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Original Research Article

# Study of correlation of red cell distribution width with acute exacerbation of chronic obstructive pulmonary disease

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ABSTRACT

**Background:** Acute exacerbation of COPD is one of the most common disease in patients with infections, having frequent hospitalization. The aim of this study is to find whether there is any relationship between RDW with mortality in AECOPD.
**Materials and Methods:** The hospital based case control Study is was conduct on hospitalized 50 patient with primary and final diagnosis of AECOPD and 50 patient of stable period of COPD.
**Results:** Socio-demographic variable in both groups were comparable. BMI was significantly lower in AECOPD patients. The mean PACK/YR in AECOPD group was 24.44±6.23 and in Stable COPD was 20.66±8.21. Mean admission per year were significantly higher in AECOPD patients (1.88±0.80 per year) as compare to stable COPD patients (0.80±0.67 per year). Mean FEV1 % was significantly lower in AECOPD patients (43.87±14.26) as compare to stable COPD patients (48.12±20.18). Mean RDW significantly higher in AECOPD (17.60±5.70%) as compare to stable COPD patients (13.80±3.33%). The difference in both groups was found statistically significant. MCV was significantly lower in AECOPD (82.04±1.49) as compare to stable COPD patients (86.50±1.87). The difference in both groups was found statistically significant. RDW was significantly higher in those patient who were died (19.50±0.70%) as compare to survived patients (17.52±5.61%). The difference in both groups was found statistically significant. 4.00% hospital mortality in AECOPD group.
**Conclusions:** We have concluded that the mean red cell distribution width on the day of presenting the illness was significantly higher in AECOPD as compare to stable COPD. Those patients who had a high red cell distribution width during admission were associated with poor prognosis.

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## 1. Introduction

COPD is a persistent, progressive airflow limitation associated with enhanced chronic inflammatory response in the airways. Chronic obstructive pulmonary disease is the third leading cause of death worldwide; COPD led to 3.84 million deaths in 2019, a toll expected to reach 4.4 million yearly by 2040. With a worldwide prevalence of 10.1%, COPD afflicts many people in low-income, middle-income, and wealthy countries and years of life lost prematurely increased 14.00% between 2007 and 2019. Although COPD is a substantial problem everywhere, China and India accounts for more than 50% of all cases of COPD in the world.[1]

With the pace of demographic and epidemiological transitions, the changes in socio-behavioral dimensions and their impacts on population health are evident. In India, the burden of all non-communicable diseases has increased since 1990.[2] As on 2019, three out of five leading causes of mortalities constitute non-communicable diseases whereas COPD is the second biggest cause of death in India today.[3] Different studies have revealed varying range of prevalence

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of COPD in different states. The prevalence ranged between 2 to 22% among the men and 1.2 to 19% among women in different population-based studies across India.[4] It became fourth leading cause of years of life lost in Empowered Action Group (EAG) States including Bihar, Jharkhand, Madhya Pradesh, Chhattisgarh, Odisha, Rajasthan, Uttar Pradesh and Uttarakhand.[4] Also, COPD ranked seventh among the North-East States including Assam, Mizoram, Arunachal Pradesh, Meghalaya, Nagaland, Tripura, Sikkim and Manipur. Among the remaining states of India, COPD ranked fourth among all causes of years of life lost. In this varying range of disease burden, the highest rate of death from COPD was nine times the lowest rate among all the states.[5]

COPD has been among the top eight leading causes of disabilities in all the states. Comprising all these, DALYs due to COPD increased 36.3% from 1990 to 2016 and it became second leading cause of DALYs in India followed by diarrheal disease, lower respiratory tract infections, stroke and iron deficiency anemia . The prevalence of COPD has increased by 29.2% within the same period which is a serious public health concern.[5]

Our understanding of COPD has evolved rapidly, and it has become clear that COPD is not an isolated disease of the lungs. Instead, COPD is a complex interplay between emphysema and airway obstruction, systemic inflammation, comorbidities, and metabolism, which all contribute to prognosis.[6,7]Recently developed prognostic tools take this multifaceted pathology into account by incorporating systemic as well as lung-specific parameters.

Clinically, acute exacerbations of COPD (AECOPD) are the most important events in the history of this disease, and it's in hospital mortality is reported at 2.5%,[8] 7.25%,[9] 7.4%,[10] and 12%.[11] The identification of predictive markers for outcome in AECOPD patients following hospitalization may help the physicians in making better decisions and management. Many biomarkers (fibrinogen, CRP, IL 6, IL 8, TNF alfa) are used for prediction of outcome, but some are expensive or are not available in many hospitals.

A red cell distribution width (RDW) test is a measurement of the range in the volume and size of red blood cells (erythrocytes). Red blood cells move oxygen from your lungs to every cell in body. Cells need oxygen to grow, reproduce, and stay healthy. If red blood cells are larger than normal, it could indicate a medical problem.

The red RDW test measures variation in red blood cell size or red blood cell volume as a part of a complete blood count (CBC), and it is used along with other RBC indices, especially mean corpuscular volume (MCV), to help determine the causes of anemia.

RDW in complete blood count (CBC) shows variations in size of circulating red blood cells (anisocytosis). RDW is used for the differential diagnosis of anemia. RDW has also been shown as a possible marker for mortality in AECOPD, congestive heart failure, MI, CABG, etc.[12,13]

In the Third National Health and Nutrition Examination Survey of 15852 adults, mortality rates increased 5-fold from the lowest to the highest quintile of RDW.[10] Prior studies have investigated the association of RDW with mortality in internal medicine ward,[14] critical care unites (adult and pediatric),[15] and emergency department.[16]

Many studies have described RDW as a prognostic marker in several cardiovascular disease including congestive heart failure, coronary artery disease, carotid atherosclerosis, peripheral artery disease, and cerebrovascular accidents.[17–19]

RDW has also been described to be predictive of mortality in hip fracture pancreatitis, acute kidney injury, hemodialysis, necrotizing fasciitis, infective endocarditis, sepsis and even organophosphate poisoning.[20]

In respiratory medicine area, the relation of higher RDW with mortality have been shown for lung cancer, pulmonary hypertension, pulmonary embolism, acute dyspnea, community acquired pneumonia and stable COPD patients but not AECOPD.[21]

To the best of our knowledge, there is only one published article, by Seyhan et al.,[22] that has investigated and shown that elevated RDW levels have been associated with increased mortality risk in stable COPD patients. As relation between RDW and in-hospital mortality in AECOPD has not been reported in the literature so far, the aim of this study is to find whether there is any relationship. The present study was done:

1. To observe the correlation between Red Cell Distribution Width (RDW) with acute exacerbation of Chronic Obstructive Pulmonary Disease (COPD).
2. To investigate the relation of RDW to in-hospital mortality in patients with AECOPD.

## 2. Materials and Methods

It was a hospital based case control study .The patient presented to Department of Medicine, S.P. Medical College and A.G Hospital, Bikaner, Rajasthan over a period of 12 months ($1^{st}$ August 2019 to $31^{st}$ July 2020).This was consecutive sampling. We have included hospitalized 50 patients with primary and final diagnosis of AECOPD. 50 subjects in stable period of COPD. An ethical committee approval was taken.

### *2.1. Inclusion criteria*

1. Diagnosed case of COPD with clinical criteria's of exacerbation including increased dyspnea, increased sputum volume or sputum purulence, cough.
2. Age group above 30 years age
3. Those who are giving informed consent

### 2.2. Exclusion criteria

1. Primary reason for admission other than AECOPD.
2. Any Hematological disease, oncologic disease.
3. Any auto-immune disease.
4. Any history of systemic illness like diabetes, hypertension on medication.
5. Not given informed consent.

Sample collection

Blood Samples

A random sample was collected from the anticubital vein of the study subjects. The blood samples were analyzed on the same day within 3 hours of collection. The biochemical parameters relevant to the study were analyzed by the following methodologies.

Estimation of RDW, RBC Count and CBC

With differential test method

WBC: Flow cytometry

RBC: Impedance counting

Platelet Count: Impedance counting

HGB: Converted to SLS-hemoglobin and read photometrically.

MCV: The average volume of individual erythrocytes derived from the RBC histogram.

RDW: The size distribution spread of the erythrocytes population derived from the RBC histogram

MPV: The average volume of individual platelets derived from the PLT histogram.

Red cell distribution (RDW)

Red cell distribution width is an index of variation in RBC size or RBC volume. Most automated instruments produce a quantitative assessment of the variation in red cell volume indicated by RDW which corresponds to the microscopic analysis of the degree of anisocytosis.

The RDW derived from pulse height analysis can be expressed either as (SD) standard deviation in fl (famtolitre) or as the percent of coefficient of variation (CV) of the measurements of red cell volume. RDW-SD is a measurement of width of RBC size distribution histogram and it is measured by calculating the width at the 20% height level of the RBC size distribution histogram. Hence RDW-SD is not influenced by the average RBC size, that is, mean corpuscular volume. RDW-CV is calculated from standard deviation and MCV by the formula.

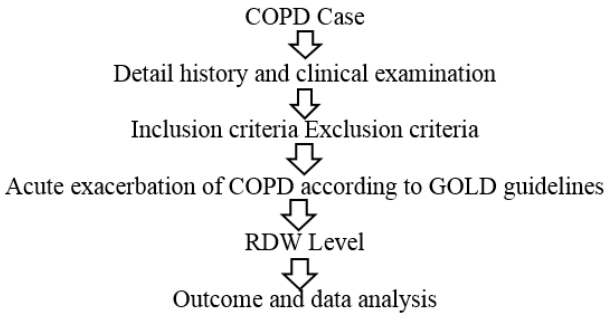
RDW-CV (%) = 1 SD of RBC volume / MCV x 100%Since RDW-CV is obtained mathematically from MCV it is affected by changes in average size of RBCs.

Significance of elevated RDW

1. Early diagnosis of nutritional deficiency (d/t) iron, B12 and folic acid
2. Differentiation of iron deficiency anemia from thalassemia.
3. Differentiation of megaloblastic anemia from other causes of macrocytosis.
4. Identification of Red cell fragmentation, agglutination and dimorphic red cells in peripheral smear examination. Red cell distribution width in sepsis.

### 2.3. Data analysis

Data was recorded as per Performa. The data analysis was computer based; SPSS-22 was used for analysis. For category variables chi-square test was used. For continuous variables independent samples' t-test was used. P-value <0.05 was considered as significant.




## 3. Observationsand Results

**Table 1:** Age wise distribution of study subject

| Age in years | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| 30-45 years | 1 | 1 | 0.425 |
| 45-60 years | 12 | 14 | |
| >60 years | 37 | 35 | |
| Total | 50 | 50 | |
| Mean age in years | 64.62±8.24 | 63.22±9.18 | 0.455 |

Table 1 shows that maximum patients in both groups were found in>60 years age group. The mean age in AECOPD group was 64.62±8.24 years and in Stable COPD was 63.22±9.18 years. Both groups were comparable.

**Table 2:** Sex wise distribution of study subject

| Sex | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Male | 44 | 41 | 0.576 |
| Female | 6 | 9 | |

Table 2 shows that maximum patients in both groups were male. Both groups were comparable.

Table 3 shows that maximum patients in both groups were from middle class followed by lower socio-economic class. Both groups were comparable.

Table 4 shows that mean BMI was significantly lower in AECOPD patients (20.94±2.15 kg/m$^2$) as compare to stable COPD patients (21.37±3.10 kg/m$^2$).

**Table 3:** Socio-economicstatus (SES) wise distribution of study subject

| SES | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Upper | 0 | 0 | |
| Middle | 32 | 31 | 0.99 |
| Lower | 18 | 19 | |

**Table 4:** BMI wise distribution of study subject

| BMI in kg/m $^2$ | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Mean | 20.94 | 21.37 | 0.01 |
| SD | 2.15 | 3.10 | |

**Table 5:** Symptoms wise distribution of study subject

| Symptoms | AECOPD | Stable COPD |
|---|---|---|
| Breathlessness | 50 | 23 |
| Expectoration | 30 | 20 |
| Cough | 35 | 32 |
| Wheezing | 9 | 8 |
| Chest pain | 15 | 9 |

Table 5 Shows that maximum patients in both groups were presented with cough and breathlessness.

**Table 6:** Smoking status wise distribution of study subject

| Smoking | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Smoker | 29 | 15 | |
| Ex-smoker | 16 | 30 | 0.01 |
| No smoker | 5 | 5 | |

Table 6 shows that maximum patients in both groups were smoker. 58.00% patients in AECOPD and in 30.00% patients in stable COPD group werepresent smoker. The difference in both group was found statically significant.

**Table 7:** Pack /Year wise distribution of study subject

| Pack/Year | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| 0-10 Pack/Year | 1 | 1 | |
| 11-20 Pack/Year | 1 | 6 | 0.01 |
| 21-30 Pack/Year | 31 | 39 | |
| >30 Pack/Year | 8 | 4 | |
| Total | 45 | 45 | |
| Mean pack/year | 24.44±6.23 | 20.66±8.21 | 0.02 |

Table 7 shows that maximum patients in both groupshave used 21-30 Pack/Year. The mean Pack/Year in AECOPD group was 24.44±6.23 and in Stable COPD was 20.66±8.21. The pack per year wise difference in between both groups was found statistically significant.

Table 8 shows that maximum patients in AECOPD group were from grade 4 and in stable COPD were from grade 3. The difference in both groups was found statistically significant.

**Table 8:** mMRC wise distribution of study subject

| mMRC grade | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| 0 | 0 | 0 | |
| 1 | 0 | 0 | |
| 2 | 0 | 10 | 0.001 |
| 3 | 16 | 30 | |
| 4 | 34 | 10 | |

**Table 9:** GOLDcriteria wise distribution of study subject

| GOLD stage | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| A | 7 | 13 | |
| B | 3 | 8 | 0.006 |
| C | 14 | 8 | |
| D | 26 | 21 | |

Table 9 shows that maximum patients in AECOPD group was from GOLD stage 4 and in stable COPD was also from GOLD stage 4. The difference in both group was foundstatically significant.

**Table 10:** Admission per year wise distribution of study subject

| Admission per year | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Mean | 1.88 | 0.80 | 0.001 |
| SD | 0.80 | 0.67 | |

Table 10 shows that mean admission per year significantly higher in AECOPD patients (1.88±0.80 per year) as compare to stable COPD patients (0.80±0.67 per year)

**Table 11:** FEV1 wise distribution of study subject

| FEV1% | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Mean | 43.87 | 48.12 | 0.001 |
| SD | 14.26 | 20.18 | |

Table 11 shows that mean FEV1% significantly lower in AECOPD patients (43.87±14.26) as compare to stable COPD patients (48.12±20.18). The difference in both groups was found statistically significant.

**Table 12:** Outcome wise distribution of study subject

| Outcome | AECOPD | Stable COPD |
|---|---|---|
| Death | 2 | 0 |
| Survived | 48 | 50 |

Table 12 shows that 4.00% hospital mortality in AECOPD group.

Table 13 shows that mean RDW was significantly higher in AECOPD (17.60±5.70%) as compare to stable patients (13.80±3.33%). The difference in both groups was found statistically significant.

Table 14 shows that mean MCV was significantly lower in AECOPD (82.04±1.49 fl) as compare to stable patients

**Table 13:** RDW% wise distribution of study subject

| RDW% | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| 10-20% | 35 | 45 | 0.024 |
| 21-30% | 15 | 5 | |
| Total | 50 | 50 | |
| RDW% | 17.60±5.70% | 13.80±3.33% | 0.01 |

**Table 14:** MCV wise distribution of study subject

| MCV | AECOPD | Stable COPD | P-value |
|---|---|---|---|
| Mean | 82.04 | 86.50 | 0.001 |
| SD | 1.49 | 1.87 | |

(86.50±1.87 fl). The difference in both groups was found statistically significant.

**Table 15:** Association between RDW and outcome in AECOPD patients

| RDW | Death | Survived | P-value |
|---|---|---|---|
| Mean | 19.50 | 17.52 | 0.001 |
| SD | 0.70 | 5.61 | |

Table 15 shows that mean RDW was significantly higher in death(19.50±0.70%) as compare to survived patients (17.52±5.61%). The difference in both groups was found statistically significant.

## 4. Discussion

The hospital based case control Study was conducted on patients attending department of General medicine in Sardar Patel Medical College Hospital, Bikaner. We have included hospitalized 50 patients with primary and final diagnosis of AECOPD and 50 patients of stable period of COPD.

AECOPD is associated with increased risk of subsequent exacerbations, worsening of coexisting pathological conditions, poor performance status and physical activity, deterioration of respiratory function and, ultimately, death.[23]

AECOPD is among the most common diseases in clinical practice, especially in patients with infections. Inflammation encompasses a complex network of interactions involving various immune-related cells, including neutrophils and lymphocytes, which can lead to persistent respiratory tissue injury and damage.[24] It has been reported that the absolute counts of key immune-related cell populations in the peripheral blood, and their ratios, can adequately reflect chronic inflammatory conditions.[25]

In our study maximum patients in both groups were found in >60 years age group. The mean age in AECOPD group was 64.62±8.24 years and in Stable COPD was 63.22±9.18 years. Maximum patients in both groups were male. Angus et al.,[26] observed that the mean age of patients with AECOPD was 63.8 years.

In another study conducted by Martin etincidence of sepsis by about 20% more in the elderly population compared to younger individuals

The incidence of sepsis was slightly higher among male patients compared to females. Studies have shown that women appear to be at a lower risk of developing sepsis than men. The reason for this is unclear though in a study Angus et al.,[26] explored and published the possible role of estrogens and androgens that lead to gender differences in the incidence of sepsis.

We could not come to a conclusion based on gender incidence as our study group was small and as there was not much significant difference in male and female incidence.

Our study was compatible with Ercan Kurtipek et al.,[27] who reported that out of the 94 patients, 48(51%) had stable COPD with a mean age of 66.65±10.17 years (range: 49-79 years), and 46(49%) patients having acute exacerbation with a mean age of 62.67±9.41 years (range: 48-92 years). Another study by Recai Ergün et al.,[28] reported the mean age of the patients as 69.0±9.2 and 104 (78.2%) of patients were male.

In our study maximum patients in both groups were from middle class followed by lower socio-economic class because our hospital was government sector hospital, so maximum patients in our hospital come from lower and middle socio-economic class. BMI was significantly lower in AECOPD patients (20.94±2.15 kg/mt$^2$) as compare to stable COPD patients (21.37±3.10kg/mt$^2$). The loss of weight is most likely multi factorial in origin. Established explanations for weight loss in COPD include increased basal metabolic rate due to the increased energy cost of breathing, as well as physical inactivity and malnutrition due to eating difficulties.

Systemic inflammation and hypoxia are particularly prevalent among COPD patients with low body weight.[29] There is increasing evidence that the immune system, in particular inflammatory cytokines, play an important role in the development of weight loss and cachexia. The central cytokine in the loss of muscle mass is TNF-$\alpha$. TNF-$\alpha$, which in laboratory animals is associated with accelerated metabolism and protein turnover, was shown to be elevated in the blood of COPD patients suffering from involuntary weight loss.[30,31]

The present study observed that maximum patients in both groups were smoker. 58.00% patients in AECOPD and in 30.00% patients in stable COPD group were present smoker. The difference in both groups was found statistically significant. The mean PACK/YR in AECOPD group was 24.44±6.23 and in Stable COPD was 20.66±8.21. The difference in both groups was found statistically significant.

Fletcher et al[32] revealed that in susceptible smokers (comparable with the host factors), tobacco smoking is strongly related to chronic bronchitis and airflow

obstruction, and that these were two different diseases. Cigarette smoking is recognized as the cause of COPD in the vast majority of patients. Although not fully understood, it is widely accepted that an abnormal inflammatory response of the lungs to noxious particles and gases beyond the normal protective inflammatory response is involved in the development of COPD.

In our study maximum patients in AECOPD groups were from GOLD stage 4 and in stable COPD were also from GOLD stage 4. The difference in both group was found statistically significant.

Our results were supported by a retrospective study done by TAYLAN et al.[33] who reported that out of 100 patients, 43 cases were classified as Global Initiative for Chronic Obstructive Lung Disease (GOLD) III and 57 as GOLD IV. Ercan Kurtipek et al.,[27] who found that among the stable COPD patients, 16(33.3%) were in category B, and 18(37.5%) in category D. Among AECOPD patients, 34(73.9%) were in category D, which was conflict of our results.

RDW is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes. In the past RDW usually had been used for the differential diagnosis of iron-deficiency anemia and acute appendicitis. In recent years, RDW has been demonstrated to predict mortality and other outcome in septic and septic shock in aged adults.

Mean RDW was significantly higher in AECOPD (17.60±5.70%) as compare to Stable patients (13.80±3.33%). The difference in both groups was found statistically significant in our study.

Similar result was observed by Tertemiz KC et al.,[34] that RDW was found significantly different between AECOPD and stable COPD patients. The highest RDW was observed in the very severe stage ($p<0.001$). Median of BODE index was 1 (0-3). As the BODE index increased RDW also increased ($p<0.001$). When the patients were grouped according to the laboratory upper limit of RDW, survival rate was 31% in the RDW >14.3% group and 75% in the RDW <14.3% group. The variability in the size of circulating erythrocytes increases as the COPD severity progresses.

In our study, the mean red cell distribution width on the day of presenting the illness was significantly higher in non survivors than survivors. Those patients who had a high red cell distribution width during admission were associated with poor survival.

This result correlates with the study of Mahmood et al.,[35] in which RDW greater than16 was concluded to be associated with increase in severity of illness. In another study by Jo YH et al.,[36] RDW was significantly higher in non-survivors than in survivors. Red Cell Distribution Width is an indicator which can vary in sepsis under the influence of TNF-$\alpha$, IFN-$\gamma$, IL-1β, IL-6, the pro inflammatory cytokines which are released during the inflammatory process.[37] These cytokines cause inefficient erythropoiesis resulting in structural and functional changes of erythrocytes with volume variation. This may be accounted for an increased value of RDW.

## 5. Summary and Conclusion

The hospital based case control study was conducted on patients attending department of General medicine in Sardar Patel Medical College Hospital, Bikaner. We have included hospitalized 50 patients with primary and final diagnosis of AECOPD and 50 patients of stable period of COPD. Maximum patients in both groups were found in >60 years age group. The mean age in AECOPD group was 64.62±8.24 and in Stable COPD was 63.22±9.18 years. Maximum patients in both groups were male. Maximum patients in both groups were from middle class followed by lower socio-economic class. BMI(21.37±3.10kg/mt2). Maximum patients in both groups were having cough and breathlessness. Maximum patients in both groups were smoker. 58.00% patients in AECOPD and 30.00% patients in stable COPD group were present. The mean PACK/YR in AECOPD group was 24.44±6.23 and in Stable COPD was 20.66±8.21. Maximum patients in AECOPD group were from mMRC grade 4 and in stable COPD were from mMRC grade 3. Maximum patients in AECOPD group wereere. Mean admission per year were significantly higher in AECOPD patients (1.88±0.80 per year) as compare to stable COPD patients(0.80±0.67 per year). Mean FEV1 % was significantly lower in AECOPD patients (43.87±14.26) as compare to stable COPD patients(48.12±20.18). The difference in both groups was found statistically significant higher in AECOPD (17.60±5.patients (13.80±3.33%). The difference in both groups was found statistically significant.MCV was significantly lower in AECOPD (82.04±1.49) as compare to stable COPD(86.50±1.87). The difference in both groups was found statistically significant RDW was significantly higher in deathed patients (17.52±5.61%). The difference in both groups was found statistically significant. 4.00% hospital mortality in AECOPD group.

## 6. Conclusions

Acute exacerbation of COPD (AECOPD), is one of the most common disease in patients with infections, having frequent hospitalization.

RDW readily available (Available at PHC) and simple parameters, could also be used as a cost-effective marker of inflammation in AECOPD. However, more studies with higher patient series are required in order to highlight the role of RDW in AECOPD patients' response to the treatment and follow-up of exacerbations. But further studies can be conducted to reach better results that can explain the relationship of RDW among patients with COPD

and hospitalized in intensive care unit.

In our study, we have concluded that the mean red cell distribution width on the day of presenting the illness was significantly higher in AECOPD as compare to stable COPD. Those patients who had a high red cell distribution width during admission were associated with poor survival.

## 7. Acknowledgements

None.

## 8. Conflicts of Interests

None.

## 9. Source of Funding

None.

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