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The Association of Red Blood Cell Distribution Width with Secondary Infection and Prognosis in hospitalized patients with COVID -19 pneumonia

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ABSTRACT

Introduction: Novel Coronavirus outbreak has posed a global threat. While the infection appears to be mild in most patients, considering its high rate of transmission, a large number of people are at risk of developing severe to critical illness in total which makes prognosis studies a priority. The aim of the present study was to evaluate red blood cell distribution width (RDW) as a predictive factor for diagnosing severe cases of coronavirus disease 2019 (COVID-19).

Materials and Methods: A total number of 204 inpatients diagnosed with COVID-19 including 122 men and 82 women (Mean age: 58.83±15.93 years old) treated at Imam Reza Hospital, Mashhad, Iran were included in the study. Patients were divided into severe and moderate groups according to their clinical signs and examinations and pulmonary imaging features. Demographic Data, laboratory test results, treatments, patients' complications and outcome were recorded. Mann-Whitney U test and spearman correlation coefficient (r) were performed to assess RDW correlation with severity and serious complications in patients including intensive care unit (ICU) admission, shock, secondary infections, intubation, length of hospitalization and death. Receiver operating characteristics (ROC) curves analysis was carried out to define the reliability of RDW as a predictive indicator in severe COVID-19.

Results: The results showed statistical significant correlations between high levels of RDW and developing secondary infections and longer hospitalization (P values ≤0.001). The optimal cutoff for RDW to predict the length of hospitalization (≤ 7 days or more than 7 days) was estimated to be 14.65% with 94% sensitivity and 71.3% specificity. The area under curve was calculated to be 0.895 through Roc curve analysis.

Conclusion: High predictive value of RDW, a routine blood test parameter, could be used in diagnosing COVID-19 patients at higher risk for developing secondary infections and longer hospital stay which in turn helps with better management of the disease.

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Introduction

Coronaviruses are a large family of viruses identified in the mid-1960s and are known to cause multiple system infections in numerous animals and also infect humans with common colds and serious respiratory tract illnesses (1-4). Two outbreaks of coronaviruses in humans have occurred since 2002; SARS-CoV (2002) causing Severe Acute Respiratory Syndrome (SARS) and MERS-CoV (2012) causing Middle East Respiratory Syndrome (MERS) (2, 5, 6).

In December 2019, an outbreak of pneumonia cases of unknown a etiology, referred to as Novel Coronavirus Pneumonia (NCP) (later named as Coronavirus Disease 2019 (COVID-19) by WHO), was reported in Wuhan, Hubei Province, China and rapidly spread elsewhere (7).Genetic analysis of the novel coronavirus (2019-nCoV) revealed a great deal of similarity (88%) to SARS-CoV, suggesting that they are closely related and (4, 8, 9) finally led to designating it as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (10, 11). Since Then, a surge of new cases infected with (SARS-CoV-2) has been reported throughout the world (4, 12)which immediately became a serious public health problem globally (13). While the outbreak initially originated from a zoonotic transmission (14), soon the ability of human-to-human transmission became evident (15). The rapid transmission (median Ro ≈3.0) (16) led to a world-wide emergency. The total number of laboratory-confirmed cases has exceeded 1,991,562with over 130,885 Deaths as of Apr 16, 2020 (17).

Patients' common symptoms mainly include fever, cough, dyspnea and myalgia or fatigue (4, 7, 18). Most patients infected with SARS-CoV-2 experience a mild clinical course. However, Severe cases are often in urgent need of intensive medical resources as they progress rapidly (particularly within 7-14 days from onset of symptoms) (15) to acute respiratory distress syndrome (ARDS) leading to acute respiratory failure, metabolic acidosis, coagulopathy, and septic shock with high mortality rates in a short time (20 times higher than that of non-severe COVID-19 patients) (19, 20). This situation denotes the necessity of prognosis assessments. Early identification of risk factors to prognoses and recognize the COVID-19 patients at high risk for developing serious complications among the infected crowds using clinical data is an urgent yet demanding mission. It could help with providing critically ill cases with early treatment, facilitating proper supportive care and immediate access to the intensive care unit (ICU) if necessary and reducing unnecessary or inappropriate health care utilization through screening and prioritizing patients, all of which lead to a potential decrease in mortality (13, 19, 20).

Red blood cell distribution width (RDW), a hematological indicator, could reflect subclinical inflammation (21) and has been recently regarded as a powerful prognostic biomarker in a variety of disorders such as cardiovascular diseases (22), acute and chronic kidney diseases (23), diabetes (24), cancer (25). chronic obstructive pulmonary diseases (COPD) (26), ARDS (27), hepatic fibrosis and necro inflammation(28, 29) and critically ill patients (30). The increase of RDW level in the abovementioned conditions is reported to be an independent risk factor for severe morbidity and increased mortality (30). So far, not enough prognostic studies have been carried out regarding predicting severity in COVID-19 patients. Considering RDW high predictive value in various disorders, the present study was carried out to investigate RDW potential as a prognostic factor for COVID-19 patients at high risk for developing severe illness.

Materials and Methods

Patients

A total number of 204 adult inpatients (≥18 years old) diagnosed with COVID-19 who were referred to Imam Reza Hospital, the main center for COVID-19 patients in Mashhad, Iran during 14-20 March 2020 were included in this study. Patients younger than 18 and those with hematologic malignancies or those having undergone a recent chemotherapy were excluded from the study. The following diagnostic criteria were applied according to the recent guidelines about COVID-19. Clinical Symptoms including fever, myalgia or fatigue, respiratory symptoms such as cough and dyspnea, laboratory test results; elevated C-reactive protein (CRP), leukopenia or lymphopenia, and typical imaging features in the chest computed tomographic scans (CT scan). Diagnosis was ultimately confirmed if the RNA of SARS-CoV-2 was found in the patients' nasopharyngeal swab samples using real-time reverse transcription-polymerase chain reaction (RT-PCR). Patients were divided into two groups (severe and moderate) based on clinical features. Severe cases were identified as patients with respiratory rate (RR) >30 times/min and or oxygen saturation (SpO2) ≤ 93% at rest on room air, while others were classified as moderate. Cases were also categorized into severe and non-severe groups considering the features in their lung CT scan, in which involvements of three lobes were defined as severe and two lobes involvement were considered non-severe. This research was approved by the Ethics Committee of Mashhad University of Medical Sciences. All the patients were fully informed about the study and signed the written consent.

Data Collection:

Demographic data, past medical history, signs and symptoms were recorded for each patient and clinical laboratory test findings including complete blood count with differential (CBC with diff), C-reactive protein (CRP) and other tests and also Lung CT scans were achieved through routine clinical practice. Treatments, length of hospitalization, outcome data, course of the disease such as being admitted to ICU, being intubated, going into shock and being affected by secondary infections were precisely monitored and recorded in detail for all the participants. All the patients received either Hydroxychloroquine and or Lopinavir/Ritonavir (Kaletra) as antiviral. Empiric antibiotic therapy including Ceftriaxone and azithromycin were prescribed and were substituted by other antibiotics if secondary infections were suspected.

Statistical Analysis:

Analyzes were performed using SPSS software (Version 26.0, SPSS, Inc., Chicago, IL, USA). Frequency and percent were used to report categorical variables while mean and standard deviation were tools to present the continuous variables such as age, length of hospitalization and RDW levels. Spearman correlation coefficient (r) was used to compare RDW levels in different lengths of hospitalization (an indicator of severe illness in this study). Correlation analysis between categorical variables indicating severe illness (Hospitalization more than 7 days, ICU admission, intubation, shock, secondary infection, radiologic and clinical severity and death) and RDW levels were carried out using Mann-Whitney U Test. Correlations were considered statistically significant where P values were less than 0.05. The usefulness of RDW to predict severity in COVID-19 patients, its optimal cutoff, sensitivity and specificity were assessed through receiver operating characteristics (ROC) curves analysis.

Results

Among the total number of 204 patients diagnosed with COVID-19 including 122 (59.8%) men and 82 (40.2%) women with the mean age of 58.83±15.93 years old. The frequency and percentage of the COVID-19 patients' gender and comorbidities have been presented in table1, that shows diabetes mellitus (62 patients) and Hypertension (60 patients) as the most prevalent diseases respectively (30.4% and 29.4%). Out of the 204 COVID-19 patients of this study, 33 (16.2%) were considered moderate and 167 patients (81.8%) developed severe to critical illness having one or both of the above mentioned criteria (RR >30 times/min, SpO2 ≤ 93%). Moreover, 145 patients (71.1%) were considered severe in terms of lung CT scan features, having three lobes of the lung involved, while the other 59 patients (28.9%) had only 2 lobes involved. In total, 67 patients (33%) were hospitalized for more than 7 days; while 115 patients (56%) had shorter hospital stay (equal or less than 7 days) (Information regarding 22 cases (11%) was missed). The minimum and maximum days of hospitalization were 1 and 22 days respectively, with 7.19 ± 3.67 days as the average hospital stay. Fourteen patients (6.9%) needed intensive medical care and were transferred to (ICU). Intubation was applied in 23 cases (11.3%), 7 patients (3.4%) went into shock and 83 patients (40.7%) developed secondary infections. Among all, 22 patients (10.8%) died during the period of observation while others were discharged.

Table1. Demographic Characteristics of COVID-19 patients

Demographic Characteristics		Frequency	Percent
Gender	Male	122	59.8%
	Female	82	40.2%
Medical History	Diabetes mellitus	62	30.4%
	Ischemic Heart Disease	36	17.6%
	Hypertension	60	29.4%
	Asthma	6	2.9%
	Autoimmune diseases	5	2.5%
	Chronic kidney disease	3	1.5%
	Transplantation	1	0.5%
	COPD [a]	16	7.8%
	Cerebrovascular disease	3	1.5%
	CNS [b] diseases	2	1%
	Gastrointestinal diseases	204	100%
	Hepatitis	1	0.5%
	Hypothyroidism	3	1.5%
	Malignancy	8	3.9%

a. Chronic Obstructive Pulmonary Disease, b. Central nervous system

Variables		Frequency	Percent	RDW (Mean) %	P Value*
Length of Hospitalization	115	≤ 7 days [c]	56%	13.86 ± 1.40	≤0.001
	67	> 7 days [d]	33%	16.50 ± 1.68	
	22	Missing [e]	11%		
ICU	No	190	93.1%	14.82 ± 1.95	0.472
	Yes	14	6.9%	14.52 ± 2.28	
Intubation	No	181	88.7%	14.87 ± 2.01	0.262
	Yes	23	11.3%	14.27 ±1.59	
Shock	No	197	96.6%	14.85 ± 1.99	0.129
	Yes	7	3.4%	13.64 ± 0.94	
Clinical Severity	Moderate	33	16.2%	14.34 ± 1.83	0.153
	Sever/critical	139+28	81.8%	14.90 ± 1.99	
	Missing [e]	4	2%		
Secondary Infections	No	121	59.3%	14.37 ± 1.76	≤0.001
	Yes	83	40.7%	15.41 ± 2.10	
Radiologic Severity	Moderate [a]	59	28.9%	14.72 ± 1.99	0.798
	Severe [b]	145	71.1%	14.83 ± 1.97	
Death	No	182	89.2%	14.88 ± 2.00	0.159
	Yes	22	10.8%	14.14 ± 1.53	
Total		204		14.80 ± 1.97	

a. Two lobes of lung were involved, b. Three lobes of lung were involved, c. Hospitalization equal or less than 7 days, d. Hospitalization more than 7 days, e. Missed data, * P values calculated by Mann-Whitney U Test.

To investigate the prognostic value of RDW, correlation studies were carried out to compare RDW levels in different groups of variables. Table 2 shows RDW levels (mean) in different variables and the p values calculated for each analysis. The average level of RDW was 14.80% ± 1.97 ranging from 11.70% to 20%. It showed a higher average in people categorized in the severe group compared to the moderate ones both in terms of clinical examination and imaging features, however no statistically significant difference was observed. There were no statistical significant correlation between RDW level and death, ICU, intubation and shock. However, a significant relationship was observed between RDW and secondary infections and the length of hospitalization in which higher levels of RDW were correlated with longer hospitalization (Spearman Correlation Test- P value≤0.001) and getting secondary infections (Mann-Whitney U Test - P value≤0.001). Moreover, in average, the highest RDW (15.41%± 2.10) was associated with patients who ultimately got secondary infections among all the categories studied in this research.

The efficiency of RDW as a marker to predict hospital stay (more than 7 days/equal or less than 7 days) was evaluated using Roc curves (Shown in Figure 1). The area under curve (AUC) was 0.895 and the optimal cutoff of RDW was estimated to be 14.65% with sensitivity and specificity of 94% and 71.3%, respectively.

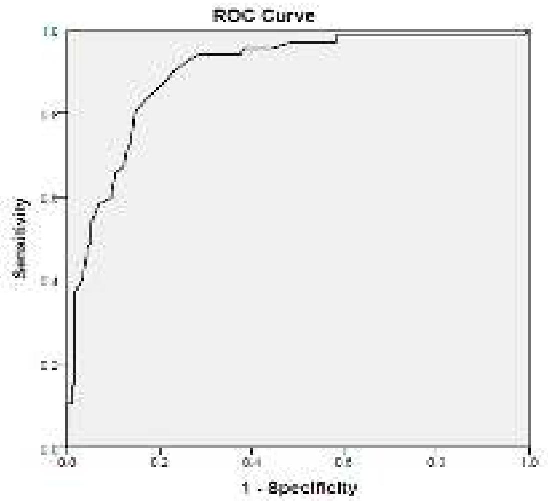

Figure1. Roc analysis of RDW

Discussion

In this study we assessed the prognostic value of RDW in early prediction of secondary infection in COVID-19 patients. Diagnosing COVID-19 patients at higher risk for developing severe illness is of great importance since it could effectively serve the purpose of better managing the patients, providing optimal treatment as soon as possible and preventing from wasting medical resources in coronavirus outbreak, all in turn contribute to a reduction in mortality rate. Few studies have been carried out to design a model for early prediction of severe cases of COVID-19. Feng et al. (2020) reported CT severity and neutrophil-to-lymphocyte ratio (NLR) as independent risk factors for short-term progression of COVID-19 (15) which was in accordance with the study done by Liu et al. (2020) also reporting NLR as a risk factor for severe COVID-19 (20). Gong et al. (2020) emphasized on the role of RDW in predicting severity in COVID-19 among all 7 indicators (age, serum lactate dehydrogenase, CRP, RDW, blood urea nitrogen, albumin, direct bilirubin) they found to be associated with severe COVID-19 (19).Red cell distribution width (RDW), the indicator of variation in the size of red blood cells (RBC), has been regarded as a useful predictive index for numerous disorders. It is a routine laboratory parameter which is reported as a part of a standard complete blood count (CBC) and the cost of measuring it is low enough to be extensively used (31).

The results of the present study suggest that higher RDW on admission is statistically correlated with higher occurrence of secondary infections and longer hospitalization. Moreover, RDW was estimated to be a reliable tool to predict the length of hospital stay according to Roc curve analysis which made it possible to define the optimal cutoff (14.65%) for RDW with high sensitivity and specificity, suggesting that COVID-19 patients with RDW levels higher than 14.65% on admission are more likely to be hospitalized for more than 7 days. Therefore, it seems that this easy and economical tool, RDW, could independently predict the development of a secondary infection in coming days and also the length of hospitalization which seems to be the inevitable consequence of secondary infections.

In the present study, 40.7% of the patients showed secondary infection which is the most prevalent complication among the several factors associated with severity in COVID-19 patients investigated in this research. This might be due to the reason that secondary infection itself could lead to other serious conditions such as septic shock, requiring intubation and ICU admission. In the study done by Zhou et al. (2020), 112 patients (59%) out of the total number of 191, suffered from sepsis which was the most common complication. Secondary infections were observed in 28 (15%) patients, among whom 27 died, consisting 50% of the non-survivors' population (54 death) (14). The high prevalence of secondary infections in patients with severe COVID-19 and its contribution to other severities make it an especially important and useful factor to be predicted. Early prediction of secondary infections could help with more efficient decisions regarding treatment course including prescription of broad spectrum antibiotics (e.g. Vancomycin +_ Meropenem instead of Ceftriaxone) at the first days of admission to prevent from development of the infection and longer hospitalization, considering more specific patients isolation measures and being prepared for providing other appropriate medical care. Accordingly, RDW, particularly levels higher than 14.65%, could work as an efficient alarm, revealing a latent infection and severity in patients with COVID-19. The increased inflammatory response could probably explain the reason of increase in RDW in severe COVID-19. Inflammatory reactions affect bone marrow function. Some pro-inflammatory cytokines inhibit erythrocyte maturation, resulting in immature red blood cells entering the bloodstream and increasing RDW (31, 32). Therefore, a hidden infection could be the underlying reason of significance increase in RDW in severe cases of COVID-19.

Conclusion

In conclusion, early prediction of severity in COVID-19 is of great clinical importance which could considerably improve the health care and prevent from wasting medical resources in the critical situation resulted from the SARS-Cov-2 outbreak. RDW is suggested to be a valuable prognostic factor for prediction of secondary infections, length of hospitalization and severity in COVID-19 patients which is both inexpensive and easy to measure in routine blood tests. However, more studies on wider populations of patients are needed to be done to determine a more precise cutoff for this index.

Conflicts of interest

The authors have no competing interest.

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