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Investigation on the Relationship between D-Dimer and Cell Blood Count Indices in COVID-19 Prognosis: A Retrospective Study on 320 COVID-19 Patients

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ABSTRACT

Introduction:
Due to the spreading of coronavirus infection in 2019 (COVID-19) throughout the world, tracking cell blood count (CBC) of moderate to severe COVID-19 patients could provide new insights for the prognosis prediction.

Materials and Methods:
In this observational-retrospective study, D-dimer and CBC documents of 320 confirmed COVID-19 patients hospitalized in Shamsoshomus Clinic, Mashhad, Iran, were evaluated. Receiver operation characteristics (ROC) curve was analysed to determine specificity and sensitivity of D-dimer and hematological indices, including white blood cell (WBCs), lymphocytes, monocytes, eosinophil, red blood cell width (RDW), platelets (PLT), and mean of platelet volume (MPV).

Results:
This study included 157 (49.1%) male and 163 (50.3%) female COVID-19 patients between 14 to 96 years old. According to their status in the duration of hospitalization, patients were considered in the good outcome group (N=215) and poor outcome group (N=105). A significant difference was observed in D-dimer, WBCS, PMN, Lymph, monocytes, eosinophil, and RDW between the two groups (P<0.001). The highest sensitivity and the lowest specificity belonged to RDW (99%, 4%), WBCs (98%, 4%), PMN (99%, 11%) and D-dimer (96%, 42%). D-dimer indicated a significant association with WBCs, PMN, and RDW (P<0.05).

Conclusion:
The present study revealed that WBCs and RDW might be recommended for the COVID-19 prognosis prediction due to their high comparable sensitivity to D-dimer.

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Introduction

Coronavirus pneumonia in 2019 (COVID-19) is a disease related to a high mortality rate among hospitalized patients and caused expensive hospitalization bills and long-term side effects. Finding the best methods of COVID-19 diagnosis and related prognosis is in progress.

Hypercoagulability and the increment of the risk of venous thromboembolism are present in the severe prognosis of COVID-19 patients (1). Therefore, the coagulation factors like D-dimer as the fibrin degradation product may designate the disease severity and mortality. Moreover, D-dimer might help a decision for anticipation of prognosis in patients triage and the assumption of suitable therapeutic strategies (2).

Previous investigations revealed the role of increased D-dimer level in poor outcomes versus good outcomes of COVID-19 patients' survivors (3-5).

Monitoring of COVID-19 patients to prevent any adverse effect due to its high rate of mortality and prediction of its prognosis is routine essential advice for hospitalized patients. Due to the high costs of COVID-19 diagnosis, some low-income countries favored exploring the chip, easy and available laboratory tests for diagnosis or prediction of prognosis (6).

Generally, monitoring by the complete blood count (CBC) tests is presented as the most commonly available and quickly diagnosis tool in all medical institutions due to its low detection costs and high automation. As the treatment guideline for respiratory disease, including severe acute respiratory syndrome (SARS) and COVID-19, were recognized the role of White blood cells (WBCs) during different stages of disease (7,8).

Besides, progressive lymphocytopenia and decreased lymphocytes in severe patients were demonstrated. The dynamic variations of WBCs during hospitalization showed that WBCs increased due to the privilege of the virus and its fighting.

Also, the role of decrement of lymphocyte count (3,9-11), increment of red cell volume distribution width (RDW), platelet (PLT) count, and mean platelet count (MPV) in the severe cases of COVID-19 compared to its moderate ones were previously demonstrated (12-14).

However, there are limited research on the predictive role of hematological factors in the prognosis of patients infected with COVID-19. Therefore, this study aimed to investigate the value of the hematological factors along D-dimer as the prognostic indices among moderate to severe COVID-19 patients and explore its importance in anticipating the prognosis.

Materials and Methods

Study Patients

This single observational-retrospective study included 320 COVID-19 patients at a time of hospitalization at the single medical center, Shamsoshomus Clinic, Mashhad, Iran, from January 14 to February 2021. All studied patients had positive tests of COVID-19 validated by nucleic acid detection kit of the SARS-CoV-2 (Shanghai BioGerm Medical Biotechnology Co., Ltd, fluorescence polymerase chain reaction (PCR)).

Patients' documents were collected either from the medical ward or from the intensive care unit directly. Patients were divided into the two groups of good and poor outcome due to the patients getting substantially sick in the duration of hospitalization.

Subjects in the good outcome group presented moderate to severe COVID-19 pneumonia, and cases with the poor outcome had severe to critical disease. Patients with severe anemia (hemoglobin under 11), diabetes, hyperthyroidism, and pregnant women were excluded. Patients with moderate COVID-19 pneumonia experienced a fever, symptoms related to the respiratory tract and pneumonia imaging manifestations during hospitalization.

Subjects with severe pneumonia had each of the following criteria as; a) rate of respiratory ≥30 times/min, (b) saturation of resting oxygen (based on finger) ≤93%, (c) oxygen partial pressure (PaO_2)/ inspired oxygen fraction (FiO_2) ≤300 mmHg, and (d) lesion progression of above 50% in the duration of 24–48 h identified by lung imaging. Furthermore, patients under the fatal status of COVID-19 pneumonia had respiratory failure and the requirements for ventilation of mechanical form, shock, and care of custodial form in the intensive care

unit due to the failure in organs other than failure in the lung. This classification of severity of COVID-19 was approved based on the Seventh Edition of the *Guidelines for the Diagnosis and Treatment of COVID-19* issued by the National Health Commission (NHC) of China (15).

Laboratory data collection

Hematological tests performed within 24 hours after admission were collected for 320 patients. These tests included white blood cells (WBCs), platelet (PLT), mean platelet volume (MPV), monocyte count, lymphocyte count, eosinophil, and red cell volume distribution width (RDW), and were measured using an Automated Standard Hematology Analyzer (Sysmex KX-21N, Sweden). Besides, D-dimer was evaluated on CS5100 coagulation automatic analyzer (Sysmex, Kobe, Japan) using a photometric latex-enhanced immunoassay (Germany, Siemens) and expressed in μg/mL fibrinogen equivalent unit. All measurements were done within 2 hours after blood sampling. All of the procedures performed in this work were conducted based on the Declaration of Helsinki (revised in 2013).

The Ethics Committee of University confirmed the integrity and morality of the work. The study was retrospective, and there was no private data of patients, such as the name, the ID number, the cell phone number, and the address.

Demographic information and laboratory testing data of patients were only collected and analyzed; therefore, no informed consent was required.

Statistical analysis

Data were analyzed using a Microsoft Windows 7 based SPSS software (SPSS Inc., version 20, Chicago, Illinois, USA). The continuous variables with a normal distribution were defined by the mean ± standard error. The comparisons between variables with normal distribution have been performed under the independent samples Student's T-test. Pearson correlation was used for correlation analysis by the method of two-tailed bivariate. Binary logistic linear regression was conducted to determine the relation of each investigated factor and outcome groups. Receiver operation characteristics (ROC) curve analyses were applied to determine the area under the curve (AUC), the specificity and sensitivity of D-dimer and the other studied hematological indices. Two-tailed *P* value under 0.05 was considered statistically significant for all statistical analyses.

Results

This study included 157 (49.1%) male and 163 (50.3%) female COVID-19 patients between 14 to 96 years old. Studied cases were in the good outcome group (N=215) and the poor outcome group (N=105). The hematological factors value of the two studied groups has been summarized in Table 1. A statistically significant difference was found in investigated hematological indices between the two study groups ($P<0.001$). However, there was no difference in platelet count and MPV among patients with good and poor outcome prognoses ($P>0.05$).

Table 1: Investigated hematological factors among two studied groups of COVID-19 patients

Hematologic factor	Patients group		P-value
	Good outcome	Poor outcome	
D-dimer (ng/mL)	291.71±17.61	1931.29±226.95	0.001
WBCs ($\times10^3$/μL)	5.993±1.69	10.90±5.69	0.001
PMN ($\times10^3$/mL)	68.68±0.85	83.10±1.01	0.001
Lymph ($\times10^3$/mL)	26.06±0.76	13.47±0.91	0.001
Monocytes ($\times10^3$/mL)	3.10±0.95	2.24±0.12	0.001
Eosinophil ($\times10^3$/mL)	1.81±0.06	1.13±0.08	0.001
RDW ($\times10^3$/mL)	13.36±0.94	14.33±0.14	0.001
Lymphocytes count($\times10^3$/μL)	1.43±0.079	0.962±0.008	0.001
PLT($\times10^3$/μL)	201.06±6.28	197.68±10.29	0.76
MPV($\times10^3$/mL)	9.62±0.85	9.84±0.10	0.12

White Blood cells (WBCs), Poly Mononuclear cells (PMN), Red Blood cell Widths (RDW), Platelet count (PLT), Mean Platelet Volume (MPV). P-value calculated by T-Independent Test. P-value less than 0.05 was considered a significant level.

According to prognosis, sensitivity and specificity of each investigated hematological indices were calculated (Table 2). Among different investigated hematologic indices, the highest sensitivity and the lowest specificity belonged to D-dimer, white blood cell (WBCs), poly-mononuclear (PMN), and red blood cell width (RDW) (Figure 1).

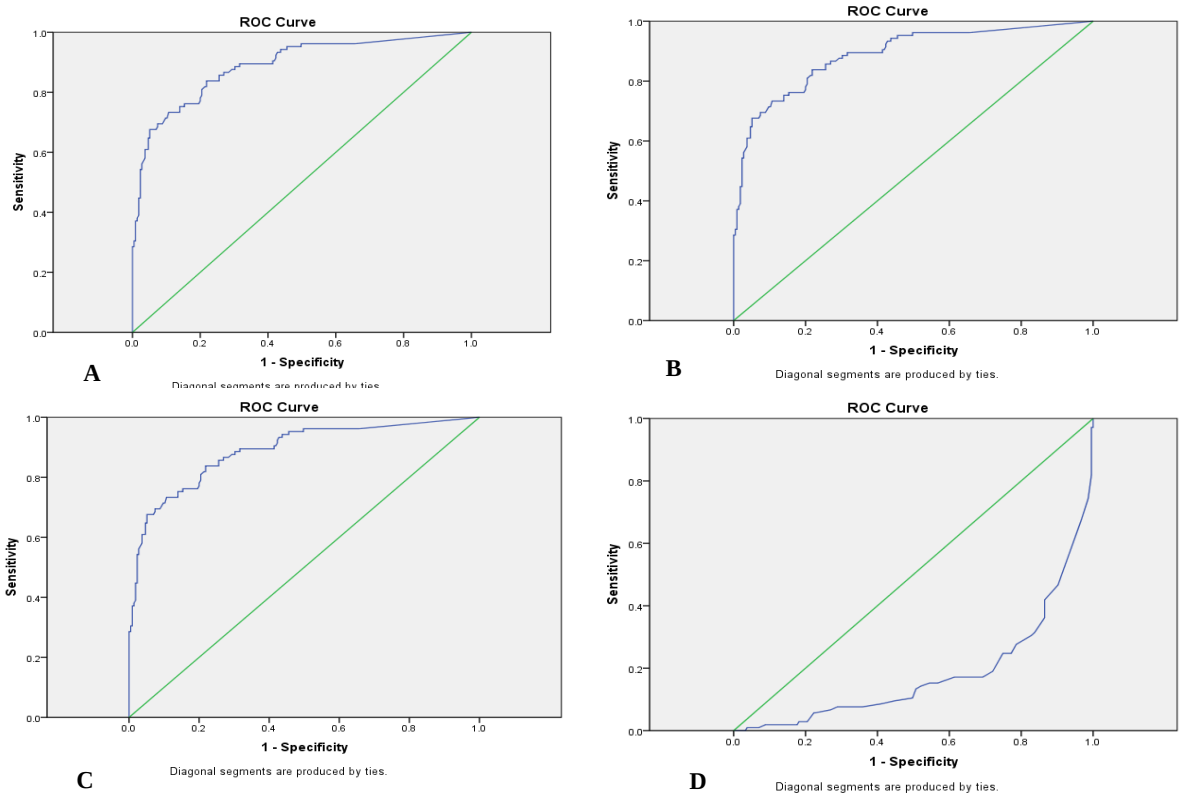

Figure 1: Receiver operating characteristics (ROC) curve of D-dimer (A), white blood cells (B), poly-mononuclear (C), and red blood cell width (D) for determination of COVID-19 prognosis

Besides, the highest validity due to area under curve (AUC) amount demonstrated for respected factors. The lower AUC and sensitivity for lymphocytes, monocytes, and eosinophil counts compared to D-dimer, WBCs, PMN, and RDW indicated that these factors were not reliable for the prediction of COVID-19 prognosis.

The diagnostic sensitivity of D-dimer for severity in 320 COVID-19 patients ranged from 76% to 96%, and the specificity was 35% to 85%. The pooled sensitivity and specificity were 86% and 60% (95% CI: 84%-92%), respectively.

Also, the sensitivity diagnosis of WBCs for severity in 320 patients of COVID-19 ranged from 25- 100%, and the specificity was 1% to 99%. The pooled specificity and sensitivity were 62.5% and 50% (95% CI: 69%-82%), respectively. The diagnostic sensitivity of PMN for severity in 320 COVID-19 patients ranged from 1% to 100%, and the specificity was 1% to 99%. The pooled sensitivity and specificity were 74% and 49% (95% CI: 76%-87%), respectively. Furthermore, the diagnostic sensitivity of RDW among studied patients ranged from 1-100%, and the specificity has been 1- 99%. The pooled sensitivity and specificity were 46% and 39% (95% CI: 67%-79%), respectively.

Furthermore, correlations of studied hematologic factors and D-dimer were investigated (Table 3). Statistical analysis showed that the association of D-dimer with WBCs, PMN, and RDW were significant (P<0.05).

Besides, the correlation of D-dimer with eosinophil, monocytes and lymphocytes count was statistically significant (p<0.05). However, there was no correlation between D-dimer and PLT and MPV (P>0.05).

Table 2: Evaluation of sensitivity and specificity of investigated hematological indices

Hematologic factor	AUC	Sensitivity	1-specificity	CI	P-value
D-dimer (ng/mL)	0.88	0.96	0.58	0.84-0.92	0.001
WBCs ($\times10^3/\mu L$)	0.76	0.98	0.96	0.69-0.82	0.001
PMN ($\times10^3/mL$)	0.81	0.99	0.89	0.76-0.87	0.001
RDW ($\times10^3/mL$)	0.73	0.99	0.96	0.67-0.79	0.001
Lymph ($\times10^3/mL$)	0.18	0.24	0.77	0.12-0.23	0.001
Monocytes ($\times10^3/mL$)	0.32	0	0.04	0.26-0.39	0.001
Eosinophil ($\times10^3/mL$)	0.31	0.01	0.07	0.25-0.37	0.001
Lymphocytes count($\times10^3/\mu L$)	0.29	0.48	0.13	0.23-0.35	0.001
PLT($\times10^3/\mu L$)	0.47	0.97	0.97	0.40-0.54	0.42
MPV($\times10^3/mL$)	0.56	0.94	0.91	0.49-0.62	0.06

Area under curve (AUC), White Blood cells (WBCs), Poly Mononuclear cells (PMN), Red Blood cell Widths (RDW), Platelet count (PLT), Mean Platelet Volume (MPV). P-value was calculated by ROC Curve analysis. P-value less than 0.05 was considered a significant level.

Table 3: Association of D-dimer with the other studied hematologic factors

Hematologic Factor	P-value	Correlation
WBCs ($\times10^3/\mu L$)	0.001	0.59
PMN ($\times10^3/mL$)	0.001	0.36
RDW ($\times10^3/mL$)	0.001	0.23
Lymph ($\times10^3/mL$)	0.001	-0.36
Monocytes ($\times10^3/mL$)	0.001	-0.19
Eosinophil ($\times10^3/mL$)	0.001	-0.23
Lymphocytes count($\times10^3/\mu L$)	0.012	-0.14
PLT($\times10^3/\mu L$)	0.18	-0.075
MPV($\times10^3/mL$)	0.81	0.014

White Blood cells (WBCs), Poly Mononuclear cells (PMN), Red Blood cell Widths (RDW), Platelet count (PLT), Mean Platelet Volume (MPV). P-value was calculated by Pearson correlation Test. P-value less than 0.05 was considered a significant Level

Discussion

Cell blood tests for the blood state examination and disease diagnosis and sensitive indicators of pathological changes are performed as a routine laboratory test. CBC could be a usual indicator for assessing medication and recurrence of the disease. The last investigation showed increased D-dimer status with increased severity and related mortality risk in COVID-19 patients (5) (16). Therefore, D-dimer monitoring would be immediately performed in COVID patients after admission. However, there are economic barriers to assessing COVID-19 prognosis and evaluation of D-dimer is not an accessible test in all medical centers. Therefore, we aimed to compare the sensitivity and specificity of CBC factors, as the routine hematologic test for hospitalized patients, and D-dimer for prediction of COVID-19 prognosis. In the present study, the highest pooled sensitivity and specificity for COVID-19 prognosis belonged to D-dimer and WBCs. The diagnostic sensitivity of WBCs ranged from 25 to100% in 320 COVID-19 patients. The sensitivity was varied from 76% to 96% for D-dimer. Also, the pooled sensitivity and specificity of PMN and RDW were higher than the other studied hematological factors.

In clinical practice, measuring D-dimer levels has been accredited for two primary determinations, including evaluation of the

patients with suspected venous thromboembolism and as a part of the disseminated intravascular coagulation score (17). Therefore, its performance as a biomarker to guide therapy has not yet been certified in inflammatory conditions. Previously, the reports in systemic meta-analysis paper revealed that the pooled sensitivity of the prognostic value of severity of the D-dimer, specificity in COVID-19 were 77% and 71%, respectively. They concluded that D-dimer could predict the fatal and severe cases of COVID-19 with mediocre accuracy (1). In the present study, the pooled sensitivity and specificity related to D-dimer were 86% and 60%, respectively, with 95% confidence intervals ranging between 84%-92%.

The diagnosis and treatment guideline for COVID-19 addressed that WBCs in the initial stage of the illness is normal or declined. Besides, progressive lymphocytopenia and decreased lymphocytes in severe patients were demonstrated. The dynamic variations of WBCs during hospitalization showed that WBCs increased to fight the virus (7). It is due to the direct attack of the virus into hematopoietic cells or the worsening of apoptosis and hematopoietic suppression as a result of the infection of bone marrow stromal cells after SARS virus infection (8). Higher sensitivity and significant positive correlation of D-dimer and WBCs might be recognizing WBCs as a representative factor for disease progression analysis.

Previous research demonstrated that hematological parameters changed in patients with COVID-19 due to the aggravation of the disease. Due to decreasing number of lymphocytes, more patients died compared to the survivors (3, 9-11). Lu et al. found that during 26 days of hospitalization of COVID-19 patients, the number of monocytes and eosinophils decreased drastically after reaching their maxima (7). However, they showed that lymphocyte levels continued to rise to destroy the virus and lately backed to the normal reference range (7). Furthermore, monocyte and eosinophil were extremely low during admission due to the severe condition of COVID-19 patients and then recovered to normal gradually (7). It might be explained using the recovery of immune cells, including eosinophil, during the first days and monocyte later (18). Previous studies believed that eosinophils count could be a significant prognostic value among COVID-19 patients. Although, we found that monocyte and eosinophil numbers were not statistically significant between COVID-19 patients with good and poor prognoses. In addition, ROC curve analysis revealed lower sensitivity and specificity of lymphocytes, monocytes, and eosinophils than RDW, PMN, and WBCs.

Also, the prior studies presented that RDW of patients with severe COVID-19 significantly increases because of the role of erythroid cell parameters as the risk indicators (12,13). It has been reported that RDW was related to increased risk of mortality and morbidity in a wide range of illnesses, as a constituent of through blood counts, which reflects the cellular volume variation (19). Meanwhile, the previous research showed that the condition of COVID-19 patients was related to the hematopoietic system (20). Lu et al. (7) found that in patients with good outcomes of COVID-19 prognosis, RDW decreased gradually. After removing tracheal intubation and using the noninvasive ventilation and inhalation of high-flow oxygen, the patient's condition was progressively stabilized. In addition, increased RDW is gradually attributed to a longer recovery time of red blood cells and hemoglobin (7). Besides, a progressive increase of RDW in severe COVID-19 form was presented, and its elevated levels were connected with a 9-fold increased odds of severe COVID-19 (21). They revealed RDW as a recommended part of routine laboratory evaluation and monitoring of COVID-19 patients (21). Similarly, after rolling out the patients with iron deficiency anemia and diabetes as confounding factors related o RDW analysis, we found a significant difference between RDW amounts and the prognosis of COVID-19 patients. Also, we reported high diagnostic sensitivity and specificity of RDW among studied COVID-19 patients ranging from 1% to 100%.

According to anti-inflammatory properties connected to platelet (PLT) counts, its changes were considered during the

admission. There was a report indicating the increased level of the PLT count in severe COVID-19 patients during hospitalization (14). However, rare of them evaluated the prognostic value of these factors among patients with severe COVID-19. It was previously shown that increments of mean platelet volume (MPV) in nephrotic syndrome (similar COVID-19 with progression thromboembolic properties) could be an easy, cheap, and straightforward method for the prognosis prediction (22) and prediction of ischemic stroke risk in atrial fibrillation patients were established before (23,24). Previous investigations found that MPV and PLT counts were higher in patients with pulmonary embolism than healthy individuals Gunay et al. (25). However, similar to our results, another research found that MPV did not correlate with the diagnosis of acute pulmonary embolism (26,27). Therefore, the role of MPV and PLT count is uncertain. We resulted that increments of PLT count and MPV due to their hyper-coagulopathy properties into an inflammatory disease (28) could not be a prognostic value among COVID-19 patients. Similar to a previous study, we found a reverse correlation between MPV and PLT count and disease severity (29). Though these variations were not significantly different, these factors had not enough prognostic value for COVID-19 severity. However, there are rare documents investigating PMN roles in the pathogenesis of COVID-19. It was shown that the expanded myeloid compartment and some subtypes of PMN had been connected with the prognosis (30). As a result, expansion of the poly morph-nuclear cells could improve clinical COVID-19 outcome that revealed the potential role of PMN cells as the predictor of prognosis in cases of severe COVID-19 (30). In the present study, a significantly higher level of PMN was shown in the poor prognosis COVID-19 group than the good prognosis group. Furthermore, we found high diagnostic sensitivity and of PMN for prediction of COVID-19, which were ranged from 1% to 100%.

Conclusion

Altogether, we found high comparable sensitivity of WBCs, RDW, and PMN with D-dimer for the prognosis of patients with COVID-19, and could be recommended for the COVID-19 prognosis prediction. Besides, our statistical analysis presented that D-dimer was correlated significantly with WBCs, RDW, and PMN. These points could be valuable due to the accomplishment of CBC as a routine laboratory test in all medical institutions and the low availability of D-dimer for all medical therapists. Moreover, these findings could be deliberated according to the importance of predicting COVID-19 prognosis and related burden costs in low-income countries like our study area. Furthermore, our study results might be accredited future in a higher sample size of patients and gathering more evidence-based documents related to the clinical symptoms of disease and different privilege subtypes of COVID-19.

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