant predictor of mortality in our study and the AUC was less than 0.5. A recent study showed that estimated blood viscosity (determined from hematocrit, albumin and total protein) is significantly associated with higher mortality in COVID-19 patients.[36]

Table 6:. Comparison of NLR and PLR values and AUC, sensitivity and specificity in predicting mortality

Place of Study	No. of Survivors	No. of Non - Survivors	Type of NLR/ PLR	Mean ± SD / Median (range) NLR values survivors	Mean ± SD / Median (range) NLR values non-survivors	NLR Optimal cut-off (AUC); [Sensitivity, Specificity]	Mean ± SD / Median (range) PLR values survivors	Mean ± SD / Median (range) PLR values non-survivors	PLR Optimal cut-off value (AUC) [Sensitivity, Specificity]
Chennai, South India[13]	154	53	Initial	7.96 ± 11.45	13.6 ± 14.3	6.7 (0.61) [56,63.30]	180±390	340±560	160 (0.61) [67.90,50.70]
			Day 8	23.53 ± 3.73	35.72 ± 25.15	40.95 (0.70) [64.3,59.4]	470±640	510±820	400 (0.61) [61.50, 55.30]
Sassari, Italy[25]	90	29	Initial	5.00 (3.27 - 8.44)	9.17 (5.35 - 18.55)	NE	214 (145–339)	265 (144 - 428)	240 (0.57) [59,58]
Timisoara, Romania[7]	111	17	Initial	8.31 ± 5.74	13.83 ± 9.23	9.1 (0.689) [70, 67]	NE	NE	NE
Wuhan, China[15]	297	52	Initial	2.88 (1.79 - 6.74)	14.96 (8.52–26.58)	NE	NE	NE	NE
			Peak	4.14 (2.11 - 12.3)	46.58 (27.95–87.29)	NE	NE	NE	NE
Wuhan, China[18]	964	40	Initial	4.11 (2.44 - 8.12)	49.06 (25.71 - 69.70)	NE	NE	NE	NE
Catania,Italy[3,4]	278	133	Not specified	Not specified	Not specified	11.38 (0.772) [72.9, 71.9]	NE	NE	NE
Tehran,Iran[26]	83	17	Initial	NE	NE	NE	160.8 (124.2 - 219.4)	202.0 (120.7–201.2)	NE
Harbin,China[27]	119	12	Initial	NE	NE	NE	169.23 (115.2 - 222.9)	187.33 (139.2- 332.8)	NE
Dhaka, Bangaldesh[28]	60	39	Initial	NE	NE	NE	241.5 ± 146.9	305.47 ± 214.1	NE
Present Study	100	100	Initial	6.1 ± 5.2	10.1 ± 10.3	6.0 (0.644) [78, 74]	229.5 ± 138.1	295.5 ± 223.4	170 (0.580) [70, 43]
			Peak	10.4 ±13.5	32.8 ± 24.0	10.94 (0.843) [70, 43]	344.1 ± 349.7	609.0 ± 411.8	387.4 (0.727) [65, 88]

LIMITATIONS

The study is a Retrospective study.

CONCLUSION

Our study reveals that RDW-CV%, NLR and PLR are significantly higher in COVID-19 non-survivors. Hematocrit was significantly lower in non-survivors. Baseline and peak values of RDW-CV% and NLR are associated with mortality in patients with COVID-19. Patients with RDW-CV % value of 14.1, NLR of 10.94 and PLR of 387 require intensive monitoring. Serial blood counts are very useful to assess prognosis and predict mortality.The sample size with age matched survivors is the strength of this study. However, the present study is a retrospective record based analysis and findings need to be confirmed in multicentric studies.

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