Original article

Analysis of red cell distribution width in patients presented with interstitial lung disease

Jiss Ann Francis[1], N.A. Arun[2], Rennis Davis[3], T.A. Ajith[4]

ABSTRACT

Background: Redcell distribution width (RDW) is a prognostic tool of different clinical conditions and a powerful predictor of mortality in elder adults. Increased RDW values were related to underlying chronic inflammation including interstitial lung disease(ILD). RDW as a biomarker to assess the severity of disease in ILD patients was reported. This study was aimed to evaluatethe change in RDW in ILD patients in late stages of the disease.

Methods:A retrospective observational study was conducted among patients who died with ILD. Values of RDW during the later stages of disease (close to and 2 months beforedeath)werecollected from medical records. Variations of RDW in patients with or without smoking habits, occupational exposures, and types of ILD were also studied.Data were statistically analysed.

Results: Forty-two patients died with ILD included. The value of RDW at 2 months before death was 15.4 ±1.8, whereas the valueclose to death was 16.1 ±2.4(p=0.030). The change in RDW values during late stages of ILD is significant. There was no association between RDW value 2 months before death with smoking history(p=0.112) or occupation(p=0.119) or types of ILD(P=0.121). But 86% of people with the smoking history presented with abnormal RDW value (>14.5%) at the time of their first presentation itself.No variation in RDW was found among patients with history of smoking status, occupational exposures, or types of ILD

Conclusion: Increase in RDW was associated with later stages of ILD. Change in RDW value in later stages of can be used as a biomarker for poor survival.

Keywords: Erythropoiesis, interstitial lung disease, prognosis, pneumonia, red cell distribution width

Introduction

The interstitial lung diseases (ILD) are a heterogeneous group of diffuse parenchymal lung disorders eventually resulting in respiratory failure.[1]The diseases are grouped together because of common clinical, roentgenographic,physiologic and pathologic features.[1-4] Most of the patients present with insidious breathlessness and have a diffuse infiltrative pattern on chest roentgenogram.[5] The interstitial diseases are classically included in the restrictive lung disorders: vital capacity is reduced and respiratory flow rates are preserved.[1-3]These diffuse parenchymal lung diseases consist of disorders of known causes such as environmental or drug-related, collagen vascular disease and disorders resulting from unknown causes. ILD with unknown cause include granulomatous lung disorders (e.g. sarcoidosis), idiopathic interstitial pneumonia, Lymphangioleiomyomatosis, pulmonary Langerhans' cell histiocytosis/histiocytosis X and eosinophilic pneumonia.[4]The pathology of these diseases is characterized by inflammatory cellular infiltration and an apparent increase in the connective tissue of alveolar septae; while in some cases there will be inflammatory cells in alveolar airspaces.[5] Many of the interstitial diseases also have diseases of airways, pulmonary vasculature, and sometimes pleural diseases as well.[1,3,4.]

[1]Undergraduate Medical student.
[2]Senior Resident, Department of Pulmonary Medicine.
[3]Professor & HOD. Department of Pulmonary Medicine
[4]Professor, Department of Biochemistry
Amala Institute of Medical Sciences, Thrissur-680 555, Kerala, India.
Corresponding author :
Rennis Davis, Professor and Head,Department of Pulmonary Medicine,
Amala Institute of Medical Sciences,Thrissur-680 555
Kerala, India. Email: rennis@rediffmail.com

Red blood cell distribution width (RDW) is a numerical measurement of the variability in the size of circulating erythrocytes.[6]It is a routine laboratory parameter that indicates the variability in the size of circulating erythrocytes. RDW has been used as a marker in the differential diagnosis of microcytic anaemia. It has been defined as a prognostic tool in different clinical settings such as pulmonary arterial hypertension, congestive heart failure and coronary heart disease.[7-9] It was reported in the general population and older adults that RDW can be used as a powerful predictor of mortality.[10,11] Increased RDW values have been reported to be related to underlying chronic inflammation.[12]Studies connecting the association of RDW with ILD is scant. Recently, Katyal et al. demonstrated that RDW can be used as a biomarker to identify the severity of the disease.[13]Hence,further population-based studies are warranted to establish its role as a biomarker in ILD. This study was aimed to evaluate the variation of RDW values during the later stages of disease among patients who died with ILD.

MATERIALS AND METHODS

Study design and procedure

A retrospectiveobservational study was conducted at the Department of Pulmonary Medicine, Amala Institute of Medical Sciences, Thrissur, Kerala, India. The study was started after receiving approval from the institutional research committee and ethical clearance. ILD was diagnosed by a combination of clinical presentation with physiologic testing, lung imaging using high resolution computed tomography of the chest and lung biopsy.All the patients who were diagnosed with ILD and died in the hospital between the time intervals of January 2014-October 2019 were included in the study. Hospital records of these patients were reviewed and data such as RDW values (before death), smoking status, occupation status and type of ILD were collected.Patients with incomplete records were excluded from the study.The value of RDW 2 months prior and close to death was collected and change in value was analysed. The reference value of RDW was taken as 11.5-14.5% which was considered normal and value> 14.5% was taken as abnormal.

Statistical analysis

Data collected were entered into excel sheets and analysis was done by SPSS software version 23. Non-parametric data were subjected to Chi-square and Fisher's exact test, while the paired t-test was used for quantitative data analysis. pd"0.05 was considered as significant.

RESULTS

Forty-two patients who died with ILD were included in the study. Among the total cases studied, 15/42 (35.7%) had a history of smoking (Figure 1), while 18/42 (42.9%) were exposed to dust from occupation (Table 1).Usual interstitial pneumonia (UIP) is found in 13/42 (30.9%) cases, while non-UIP was found in only 7/42 (16.7%) cases (Table 2). Among the total cases, abnormal RDW was found in 28/42 (66.7%)cases with 15/28 (53.5%)patients had nosmoking history and 13/28 (46.4%) hada smoking history (Table 3). Among the 15 patients with smoking history,13 (86%)were presented with abnormal RDW at the time of their first presentation itself. The distribution of RDW frequency among patients with and without smoking was found to be statistically significant (p=0.040). Frequency distribution of RDW among the 29/42 patients with known occupation risk (smoke or dust) is given in table 4. Among the total 29 cases, 20 (68.1%) cases had abnormal RDW. Distribution of type of ILD and RDW value 2 months before death is depicted in table 5. Majorities of cases belonging to non-UIP (57.1%) with normal RDW values whereas 10/13 (76.9%) UPI patients were presented with abnormal RDW values.

There was no statistically significant association found between either smoking history (p=0.112) or occupation(p=0.119) or types of ILD(p=0.121) with RDW variation 2 months prior to death. The overall value of RDW at 2 months before death was 15.4 ±1.8 and close to death was 16.1 ± 2.4 (Table 6). The change in RDW values among the total cases was statistically significant (p=0.030). However, among the various group, wise cases no statistically significant change in RDW was found between 2 months prior and close to death.This includescases with distribution based on smoking and non-smoking history (Table 7), occupation exposure to dust or occupation exposure to smoke (p>0.05) (Table 8), types of ILD (Table 9).

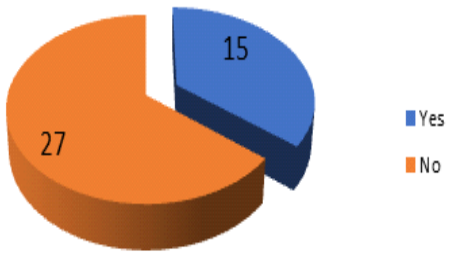

Table 1- Distribution of occupation of patients

Occupation	Frequency	Percent
Exposure to dust	18	42.9
Exposure to occupational smoke	11	26.1
Not available	13	31
Total	42	100

Table 2-Distribution of interstitial lung disease

Type of ILD	Frequency	Percent
UIP(usual interstitial pneumonia)	13	30.9
Non UIP	7	16.7
Not available	22	53.3
total	42	100

Table 3.Distribution of smoking status and RDW-CV value 2 months prior to death

Smoking History	RDW-CV 2 months prior to death		Total
	Normal value (11.5-14.5%)	Abnormal value >14.5%	
Yes	2 (14.2 %)	13(46.4%)	15
No	12(85.7%)	15(53.5%)	27
Total	14(33.3%)	28(66.7%)	42

Chi square test p value =0.040

Table 4.Distribution of occupation and RDW value 2 monthsbefore death

Occupation	RDW-CV 2 month	Prior to death	Total
	Normal value (11.5-14.5%)	Abnormal value >14.5%	
Exposure to dust	5 (55.5%)	13(65.0%)	18
Exposure to occupational smoke	4 (44.4%)	7 (35%)	11
Total	9(31.1%)	20(68.1%)	29

Fishers exact test p value=0.628

Table 5.Distribution of type of ILD and RDW value 2 months prior to death

Type of ILD	RDW-CV value 2 months prior to death		Total
	Normal(11.5-14.5%)	Abnormal >14.5%	
UIP (usual interstitial pneumonia)	3 (42.8%)	10 (76.9%)	13
Non UIP	4(57.1%)	3(23.0%)	7
Total	7 (35%)	13 (65.0%)	20

Fisher's exact test p-value =0.173

Table 6 -Value of RDW variation close to death and 2 months prior to death

Time of detection of RDW	RDW value (%)	P value
RDW -CV value 2 month prior to death	15.4 ±1.9	0.030
RDW –CV value close to death	16.1 ± 2.5	

Values are mean ± SD, n= 42

Table 7-Value of RDW variation close to death and 2 months prior to death in smokers

Cases	Time of detection of RDW	RDW value (%)	P-value
Smokers (n=15)	RDW-CV value close to death	16.7 ± 2.7	0.112
	RDW-CV value 2 months prior to death	15.8 ± 1.9	
Non-smokers (n=27)	RDW-CV- value close to death	15.8 ± 2.3	0.130
	RDW –CV value 2 months prior to death	15.1 ± 1.9	

Table 8-Value of RDW variation close to death and 2 months prior to death in people with exposure smokeand exposure to occupationalto dust

Cases	Time of detection of RDW	RDW	P-value
Exposure to Occupational smoke (n=11)	RDW-CV-close to death	15.9 ± 2.6	0.093
	RDW -CV-2 month prior to death value	15.2 ± 2.5	
Exposure to Dust (n=18)	RDW-CV-close to death	16.3 ± 2.5	0.119
	RDW -CV-2 month prior to death value	15.3 ± 1.7	

Table 9-Value of RDW variation close to death and 2 months prior to death in patients with non-UIP and UIP type of ILD

Type of ILD	Time of detection of RDW	RDW	P-value
Non UIP (n=7)	RDW-CV- value close to death	15.5 ± 2.1	0.428
	RDW -CV- value 2 months prior to death	14.9 ± 1.4	
UIP (usual interstitial	RDW-CV- value close to death	16.1± 2.3	0.121
Pneumonia) (n=13)	RDW -CV- value 2 months prior to death	15.3 ± 1.3	

Discussion

The present study explored the value of RDW in ILD for assessing prognosis.Forty-two patients died with ILD were studied. The value of RDW at 2 months before death was 15.4 ±1.8. The value of RDW close to death was 16.176 ±2.4643(p=0.030). Thus, the change in RDW values during later stages of ILD was found to besignificant. This may probably be due to the terminal ill condition of the patients. There was no association between either smoking history(p=0.112) or occupation(p=0.119) or types of ILD(p=0.121) with RDW. But it was observed that 86% of people with smoking presented with abnormal RDW value(>14.5%) at the time of their first presentation itself.

The most prevalent interstitial diseases are caused by occupational and environmental inhalants.[5]Of these the inorganic dust disease predominate.[5]The organic dust diseases (hypersensitivity pneumonitis) are caused by inhalation of foreign proteins or complex polysaccharides to which the person has been previously sensitized.[5]Nearly 30 clinical organic dust diseases have been defined by either antigen (aspergillosis) or specific environmental exposure (farmers lung).[1,3]. Most antigens are fungal spores, although bacterial animal proteins have been described, recently synthetic organic compounds have been implicated.[3] In this study, 29/42 patients had a history of occupational exposure to dust and smoke.

The ILD is characterized by inflammatory cellular infiltration and an apparent increase in connective tissue. The clinically significant chronic interstitial disease is most common in mixed connective tissue disorder, rheumatoid arthritis and progressive systemic sclerosis. In contrast, interstitial diseases are rare in polymyositis, systemic lupus erythematosis and Sjogren's syndrome.[5]Regardless of the aetiology, majority of the interstitial diseases have common pathogenesis.[1,3] Initially there is some type of injury to lung cells.[5]Many of the known agents are found directly toxic to alveolar or capillary endothelial cells.[5]Other agents cause injury tothe lung through the generation of free radicals in the inflammatory cells.Many of the interstitial diseases of unknown aetiology are associated with alterations in immune mechanism.[5]The organic dust and some drugs injure lung through immune mechanisms.[5]As a result of injury to lung cells, there is an influx of inflammatory and immune effector cells into alveolar septa resulting in alveolitis.[5]The alveolitis will become chronic and structural derangements will result.[1,3]The final common pathway for most interstitial diseases is the end-stage (honeycomb) lung.[5]Injury, alveolitis and repair coexist; fibrosis is a result of the inflammatory and reparative process.[1] Increased RDW can be due to the underlying chronic inflammation which promotes red blood cell membrane deformability and changes in erythropoiesis.[12]

A study conducted by Katyal et al. on RDW as a biomarker of disease severity in ILD patients in 24 patients with ILD were evaluated in whom baseline complete blood count was available.[13]The study demonstrated that CT score was found to be high in subjects with RDW value > 15 whereas cases with RDW >20 had dyspnoea score V. Furthermore, patients with normal RDW (<14%) values had a less CT and dyspnoea scoreswhen compared with those with RDW >15. Thus,RDW can be used as a biomarker to identify the severity of disease or pulmonary compromise in ILD patients.[13]In our study, patients who died withILD were showed significant variation in RDW at the end stages of their life.

A study conducted by Rahimirad et al. in patients with AECOPD in two referral teaching hospitals of East Azerbaijan and West Azerbaijan, Iran found that increased mortality among patients with higher RDW values even after applying the correction for thrombocytopenia, age, leukocyte count, mean corpuscular volume and

anaemia.[14] The study concludes that RDW on admission day found to be a useful indicator to predict in-hospital death in AECOPD.In our study, the patients who died of ILD showed an increase in RDW value close to death than 2 months before death.The prognostic value of RDW is also proved in patients with pulmonary embolism and heart failure.[6,15]Ozsu et al. demonstrated that an elevated RDW was associated with adverse outcomes of heart failure and pulmonary hypertension. The optimal cut-off value of RDW for predicting in-hospital mortality was >15%. The multivariable regression analysis showed RDW remained associated with an increased odd of death (odds ratio: 1.2, 95% CI: 1.1-1.4).

Limitations of the study: Small sample size due to a single centre study is the major limitation of the study. The variations in each type of ILD and demographic patterns need more sample size. Therefore, the study period and sample size need to be augmented for better results. Confounding parameters like co-morbid illness, family history, other blood values (Hb, WBC, Platelet Count etc.) were not included in the study.Furthermore, the dyspnoea indices and CT scoring need to be incorporated along with RDW variation to assess prognosis in ILD in the future.

Conclusion

Increase in RDW was associated with later stages of ILD. Change in RDW value can be used as a biomarker for poor survival in ILD patients. No variation in RDW found among patients with history of smoking status, occupational exposures,or types of ILD. RDW in smokers with ILD showed abnormal high values at the time of first presentation itself.

References

1. Talmadge E King Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases.Am J Respir Crit Care Med. 2005;172(3):268-79.
2. Weinberger SE, Kelman A, Elson NA, Young RC, Reynolds, Fulmer JD, et al. Bronchoalveolar lavage in interstitial lung disease. Ann Intern Med. 1978; 89:459-66
3. Crystal RG, Gadek JE, Ferrans VJ, Fulmer JD, Line BR, Hunningbalce GW. Interstitial lung disease: current conceptsof pathogenesis, staging and therapy. Am J Med

   1981;70:54-67
4. ATS board of Directors and ERS executive committee. American thoracic society/European respiratory society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med.2002;165:277–304.
5. Fulmer JD.The interstitial lung diseases. Chest, 1982;2:172-178.
6. Salvatori M, Formiga F, Moreno-Gonzalez R,Chivite D,De Amicis MM, Cappellini MD, et al. Red blood cell distribution width as a prognostic factor of mortality in elderly patients firstly hospitalized due to heart failure.kardiologia polska.2019;77:632-638.
7. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ.Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol. 2009; 104:868-872
8. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, *et al.*Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail. 2010;16(3):230-238.
9 Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. for the Cholesterol and Recurrent Events (CARE) Trial Investigators.Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation. 2008;117:163-168.
10. Perlstein TS, Weuve J, Pfeffer MA, BeckmanJA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med. 2009;169:588-594.
11. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al.Red cell distribution width and mortality in older adults: a meta-analysis. J GerontolABiol Sci Med Sci. 2010; 65:258-265.
12. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, GuidiGC.Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133:628-632.
13. Katyal R, Janmeja A, Ku V. Red cell distribution width (RDW) as a biomarker of disease severity in ILD patients. Eu Respir J.2015;46:PA3689.
14. Rahimirad S,Ghafari M,Ansarin K,Rashidi F,Rahimi-Rad MH. Elevated red blood cell distribution width predicts mortality in acute exacerbation of copd.Pneumolgia.2016; 65:85-89.