Red blood cell distribution width in Obstructive Sleep Apnea Syndrome and its association with cardiovascular disease

Indice de distribution des globules rouges dans le syndrome d'apnées obstructives du sommeil et son association avec les maladies cardiovasculaires

Souha Kallel, Khouloud Kchaou, Wadii Thabet, Youssef Hbaieb, Bouthaina Hammami, Ilhem Charfeddine

Département d'ORL et de Chirurgie Cervico-faciale -CHU Habib Bourguiba Sfax, University of Sfax. Tunisia

Abstract

Background: Obstructive sleep apnea syndrome (OSAS) is associated with cardiovascular disease (CVD). Red blood cell distribution width (RDW) is reported as a novel marker of cardiovascular disease (CVD) risk. We aimed to investigate the correlation of RDW level with the severity of Obstructive Sleep Apnea Syndrome (OSAS) defined with the apnea–hypopnea index (AHI) and to study the relationship between RDW and CVD in OSAS.

Methods: From retrospective analyses of patients admitted to our department for polygraphy between January 2018 and January 2020, OSAS patients with complete medical records and hemogram analyses were evaluated.

Results: The study population consisted of 160 patients (101 females/59 males). The mean age was 52.32 ± 10.83 years. RDW correlated positively with the apnea hypopnea index (AHI) (r=0.392; p <0.0001) and C-reactive protein (CRP) (r = 0.3, p < 0.001). RDW and CRP were significantly higher in patients with CVD than whom without CVD (p <0.0001). In multivariate analysis, the independent predictors of CVD in OSAS were RDW (p<0.0001; OR=3.095; CI: 1.69-5.66), CRP (p=0.046; OR=1.136; CI: 1.002-1.287) and age (p=0.013; OR=1.085; CI: 1.017-1.157). The cut-off level for RDW with optimal sensitivity and specificity was calculated as 14.45 with sensitivity of 81% and specificity of 75%.

Conclusions: The findings of this study suggest that RDW, a simple, relatively inexpensive and universally available marker could have the ability to predict CVD in OSAS.

Keywords: Apnea-hypopnea index, red blood cell distribution width, obstructive sleep apnea syndrome, cardiovascular disease.

Résumé

Introduction : Le syndrome d'apnées obstructives du sommeil (SAOS) est associé aux maladies cardiovasculaires (MCV). L'indice de distribution des globules rouges (IDR) est rapporté comme un nouveau marqueur de risque des MCV. Notre objectif était d'étudier la corrélation entre le niveau de l'IDR et la sévérité du SAOS et d'étudier la relation entre l'IDR et les MCV dans le SAOS.

Méthodes : Nous avons analysé rétrospectivement les dossiers médicaux des patients admis dans notre service pour polygraphie entre janvier 2018 et janvier 2020. Les patients présentant un SAOS avec un dossier médical et des analyses d'hémogrammes complets ont été retenus.

Résultats : Parmi les patients, 160 étaient inclus dans l'étude (101 femmes/59 hommes). L'âge moyen était de 52,32 ± 10,83 ans. L'IDR était corrélé positivement avec l'index d'apnées hypopnées (IAH) (r=0,392 ; p <0,0001) et la protéine C réactive (CRP) (r=0,3, p < 0,001). L'IDR et la CRP étaient significativement plus élevés chez les patients atteints de MCV que chez ceux sans MCV (p <0,0001). En analyse multivariée, les prédicteurs indépendants de MCV dans le SAOS étaient l'IDR (p<0,0001 ; OR=3,095 ; IC : 1,69-5,66), la CRP (p=0,046 ; OR=1,136 ; IC : 1,002-1,287) et l'âge (p= 0,013 ; OR = 1,085 ; IC : 1,017-1,157). Le seuil d'IDR avec une sensibilité et une spécificité optimales a été calculé à 14,45 avec une sensibilité de 81 % et une spécificité de 75 %.

Conclusion : L'IDR, un marqueur simple, relativement peu coûteux et universellement disponible, pourrait avoir la capacité de prédire les MCV dans le SAOS.

Mots-clés : Index d'apnées-hypopnées, Indice de distribution des globules rouges, syndrome d'apnées obstructives du sommeil, maladie cardiovasculaire.

Correspondance

Souha Kallel
Département d'ORL et de Chirurgie Cervico-faciale -CHU Habib Bourguiba Sfax, / University of Sfax. Tunisia
Email: souha.kallel@yahoo.fr

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by repeated episodes of upper airway obstruction during sleep, which lead to intermittent arterial oxygen desaturation, hypercapnia, arousals, and sleep disruption (1). OSAS has been established as an independent risk factor for the development of cardiovascular events such as coronary artery disease, hypertension and myocardial infraction (2–4). OSAS predisposes to cardiovascular disease (CVD) through several proposed mechanisms : sympathetic excitation, altered vascular regulation, endothelial dysfunction, oxidative stress and chronic systemic inflammation caused by recurrent intermittent hypoxia (5). In addition to the mentioned mechanisms, various conditions associated with OSAS such as obesity and hyperlipidemia increase the risk of CVD (6). Several studies reported that frequency of cardiovascular complications of OSAS increases with severity of the disorder (3). Red blood cell distribution width (RDW), a numerical measure of the size variability of circulating erythrocytes, is known as a possible pathogenic link in CVD. The normal reference range of RDW for human red blood cells (RBCs) is 11% to 15% (7–9). Higher values of RDW reflect greater heterogeneity in the size of RBCs and then more altered blood flow dynamics (10,11). Therefore, RDW is reported as a marker of CVD risk (12).

Considering the association between OSAS and CVD, we aimed to investigate the correlation of RDW level with the severity of OSAS defined with the apnea–hypopnea index (AHI) and to study the relationship between RDW and CVD in OSAS.

METHODS

Design and subjects

Our study was a retrospective study including patients aged 18 years and older, who were admitted to the Department of Otorhinolaryngology-Head and Neck Surgery (January 2018- January 2020) of our hospital and whose diagnosis of OSAS (AHI ≥ 5 per hour of sleep) was confirmed according to the criteria of the American Academy of Sleep Medicine (13–15).

The non-inclusion criteria were as follow: patients who had central sleep apnea syndrome, lung disease with hypoxemia, cerebrovascular disease, anemia defined as hemoglobin (Hb) levels <12.0 g/dL in women and <13.0 g/dL in men (16), chronic renal or hepatic diseases, use of sedatives and muscle relaxants, a history of recent blood transfusion (\2 weeks), and known hematologic disease such as leukemia or myelodysplastic syndrome.

Characteristics of the patients

Demographic characteristics (age, sex, body mass index [BMI], current cigarette smoking status, history of preexisting diseases, and current drug use), sleep history, and medical history, including cardiovascular and metabolic diseases, medication use, and habits were obtained from medical records. CVD referred to hypertension, coronary artery disease, arrythmia, valvopathy or heart failure.

Respiratory polygraphy

All participants underwent a respiratory polygraphy (Nox-T3) over a night period of at least six hours including: measurement of blood oxygen saturation by oximetry and oronasal airflow, quantification of snoring with tracheal sound recording and position analysis. Polygraphy recordings were scored according to the criteria of the American Academy of Sleep Medicine (13–15)

Apnea was defined as complete cessation of airflow at least 10 seconds. Hypopnea was defined as reduction of more than 30% the airflow signal with an associated fall of at least 3% in oxygen saturation. AHI was defined as the number of apneas and hypopneas per hour of sleep. According the American Academy of Sleep Medicine, patients were grouped into three OSAS severity groups based on the AHI: mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI > 30).

Measurement of RDW and C-reactive protein (CRP) levels

Data on CRP levels and blood cell counts at diagnosis, including RDW, were obtained from medical records retrospectively. Blood cell counts were determined using the Beckman Coulter system and CRP levels by Cobas c501 de roche.

Statistical Analysis

Statistical analysis were performed with SPSS version 20.0 software (SPSS Inc, Chicago, Illinois, USA). Simple descriptive statistics such as mean and standard deviation or percentage were calculated for continuous or categorical data. The chi-squared test and the one-way ANOVA test were used to examine the differences in characteristics between the groups. Pearson's correlation analysis was performed to determine the strength of relationship of continuous variables.

A logistic regression analysis model was used to compare the association between independent variables and dependent variables. Logistic regression analysis used CVD as a dependent variable. Receiver operating characteristic (ROC) curves were generated for the RDW using the CVD as a reference. $P < 0.05$ was considered significant.

RESULTS

The study population consisted of 160 patients (101 females/59 males). The mean age was 52.32 ± 10.83 years. Fifty-nine (36,9%) patients had CVD. Thirty-six of them had hypertension, 5 patients had coronary artery disease, 8 patients had arrythmia, 9 patients had heart failure and 1 patient had valvopathy. The median time between OSAS

diagnosis and CVD occurence was 36 months with a minimum of 6 months and a maximum of 120.

Sixty-three patients (39.4%) had mild OSAS, 39 (26.9%) had moderate OSAS, and 58 (58.3%) had severe OSAS. There were no differences in terms of age and sex among all the groups. There were no significant differences among the groups with regard to diabetes mellitus, smoking, and BMI. However, CVD were significantly different among the groups (p=0.007). Demographic and clinical characteristics, polygraphy findings and laboratory variables of the study population stratified by OSAS severity are shown in Table 1.

Table 1. Demographic and clinical characteristics, polygraphy findings and laboratory variables of the study population.

Variables	Mild OSAS group (n=63)	Moderate OSAS group (n=39)	Severe OSAS group (n=58)	p-value
Age (years)	50.92±11.45	53.3±13.28	53.18±7.97	0.420
Sex (Males/Females)	18/45	15/24	26/32	0.175
BMI (kg/m²)	30.11±5.27	32.02±6.18	32.53±5.75	0.094
CVD : n (%)	14 (20.96)	17 (25.8)	28 (45.16)	0.007
Hyperlipidemia : n (%)	11 (29.72%)	8 (18.91)	16 (43.24)	0.39
Diabetes mellitus : n (%)	13 (5.29)	8 (23.52)	12 (35.29)	0.99
Smoking : n (%)	10 (20)	10 (27.5)	17 (42.5)	0.197
AHI	8.64±.09	20.2±4.3	48.56±18.17	<0.001
Lowest saturation (%)	81.68±10.09	81.5±7.59	73.96±9.48	<0.001
Desaturation index	8.28±7.1	17.45±8.24	43.07±19.72	<0.001
Snoring rate (%)	13.76±10.87	23.36±12.52	30.27±16.63	<0.001
RDW (%)	13.8±1.13	14.33±1.3	14.97±1.33	<0.001
WBC (10^9/mm^3)	6,65±1.55	6.58±2.25	7.25±1.71	0.12
Hb (g/dL)	13.2±0.98	1 3.10±1.02	13.38±1.13	0.45
Plt (10^3/mm^3)	231.6±51.85	251.78±5.75	229.58±66.72	0.185
CRP (mg/L)	5.08±4,39	6.35±3.54	8.54±4.57	<0.001

AHI: Apnea Hypopnea Index; BMI: body mass index; CVD: cardiovascular disease; CRP: C-reactive protein; Hb: hemoglobin level; N: number of patients; OSAS: Obstructive sleep apnea syndrome; Plt: platelet count;
RDW: red cell distribution width; WBC: white blood cells.

RDW was significantly different among the groups. In fact, RDW in severe OSAS group was significantly higher than in mild (p<0.0001) and moderate OSAS group (p=0.021). A significant difference in term of RDW was also found between mild and moderate OSAS patients (p=0.034).

Correlation analysis showed a significant correlation between RDW and the AHI (r = 0.39, p < 0.0001 Figure 1), lowest SaO2 (r = - 0.26, p = 0.002), desaturation index (r = 0.396, p < 0.0001), age (r = 0.275, p < 0.0001) and CRP (r = 0.3, p < 0.001) in the study population.

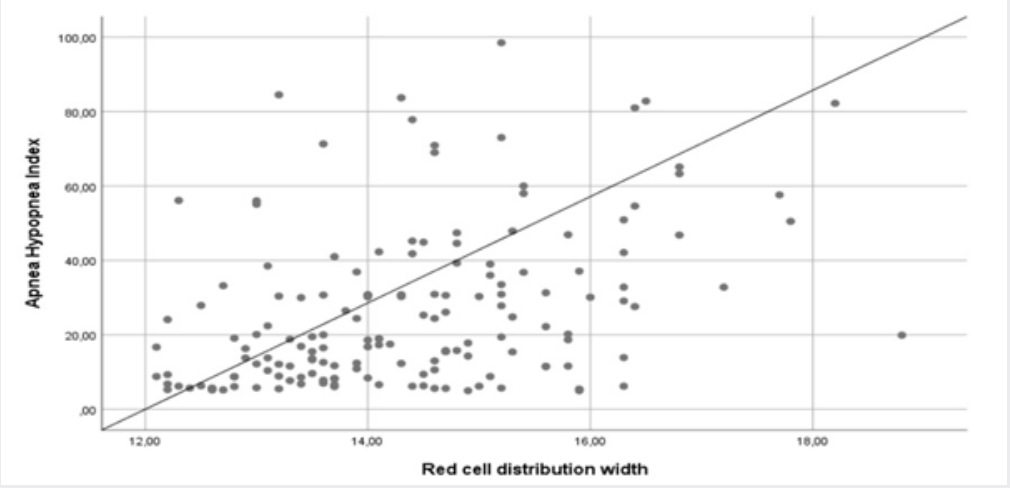

Figure 1. Correlation between Red cell distribution width and Apnea Hypopna index.

When comparing RDW and CRP between OSA patients with CVD (CVDg) [n=59] and without CVD (no-CVDg) [n=101], we found that both RDW (CVDg: 15.45 ± 1.1 vs. no-CVDg: 13.71 ± 1.02; p<0.001) and CRP (CVDg: 9.45 ± 3.81 vs. no-CVDg: 5 ± 4.06; p<0.001) were significantly higher in patients with CVD than those without CVD.

All factors (Sex, age, tobacco consumption, Diabetes mellitus, hyperlipidemia, BMI, AHI, lowest saturation, desaturation index, RDW, CRP) that can determinate CVD were evaluated by univariate analysis. Parameters associated with CVD were therefore introduced in a logistic regression analysis that included RDW, CRP, age, sex, tobacco consumption, hyperlipidemia, diabetes mellitus and BMI. The independent predictors of CVD in OSAS were RDW, CRP and age (Table 2).

Table 2. Risk factors for cardiovascular diseases in patients with obstructive sleep apnea syndrome

Variables	Mild OSAS group (n=63)	Moderate OSAS group (n=39)	Severe OSAS group (n=58)	p-value
Age (years)	50.92±11.45	53.3±13.28	53.18±7.97	0.420
Sex (Males/Females)	18/45	15/24	26/32	0.175
BMI (kg/m²)	30.11±5.27	32.02±6.18	32.53±5.75	0.094
CVD : n (%)	14 (20.96)	17 (25.8)	28 (45.16)	0.007
Hyperlipidemia : n (%)	11 (29.72%)	8 (18.91)	16 (43.24)	0.39
Diabetes mellitus : n (%)	13 (5.29)	8 (23.52)	12 (35.29)	0.99
Smoking : n (%)	10 (20)	10 (27.5)	17 (42.5)	0.197
AHI	8.64±.09	20.2±4.3	48.56±18.17	<0.001
Lowest saturation (%)	81.68±10.09	81.5±7.59	73.96±9.48	<0.001
Desaturation index	8.28±7.1	17.45±8.24	43.07±19.72	<0.001
Snoring rate (%)	13.76±10.87	23.36±12.52	30.27±16.63	<0.001
RDW (%)	13.8±1.13	14.33±1.3	14.97±1.33	<0.001
WBC (10^9/mm^3)	6,65±1.55	6.58±2.25	7.25±1.71	0.12
Hb (g/dL)	13.2±0.98	1 3.10±1.02	13.38±1.13	0.45
Plt (10^3/mm^3)	231.6±51.85	251.78±5.75	229.58±66.72	0.185
CRP (mg/L)	5.08±4,39	6.35±3.54	8.54±4.57	<0.001

BMI: body mass index; CRP: C-reactive protein; CI: confidence interval; RDW: red cell distribution width; N: number of patients.

Using the receiver operator curve analysis, the best RDW to find patients with CVD in OSA was calculated. The area under curve (AUC) was 0.884 (95% confidence interval 0.834-0.934, p < 0.001). The cut-off level for RDW with optimal sensitivity and specificity was calculated as 14.45 with sensitivity of 81% and specificity of 75%. Furthermore, the calculated AUC for the RDW was higher than the AUC for the CRP which was 0.783 (95% confidence interval 0.710-0.856, p < 0.001). (Figure 2)

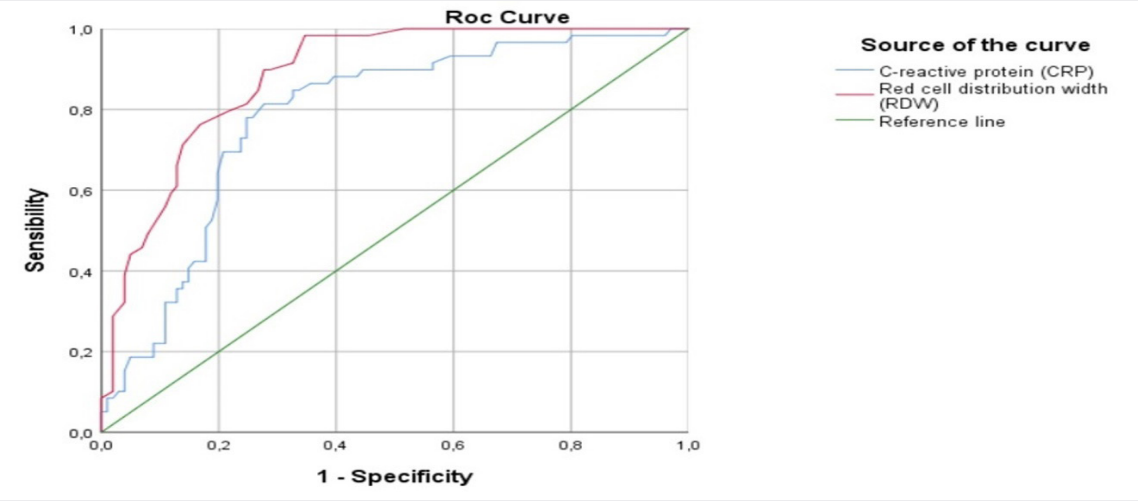

Figure 1. Correlation between Red cell distribution width and Apnea Hypopna index. Figure 2. Receiver-operating characteristic (ROC) analysis for the Red cell distribution width (RDW) and C-reactive protein (CRP) against cardiovascular disease.

CONCLUSIONS

The findings of this study suggest that there is an association between high RDW levels and cardiovascular events in patients with OSAS. Therefore, RDW, a simple, relatively inexpensive, and universally available marker could have the ability to predict CVD in OSAS. To better clarify that issue, further prospective studies are warranted.

REFERENCES

1. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA 2020;323(14):1389.
2. Sforza E, Roche F. Chronic intermittent hypoxia and obstructive sleep apnea: an experimental and clinical approach. Hypoxia 2016; 4: 99–108.
3. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. The Lancet 2005;365(9464):1046–53.
4. Dincer HE, O'Neill W. Deleterious Effects of Sleep-Disordered Breathing on the Heart and Vascular System. Respiration 2006;73(1):124–30.
5. Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J 2009; 33(5):1195–205.
6. Drager LF, Jun J, Polotsky VY. Obstructive sleep apnea and dyslipidemia: implications for atherosclerosis: Curr Opin Endocrinol Diabetes Obes 2010;17(2):161–5.
7. Lappé JM, Horne BD, Shah SH, May HT, Muhlestein JB, Lappé DL, et al. Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. Clin Chim Acta 2011;412(23–24):2094–9.
8. Romero Artaza J, Carbia CD, Ceballo MF, Díaz NB. Red cell distribution width (RDW): its use in the characterization of microcytic and hypochromic anemias. Medicina (Mex) 1999;59(1):17–22.
9. Sökücü SN, Karasulu L, Dalar L, Seyhan EC, Altın S. Can Red Blood Cell Distribution Width Predict Severity of Obstructive Sleep Apnea Syndrome? J Clin Sleep Med [Internet]. 2012 [cited 2019 Sep 6]; Available from: http://jcsm.aasm.org/ViewAbstract.aspx?pid=28671
10. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. J Thorac Dis 2015;7(10):402-411.
11. Shen C-X, Tan M, Song X-L, Xie S-S, Zhang G-L, Wang C-H. Evaluation of the predictive value of red blood cell distribution width for onset of cerebral infarction in the patients with obstructive sleep apnea hypopnea syndrome: Medicine (Baltimore) 2017; 96(29):e7320. DOI: 10.1097/MD.0000000000007320.
12. Isik T, Ayhan E, Tanboga IH, Kaya A, Aksakal E, Kurt M. Is Red Cell Distribution Width a Marker for the Presence and Poor Prognosis of Cardiovascular Disease? Eurasian J Med 2012;44(3):169–71.
13. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017;13(03):479–504.
14. Sateia MJ. International Classification of Sleep Disorders-Third Edition. Chest 2014;146(5):1387–94.
15. Park JG, Ramar K, Olson EJ. Updates on Definition, Consequences, and Management of Obstructive Sleep Apnea. Mayo Clin Proc 2011;86(6):549–55.
16. Domenica Cappellini M, Motta I. Anemia in Clinical Practice—Definition and Classification: Does Hemoglobin Change With Aging? Semin Hematol 2015;52(4):261–9.
17. Harrington AM, Ward PCJ, Kroft SH. Iron Deficiency Anemia, β-Thalassemia Minor, and Anemia of Chronic Disease: A Morphologic Reappraisal. Am J Clin Pathol 2008;129(3):466–71.
18. Arbel Y, Weitzman D, Raz R, Steinvil A, Zeltser D, Berliner S, et al. Red blood cell distribution width and the risk of cardiovascular morbidity and all-cause mortality: A population-based study. Thromb Haemost 2014;111(02):300–7.
19. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red Blood Cell Distribution Width and Mortality Risk in a Community-Based Prospective Cohort. Arch Intern Med 2009;169(6):588.
20. Wen Y. High red blood cell distribution width is closely associated with risk of carotid artery atherosclerosis in patients with hypertension. Exp Clin Cardiol 2010;15(3):37–40.
21. Pahuja M, Shah N, Handa A, Pant S, Agarwal V, Patel N, et al. Red cell distribution width and risk of cardiovascular mortality: insights from NHANES-III. J Am Coll Cardiol 2016;67(13):2019.
22. Ozsu S, Abul Y, Gulsoy A, Bulbul Y, Yaman S, Ozlu T. Red Cell Distribution Width in Patients with Obstructive Sleep Apnea Syndrome. Lung 2012;190(3):319–26.
23. Bergeron C, Kimoff J, Hamid Q. Obstructive sleep apnea syndrome and inflammation. J Allergy Clin Immunol 2005;116(6):1393–6.
24. Sökücü SN, Ozdemir C, Dalar L, Karasulu L, Aydın S, Altın S. Complete blood count alterations after six months of continuous positive airway pressure treatment in patients with severe obstructive sleep apnea. J Clin Sleep Med 2014;10(8):873–8.
25. Lattimore J o-DL, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003;41(9):1429–37.
26. Liu N, Li H, Liu HW, Wang ZQ, Zheng Y. The value of red blood cell distribution width in the evaluation of patients with obstructive sleep apnea hypopnea syndrome. J Clin Otorhinolaryngol Head Neck Surg 2019;33(6):549–52.
27. León Subías E, Gómara de la Cal S, Marin Trigo JM. Ancho de distribución eritrocitaria en apnea obstructiva del sueño. Arch Bronconeumol 2017;53(3):114–9.
28. Wael Alkhiary AMY. The Severity of Obstructive Sleep Apnea Syndrome is related to Red Cell Distribution Width and Hematocrit Values. J Sleep Disord Ther [Internet]. 2015 [cited 2019 Sep 6];04(02). Available from: http://www.omicsgroup.org/journals/the-severity-of-obstructive-sleep-apnea-syndrome-is-related-to-red-cell-distribution-width-and-hematocrit-values-2167-0277-1000192.php?aid=41002
29. Ridker PM. High-Sensitivity C-Reactive Protein: Potential Adjunct for Global Risk Assessment in the Primary Prevention of Cardiovascular Disease. Circulation 2001;103(13):1813–8.
30. Danesh J. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. BMJ 2000;321(7255):199–204.
31. Coman AC, Borzan C, Vesa CS, Todea DA. Obstructive Sleep Apnea Syndrome and the Quality of Life. Med Pharm Rep 2016;89(3):390–5.