Have You Noticed the Changes of Red Blood Cells in COVID-19?

As of January 26th, 2021, the coronavirus disease 2019 (COVID-19) pandemic has affected over 100 million people worldwide. Vaccination would help improve the situation in future. However, at this time, identifying patients at highest risk for severe disease is important. In order to facilitate early intervention and to manage local hospital resources to mitigate the critical care crises, our smart doctors conduct research in routine, low-cost, and suggestive parameters to assist with COVID-19 prognosis and the identification of severe cases[1] [2] [3].

Figure 1. Applications of routine blood tests.

Inflammatory parameters, such as white blood cell count (WBC), neutrophil count, neutrophil-to-lymphocyte ratio (NLR) could support COVID-19 diagnosis and prognosis. How about red blood cells?

Observed erythrocytes changes in critically ill patients

Dr. Wang compared hematological results from the good and poor outcome groups and found the best single parameter for predicting the prognosis of severe patients is RDW-SD[4,7]. What's more, combined parameters Lym# & RDW-CV as well as Lym# & RDW-SD are better for predicting the prognosis of severe COVID-19 (Figure 2)[7].

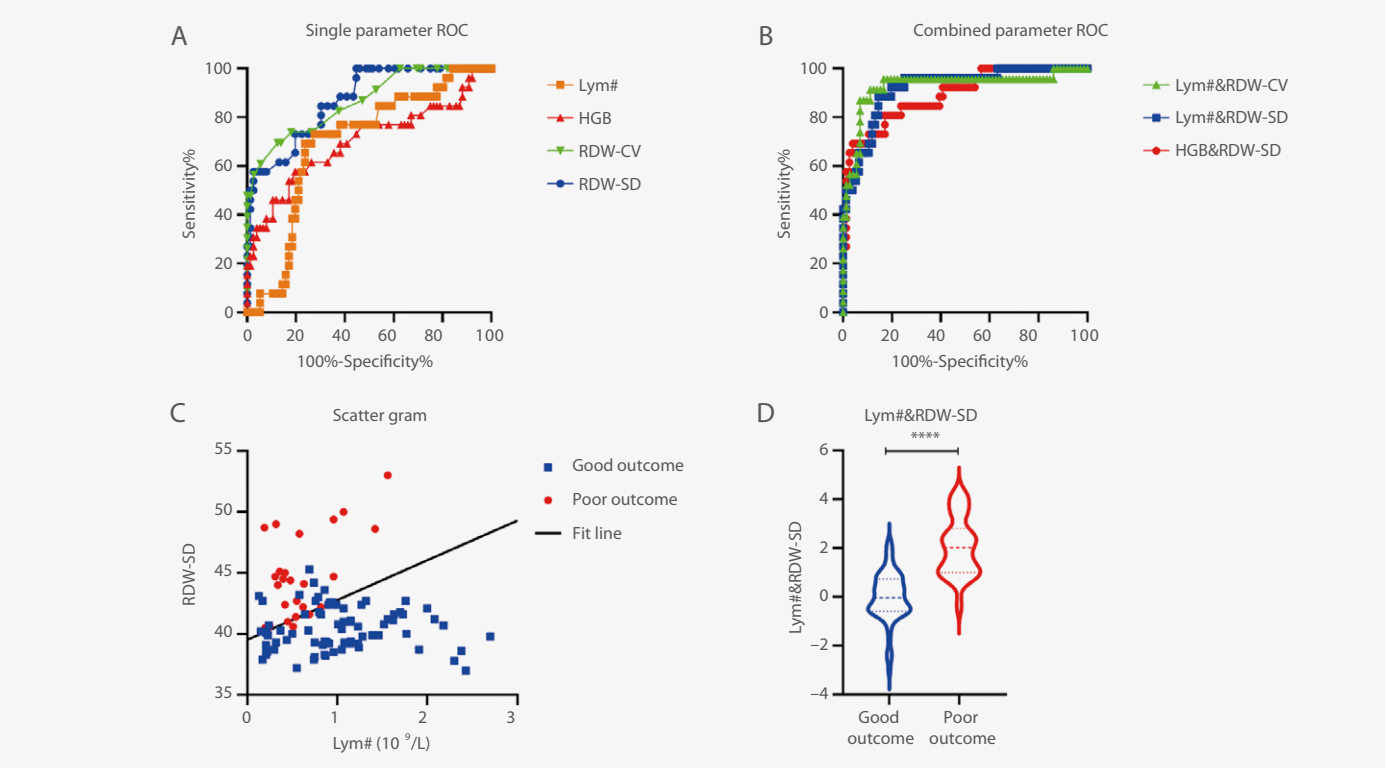


Figure 2. Prediction analysis of hematology parameters and the outcomes of patients with severe COVID-19.
(A) ROC curve, the single parameter for predicting the prognosis of ill patients; (B) ROC curve, joint parameters for predicting the prognosis of ill patients; (C) the linearly fitted schematic scatter plot for Lym# & RDW-SD; (D) comparison of Lym# & RDW-SD in ill patients with different prognoses. Lym# & RDW-SD: joint parameter generated after linear fitting of Lym# and RDW-SD. ****, P<0.0001.

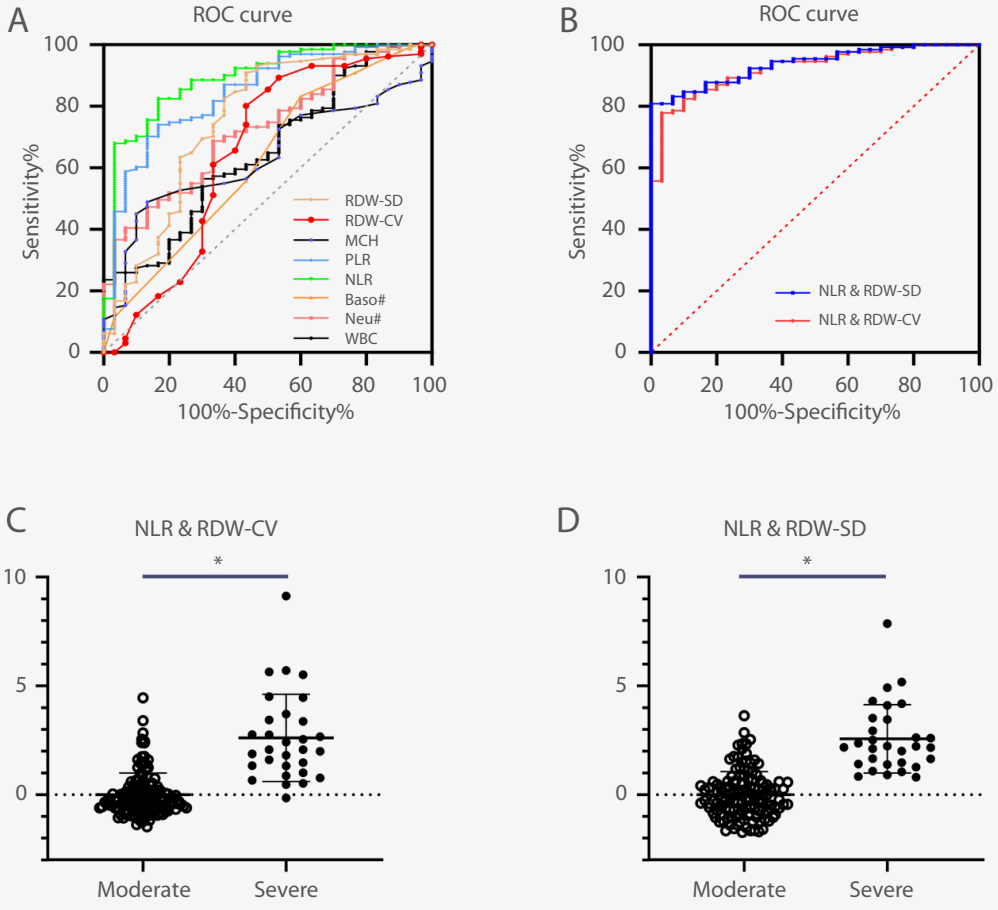
Dr. Zhang has found that HGB is lower in the severe group than in the moderate group[5]. New joint parameters Lym% & HGB have the best sensitivity and specificity (Table1). So Lym% & HGB can be used as indicators of disease prognosis..

Table 1. Receiver operating characteristic analysis results for the three parameters

Parameter	AUC	95% CI	Cutoff	Sensitivity	Specificity	Predict value (+)	Predict value (-)
Lym (%)	0.89	0.88-0.91	18.8	85.6%	77.5%	0.83	0.81
HGB (g/L)	0.79	0.76-0.81	116	71.1%	77.2%	0.80	0.68
Lym% & HGB	0.92	0.91-0.94	0.481	88.9%	79.8%	0.85	0.85

AUC, area under the ROC; Lym%, percentage of lymphocytes; HGB, hemoglobin.

Another article from Dr. Wang[6] described that many hematological parameters changed as the disease progressed, including NLR, RDW-CV, RDW-SD. The combined parameters of NLR & RDW-SD, as generated by linear fitting, had the better diagnostic efficiency (AUC =0.938), which was the best one among single parameters (Figure 3). When the cut-off value was 1.046, the sensitivity for distinguishing the severe cases from the moderate cases of COVID-19 was 90.0% while the specificity was 84.7%.



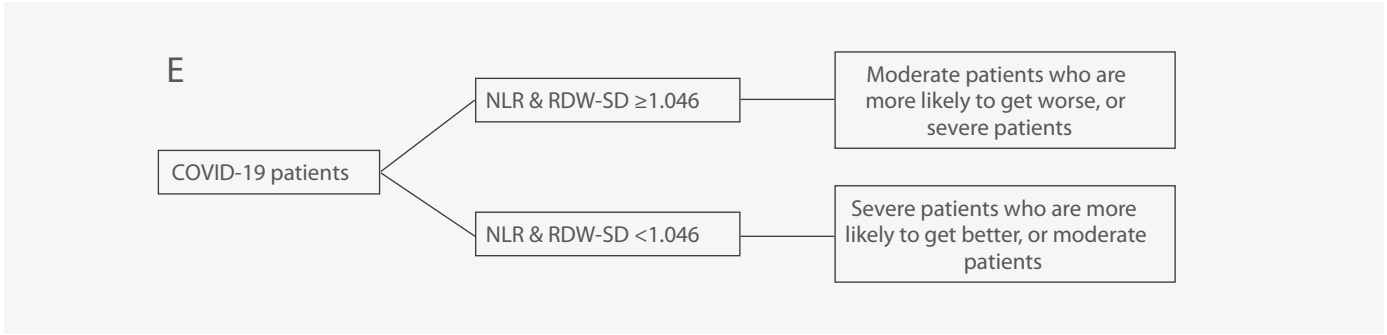


Figure 3. ROC analysis using single and combined parameters in the diagnosis of severe cases of COVID-19. Differentiated diagnosis of moderate and severe COVID-19 patients using different parameters. The positive sample is the blood routine result of the severe patient, and the negative sample is the blood routine result of the moderate patient. Panel A is an ROC plot that uses a single parameter to identify severe from moderate patients. Panel B is an ROC plot that uses the combined parameters of NLR and RDW-SD and NLR and RDW-CV to identify patients; Panels C and D are scatter plots that use the combined parameters for comparison between the two groups; Panel E is a recommendation management strategy for COVID-19 patients. "*" standing for significant deviation.

Why did these erythrocyte changes happen in critically ill patients?

It's been found that the increase in RET may contribute to elevated RDW (Figure 4). As the disease progressed, MFR and HFR increased, so did RDW-SD. The increased RET in peripheral blood may cause an increase in anisocytosis.

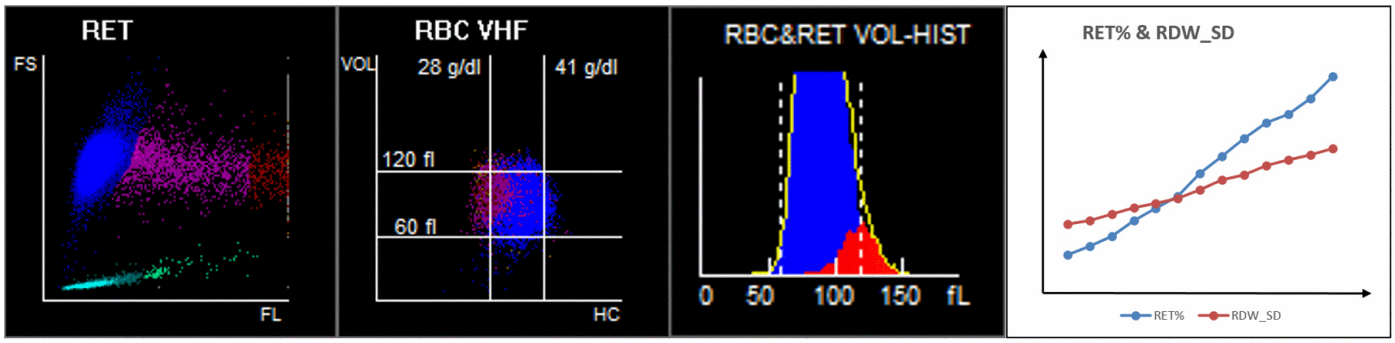


Figure 4. Dynamic monitoring of RET scattergram in critical COVID-19 cases. RET scattergram is from Mindray BC-6800Plus.

Increased RDW-SD

1. As the disease progressed, MFR and HFR increased, RDW-SD increased.

2. As the infection symptoms worsen, the level of oxidative stress in the body increases, oxygen free radicals increase. Insufficient circulating nutrients in patients may also lead to an increase in RBC membrane instability, followed by increased RDW.

Decreased HGB

1. Long-term hypoxia leads to increased synthesis of erythropoietin and active erythropoietin hyperplasia.

2. On the contrary, HGB synthesis is prevented in critically ill patients due to malnutrition or iron deficiency, resulting in low HGB and low-HC (hemoglobin concentration) RETs.

Figure 5. Mechanism of RDW-SD and HGB change in COVID-19[6].

How can we observe these erythrocyte changes in the hematology analyzer?

When we look at the 9-square scattergram, the RBC volume/hemoglobin concentration (V/HC) scattergram showed that the magenta scatters of critical patients were significantly left-skewed, indicating that RETs with a low HC (hemoglobin concentration) increased significantly, which may represent a unique pattern of erythroid hyperplasia in critical COVID-19 patients (Figure 6A)[7]. However, whether such low-HC RETs could be a diagnostic marker of critical COVID-19 still requires further investigation[7].

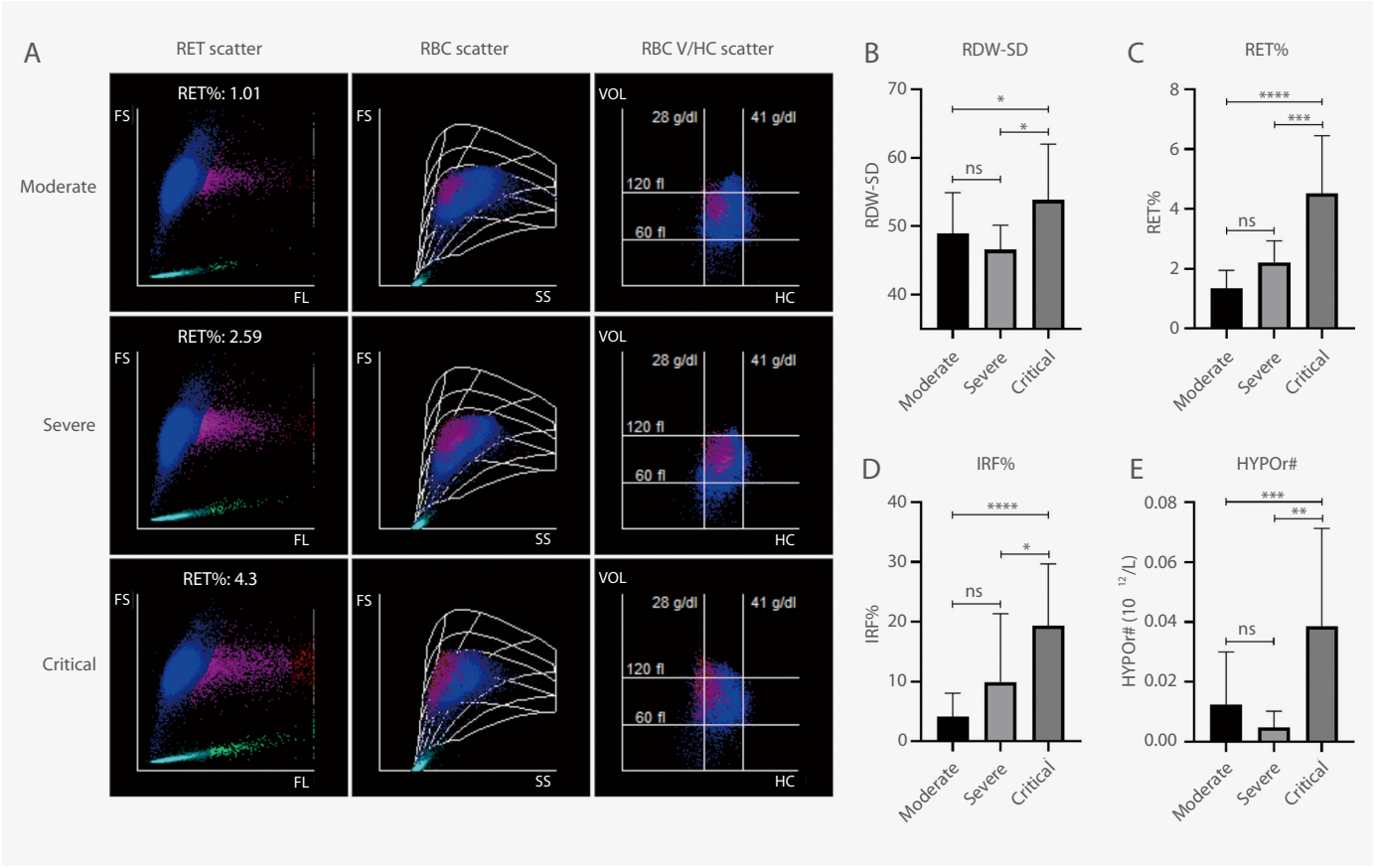


Figure 6. Differences of RET scattergram results in patients with different severity of COVID-19. (A) Scattergram of RET channel data from Mindray BC-6800 hematology analyzer. Blue scatters are RBCs, magenta, and the red scatter is the RETs, and cyan scatters are PLTs. (B,C,D,E) Comparison of parameters obtained from the RET channel for patients with different severities of COVID-19. Data are shown as the mean ± SD. ****, P<0.0001; ***, P<0.001; **, P<0.01; *, P<0.05. FS, forward scatter; SS, side scatter; FL, fluorescence; HC, hemoglobin concentration; VOL, volume; ns, nonsignificant.

With advanced technologies, the newly combined hematological parameters, such as Lym% & RDW-SD, Lym# & HGB and NLR & RDW-SD, have been found as supportive predictors during COVID-19 prognostics. More and more covariates can be studied and developed on the Mindray BC-6000 series analyzers. Especially on BC-6800Plus, the RET channel can detect the number, size, and hemoglobin concentration of RBCs and RETs highly sensitive laser scattering technology. Thus, it's recommended to start using self-defined parameters for COVID-19 prognosis now.

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