Association of Red Cell Distribution Width in Adults RT-PCR Positive Hospitalized Moderate to Severe Patients with COVID-19 Infection

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Abstract

Background: The COVID-19 pandemic has created a global health crisis posing an unprecedented public health emergency. The number of deaths and people being infected were increasing daily throughout the globe.

Aims & Objective: The primary aim of this study was to investigate association between mortality risk and elevated RDW at hospital admission and during hospitalization exists in patients with COVID-19.

Material and Methods: Clinical data retrospectively analyse for all patients who tested positive for SARS-CoV-2 infection between Feb, 2021 and June, 2021.

This cohort study will include adults diagnosed with SARSCoV-2 infection on RTPCR, with moderate to severe cases and admitted to multispeciality covid referral hospital. The study measured several variables. The patients' demographic and clinical data that was measured included body mass index, age, and sex. Patients admitted to the hospital with laboratory-confirmed positive result for COVID by RTPCR assay of a nasopharyngeal swab sample. Significance levels were tested using Chi-square tests that provided comparisons between groups of patients who survived or perished from the disease.

The Cox proportional hazards regression model was used to analyze inpatient COVID-19 mortalities of patients stratified by RDW levels, measured at their time of admission

Results: The mean age of the subjects was 59 years with a standard deviation of 17 years. Out of 820, Number 427 patients (52.07%) were male. Male patients had a worse outcome with 61% of all fatalities. when mortality rates were stratified by age and RDW at admission of patient, it was established that normal RDW levels, 14.5% or lower, mortality levels were significantly lower. The lowest mortality levels were noted in younger age groups but significantly increased with increase in age. However, when the RDW levels were higher than normal at admission, the mortality levels increased fourfold as compared with similar age groups that had normal RDW levels. The findings indicate that increased RDW at admission increased mortality levels from 11.5% to 32%. This indicates that RDW would be used as a predictor of SARS-COV-2 severity.

Conclusion: Elevated RDW levels at admission and increasing levels during hospitalization were associated with significantly higher mortality risk for patients with SARS-CoV-2 infection.

Keywords: COVID-19, Haematological parameters, red blood cell distribution width

Introduction

In December 2019 a new viral diseases emerged in Wuhan, China. It was later established that the disease was caused by the novel coronavirus which causes the coronavirus disease 2019 (COVID-19). Based on its symptoms, the disease was subsequently named as the severe acute respiratory syndrome virus-2 (SARS-COV-2). Since its emergence, covid-19 has become a significant health threat across the world. [1] Coronavirus disease 2019 (COVID-19) is an acute respiratory illness caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has a high rate of hospitalization, critical care requirement, and mortality.[1,2] Although the total mortality rates are at 2.25%, the rates are higher for patients with severe cases of SARS-COV-2 and are admitted in the Intensive Care Unit where they range between 50-60%. [2] Patients requiring mechanical ventilators have an even higher mortality rates of 97%. [3] There are varied factors that are linked to the propensity to high mortality rates.

Recent studies indicate that covid-19 patients with other underlying conditions are predisposed to severe outcomes. Age, hypertension, smoking, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular diseases, liver complications, kidney disease, and respiratory distress syndrome are some of the comorbidities noted to contribute severe SARS-COV-2 outcomes.[4,5]. Patient with underlying conditions have a faster disease progression, stay longer in critical care units, and are more likely to require intensive care. Comorbidities have also been noted to result in other complications like inflammations that negatively impact on the survivability of patients. Several parameters are used to measure the outcome of patients. One parameter that prominently comes out among them is the Red Blood Cell Distribution Width (RDW) that has been found to indicate the severity of covid-19 cases.[6]

However, several studies have established an association between higher RDW levels and mortality levels of covid-19 patients.[7] Patients with severe covid-19 cases were also found to have higher levels of RDW than those with non-severe covid-19 symptoms. [6,8] Another study established that there were high RDW levels at ICU admission and that RDW was a good measure of mortality cases over a one-month period of patient admission.[9] Previous studies have indicated that elevated RDW levels for younger patients significantly increased their mortality levels. elevated RDW is a marker of increased mortality levels in covid-19 patients.[6] The RDW is a hemoglobin parameter used in gap analysis of anemia. It entails the analysis of red blood cells' size and form in a given patient [10].

Objective: To investigate whether an association between mortality risk and elevated RDW at hospital admission and during hospitalization exists in patients with COVID-19.

Material and Methods

The study was a retrospective, cross-sectional, and analytic study that was carried out at the Intensive care unit of Tertiary care hospitals in North Maharashtra. The study was carried out from March 2021 to June2021. Research approval was received from the ethical committee. 820 patients suffering from the novel coronavirus (SARS-COV-2) were involved in the study. The study involved only patients who had been admitted with moderate to severe symptoms and whose laboratory tests had returned positive results for COVID-19 nucleic acids. The tests involved a nasopharyngeal swap sample that was subjected to real-time fluorescence reverse transcription polymerase chain reaction assay (RT-PCR).

Inclusion Criteria: Patients admitted to the hospital having moderate to severe sign and symptoms with laboratory-confirmed positive result for COVID by RTPCR assay of a nasopharyngeal swab sample.

Exclusion Criteria

1. Younger than 18 years.
2. Mild cases-did not have an inpatient hospital stay at hospitals (Home-quartine) with positive diagnosis.
3. COVID-19 brought dead patients.

In all participant cases, Red Blood Cell Distribution Width (RDW), absolute lymphocyte count, and D-dimer levels were measured on the 1st, 3rd, 5th, and 7th days of each week of admission over a period of stay. Other clinical measures that were taken included the white blood cell count, platelet count, hemoglobin measures, hematocrit, lactic acid, urea, glucose, and albumin along with other biomarkers. Patients with mild symptoms ,brought dead were excluded from the study as well as patients below 18 years. However, patients with multiple COVID-19 hospital

admissions over the study period that amounted to one month were assumed to have had a continued admission period.

Variables for the study

The study measured several variables. The patients' demographic and clinical data that was measured included body mass index, age, and sex. Clinical measures like RDW were included because other studies have established their significant link to COVID-19.[11] Severity Comorbidities measured included chronic liver disease, diabetes mellitus, chronic obstructive pulmonary disease, hypertension, chronic liver disease, cerebrovascular disease, active smoking, alcohol use, human immunodeficiency virus, Ischemic heart disease. The comorbidities were included because they had been shown as significant determinants of COVID-19 severity. [12, 13] Mortalities were evaluated based on the number of discharges with the assumption that there would be no COVID-19 related deaths for each admission.

Data analysis

Data was analyzed using the Stata software. The study used percentages, percentiles, and ranges to describe continuous and categorical data. Age was accounted for as a major confounder and patients were grouped using age ranges. Six cohorts were established comprising of patients in the age ranges of <40 years, 41-50 years, 51-60 years, 61-70 years, 71-80 years, and ≥81 years. Age was included as a parameter because other studies have revealed it as being a major determinant of SAR-COV-2 mortalities.[14] Significance levels were tested using Chi-square tests that provided comparisons between groups of patients who survived or perished from the disease.

The Cox proportional hazards regression model was used to analyze inpatient COVID-19 mortalities of patients stratified by RDW levels, measured at their time of admission. The findings were represented using the Kaplan Meier curve. For this, measure, an elevated RDW level was defined as any that was above 14.5% for males and 16.1% for females which are the limits for healthy adults.[15] To test the association between RDW and mortality over the four-week period, a regression analysis was carried out. In the study therefore, risk factors were indicated as RDW above 14.5% for male and 16.1% for females, age above seventy years, D-dimer levels above 1500 ng/ml, absolute lymphocyte below 0.8 x 10^9/l. Fluctuations in RDW were noted by assessing the first measurements at admission and the last available measure. Incident rate comparison among cohorts was calculated using the chi-square test while a two-sided t-test was used to assess the means. A 95% confidence level was deemed as ideal for the study with a $p<0.5$.

Results

Table 1: Patients characteristics at discharge

Patient demographic characteristics	Means (Standard Deviation)		P-Value
	Survivors	Non-survivors	
Number n	679	141	

Age, yrs	58.7 (16.70)	73.9 (13.40)	<0.001
Sex male n(%)	341 (50.22)	86 (61)	0.0763
Body Mass Index (kg/m^2)	27.8	30.1	0.092
Average hospital stay, d	15.4	10.3	<0.001
Comorbidities			
Diabetes mellitus n(%)	19 (2.30))	27 (18.15)	0.49
Active smoking n(%)	7 (1.03)	6 (4.26)	<0.001
Alcohol use n(%)	72 (10.60)	15 (12.77)	<0.001
Hypertension n(%)	21 (2.09)	24 (17.02)	<0.001
HIV n(%)	2 (0.3)	0	
Ischemic heart disease n(%)	21 (3.09)	19 (13.48)	<0.001
Chronic liver disease n(%)	3 (0.44)	2 (1.42)	<0.001
COPD n(%)	3 (0.44)	11 (7.80)	<0.01
RDW stratification by age (%)			
<41y	13.4 (1.8)	14.9 (3.9)	<0.001
41-50y	13.7 (1.7)	15.5 (3.7)	<0.001
51-60y	13.9 (2.2)	15.7 (2.8)	<0.001
61-70y	14. 1 (1.7)	15.3 (2.1)	0.03
71-80y	14.3 (1.6)	15.1 (1.9)	0.02
≥81y	14.3 (1.8)	15.3 (2.2)	0.03
Laboratory tests			
Absolute lymphocyte count, n × 10^9/L	1.23	1.03	0.34
Hemoglobin, g/dL	13.4 (2.1)	11.9 (2.5)	<0.001
Hematocrit, (%)	39.1 (5.61)	36.9 (7.2)	<0.001
Platelets 10^3/μL	215.3 (91.8)	186.9 (90.4)	<0.001
Lactic acid (mmol/L)	1.33 (1.06)	1.69 (1.2)	<0.001
Albumin (mg/l)	29.9 (2.1)	32.1 (3.8)	0.27
Fibrinogen (mg/dl)	536 (92.1)	734 (89.7)	0.47
Neutrophils 10^3/μL	7.7 (4.9)	8.1 (4.1)	<0.001
Neutrophil/absolute lymphocyte ratio	6.23	7.86	<0.001
Lymphocyte (%)	0.169	0.127	
Monocytes 10^3/μL	0.64 (0.34)	0.61 (0.27)	<0.001
White blood cells 10^3/μL	7.3 (6.1)	8.4 (4.4)	0.055
Red blood cells 10^3/μL	4.51 (0.69)	4.19 (0.9)	<0.001

Baseline data of the subjects

It was established that the mean age of the subjects was 59 years with a standard deviation of 17 years. Of the 820 patients, 427 or 52.07% were male. Of the 820 patients, 400 exhibited mild symptoms, 152 moderate cases, 127 had severe symptoms, and there were 141 fatalities. Male patients had a worse outcome with 61% of all fatalities being male, which is in line with other studies.[16] Women had the highest number of mild cases. Non-surviving patients were older, 74 years, than surviving patients, 59 years. Obese patients (30.1) were more likely to die than overweight patients (27.8).

The study revealed that people suffering from diabetes mellitus had an increased chance of dying from the disease, as established in other studies. [17] Patients with ischemic heart disease, chronic liver disease, and hypertension were at a higher risk of dying from the contagion than those without the condition. Active smokers were four times likely to die from coronavirus than nonsmokers. However, the study revealed that alcohol (12.77%) did not significantly increase the propensity of dying from the disease.

Correlation between RDW and mortality levels

The cox proportional hazards model was used to assess the influence of RDW in morbidity cases. Table two indicates the findings on RDW elevation at admission, patient's age and mortality levels. As indicated in table 2 below, when mortality rates were stratified by age and RDW at admission of patient, it was established that normal RDW levels, 14.5% or lower, mortality levels were significantly lower. The lowest mortality levels were noted in younger age groups but significantly increased with increase in age. However, when the RDW levels were higher than normal at admission, the mortality levels increased fourfold as compared with similar age groups that had normal RDW levels. For instance, while mortality levels were 7% for the 51-60y cohort, the mortality levels almost tripled (26%) when a similar cohort had higher than normal RDW levels. The findings confirm other research findings that higher RDW leads to higher mortality levels for COVID-19 patients even though the specific mechanism or mechanisms for the RDW alteration associated with COVID-19 remain unclear. [6,8]

The findings indicate that increased RDW at admission increased mortality levels from 11.5% to 32%. This indicates that RDW would be used as a predictor of SARS-COV-2 severity.

Table 2: Mortality levels stratified by age and increased RDW before admission

Normal RDW			**Increased RDW**		
Age	**No.**	**Mortality (%)**	**No.**	**Mortality (%)**	**Risk ratio (95% CI)[b]**
<41y	109	1	32	9	5.92 (5.06-6.78)
41-50y	101	6	33	23	5.25 (4.04-6.46)
51-60y	84	7	45	25	2.96 (2.35-3.56)
61-70y	79	24	53	31	3.99 (3.41-4.56)
71-80y	65	27	75	33	1.43 (1.06-1.79)
≥80y	57	29	87	44	1.64 (1.26-2.01)
Totals	495	11.5	325	32	2.8 (2.61-2.98)

Increase in RDW after hospitalization

The study sought to establish if an increase in RDW for admitted patients impacted on the mortality levels. The results revealed that patients who at time of their admission had an RDW of 14.5% or less, but later died, exhibited a significant rise in the RDW mean. Patients who had an RDW of 14.5% or less at admission and were alive at discharge, exhibited a stable RDW. The study established that increasing RDW levels

after hospitalization increased mortality risk levels from 7% (95% CI 5%-9%) to 23% (95% CI 17%-29%) for patients with normal RDW levels at admission and from 20% (95% CI 17%-23%) to 41% (95% CI 33%-49%) for patients with an already elevated RDW. The findings confirm those of other studies which indicate that hospitalized RDW increment increases mortality rates for SARS-COV-2 patients.[6,11] The findings indicate that admitted patients should be closely monitored to mitigate possible RDW increments to lessen mortality rates.

Discussion

The study established that having an RDW that is higher than 14.5% at the time of admission significantly increased the mortality rates of patients. It was also revealed that an increase in RDW for admitted patients also raised the mortality rates for affected patients. With reference to table 2, individuals 50 years and below had a higher twice as much risk levels of dying from covid-19, when their RDW was higher than normal rates, as compared to other age groups. Similar studies indicate that increased RDW levels lead to higher mortality levels for younger patients than in older patients. Having RDW levels above 14.5% for younger patients may be an indication of stronger inflammatory levels in younger covid-19 patients. Lee and others (2021) [18, 19] aver that hyper-inflammation is an indication of severe outcomes for covid-19 patients. In their study, they established that patients with C-reactive protein levels, high absolute neutrophil counts, and low absolute lymphocyte counts exhibited higher hyper-inflammation which in turn led to higher morbidity levels. Higher inflammation was exhibited by higher levels of RDW.

However, older patients were often found to have higher RDW levels as compared to younger patients and this translated to an overall greater mortality rate for older patients. For cohorts between the age of 51 and 60 years, the risk of dying from SARS-COV-2 tripled when their RDW were higher than normal levels. Similar studies have indicated that Covid-19 patients with a higher RDW have adverse outcomes and that severely ill covid-19 patients exhibit higher RDW levels than patients with milder symptoms who have normal RDW levels.[19] Therefore, RDW should be regularly measured and patients with elevated levels should be prioritized for aggressive interventions that may help lower the levels and contain it before patients face adverse outcomes.

Individuals with other underlying conditions exhibited higher RDW level along with other biomarkers like S. Feritin, CRP, IL6, D-Dimer, LDH, Procalcitonin and had severe covid-19 outcomes. Comorbidities like obesity, hypertension, kidney disease, diabetes mellitus, and ischemic heart disease increase RDW levels that subsequently worsen the covid-19 outcomes of victims. Other studies indicate that individuals suffering from obesity have high inflammation levels and exhibit impaired cellular immune functioning.[20,21] The studies indicate that obese patients have high levels of prothrombin factors and low levels of lower levels of anti-prothrombin factors which increases inflation and RDW levels. This increases coagulopathy and thrombosis cases in covid-19 patients that results in high mortality cases.[22] The underlying condition already makes the patient vulnerable and when the victim suffers from

SARS-COV-2, the immune system is not able to mount a strong response to fight the infection resulting in high mortality levels.

When lifestyle factors were included in the study, it was established that there was a low link between alcohol use and covid-19 severity. However, a strong association was established between smoking and covid-19 severity. The study findings indicate that smokers were 4.1 times more likely to die from SARS.COV-19 related complications than nonsmokers. Other studies from China indicate that smokers were 2.4 times more likely to be admitted in the ICU and 1.4 times more likely to exhibit severe symptoms due to covid-19 infections The clinical course for patients who are hospitalized varies dramatically, with early evidence showing that ICU admission and mortality risk are associated with an elevated D-dimer (dimerized plasmin fragment D) level and a decreasing lymphocyte count.[23] A similar study from China indicated that smoking was a risk factor in disease progression and that 27.3% of the victims with severe disease progression had a history of smoking.[24] The findings indicate that patients with smoking history should receive close supervision to mitigate their risk to covid-19 morbidities.

Red blood cell distribution width (RDW) is a parameter of the haemogram used in the differential diagnosis of anaemia and involves the variability in form and size of red blood cells in the subject.[25] Elevated RDW is associated with an increased risk for all-cause mortality; mortality from heart disease, pulmonary disease, sepsis, influenza, and cancer; complications associated with heart failure, severity of coronary artery disease and viral hepatitis, advanced stage and grade for many cancers and the development of diabetes, chronic obstructive pulmonary disease, stroke, anemia and many other conditions.[26]

An association between high RDW and mortality has been found in patients with coronary disease [26] liver disease [27], pancreatitis [28] and ischaemic stroke [29, 30]. We had previously found that RDW at ICU admission was associated with mortality in brain infarction [30] and in septic patients. [31] RDW has also been shown to correlate with measures of inflammation in non-COVID-19 settings, including tumor necrosis factor (TNF)-α in sepsis, interleukin (IL)-6 [28, 29] in heart failure and human immunodeficiency virus infection, and high sensitivity C-Reactive protein (hsCRP) and erythrocyte sedimentation rate(ESR) in other populations [30, 31].

This association has also been found in septic patients [31-33]. In one study was found that severe patients showed higher RDW than non-severe COVID-19 patients; however, the criteria of severity were not clearly established and the mortality rate was < 1% in the whole series and < 4% in the severe patients group. [34]

Conclusion

The findings lead to the conclusion that patients with higher RDW levels at admission should receive closer attention to alleviate the risk of mortality from Covid-19. Besides, patients whose RDW increases while admitted should receive a review of interventions to control the condition before it adversely affects the patients. RDW is useful in risk stratification of hospitalized patients with COVID-19.

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