Original Article

ISSN: 1735-0344 *Tanaffos 2020; 19(4): 364-370*

TANAFFOS

Clinical Utility of Red Cell Distribution Width in Patients with Pleural Effusion

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Received: 18 January 2020
Accepted: 18 June 2020

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Background: The red cell distribution width (RDW) value has been recently recognized as a valuable biomarker in clinical practice. The RDW value has not been evaluated so far in patients with pleural effusion. Thus, this study aimed to investigate whether RDW could distinguish between exudative and transudative pleural effusions.

Materials and Methods: We measured protein and lactate dehydrogenase levels on both pleural fluids and serum samples from 223 cases and classified them as transudates or exudates based on the classic Light's criteria. We collected blood cell count elements such as RDW from the medical records. We also investigated the correlation between RDW and the nature of pleural effusion.

Results: In 55.2% of the patients, pleural fluid was exudative. Although we found no significant association between RDW and the nature of the pleural fluid, we detected a significantly higher amount of RDW (14.9 ≤) in patients with exudative pleural effusion compared to transudate (66.7% vs. 33.3%; P= 0.01). In this category, neoplastic conditions were mostly observed in the patients (76.3%), followed by pulmonary thromboembolism (21.1%) and systemic lupus erythematous (2.6%).

Conclusion: The findings could not reveal any noticeable correlation between RDW and the Light criteria. However, it appears that elevated RDW levels give insights into the valuable nature of RDW in different conditions such as neoplastic diseases.

Key words: Erythrocyte Indices; Red Blood Cell Distribution Width; Pleural Effusion; Exudates; Transudates; Malignant Pleural Effusion

INTRODUCTION

The first step to evaluate the cause of pleural effusion is to determine the nature of effusions as transudates or exudates. In contrast to transudative pleural effusion, exudative effusion always requires further diagnostic investigations and, occasionally, an invasive diagnostic procedure, because it is the result of local pleural or pulmonary pathologic conditions (1, 2).

Exudative and transudative pleural effusions can be discriminated if they meet one or more of the Light's criteria (3) (pleural fluid protein divided by serum protein is >0.5, pleural fluid lactate dehydrogenase (LDH) divided by serum LDH is >0.6, pleural LDH above two-thirds of the normal upper limit of serum LDH). In Heffner's meta-analysis (4), pleural fluid protein above 2.9 g/dl, pleural fluid LDH above the 0.45 normal upper limit of serum, and pleural fluid cholesterol above 45 mg/dL were described for exudative pleural effusion.

Some clinicians investigated other biochemical parameters as alternative criteria. These parameters

include alkaline phosphatase, creatine kinase, uric acid, C-reactive protein, and pro-brain natriuretic peptide with different cut-off points.

Recently, significant attention has been paid to the red cell distribution width (RDW) value as a novel predictor in several clinical settings such as congestive heart failure (5), coronary artery disease (6), carotid atherosclerosis (7), peripheral artery disease (8), and cerebrovascular accidents (9). Moreover, the red cell distribution width (RDW) value has been defined as a predictive value in the mortality rate of hip fracture (10, 11), pancreatitis (12), acute kidney injury (13), hemodialysis (14), necrotizing fasciitis (15), infective endocarditis (16), sepsis (17), and even organophosphate poisoning (18).

However, the higher rate of mortality has been revealed in relation with higher RDW and some pulmonary diseases such as lung cancer (19, 20), pulmonary hypertension (21), pulmonary embolism (22, 23), acute dyspnea (24), community-acquired pneumonia (25), and chronic obstructive pulmonary diseases (COPD) (26).

To the best of our knowledge, no study has assessed the correlation between RDW and the nature of pleural effusion. Thus, in this study, we intended to investigate whether RDW could distinguish exudative pleural effusions from transudative ones.

MATERIALS AND METHODS

Study population

We conducted this cross-sectional study on 231 patients with pleural effusion admitted to the Imam Reza Hospital, a tertiary academic hospital affiliated to the Tabriz University of Medical Sciences, from January 2015 to December 2016. After acquiring approval from the Medical Ethics Committee (Approval ID: TBZMED.REC.1394.1205) and obtaining informed consent, we selected patients with pleural effusion above 18 years of age undergoing diagnostic thoracentesis for the evaluation of underlying diseases. We collected detailed demographic, clinical, and laboratory data for each patient, and then, obtained simultaneous specimens for biochemical parameters from pleural fluid and blood samples.

We excluded eight patients from the study due to non-definitive diagnosis, obvious hemothorax secondary to trauma, hematological disorders, or diuretic treatment prior to thoracentesis. We then classified the effusions of the remaining 223 cases as transudates or exudates based on the classic Light's criteria (3).

Laboratory measurements

After thoracentesis, we performed the following analyses on the pleural effusion samples including pleural fluid cell count and differential cell count, pleural fluid protein, and pleural fluid LDH (P. LDH). Simultaneously, a blood sample was obtained to determine leukocyte count, hemoglobin level, mean corpuscular volume, red cell distribution width (RDW), platelet count, mean platelet volume, total serum protein (S. Pro), and lactate dehydrogenase (S. LDH). Subsequently, the pleural fluid to serum LDH ratio and the pleural fluid to serum protein ratio were calculated to determine whether pleural effusion was either exudative or transudative.

Additionally, a pleural fluid sample was sent for routine microbiologic (Gram staining, and acid-fast bacilli) and cytological examination. Further examinations, such as pleural biopsy, thoracoscopy, or diagnostic thoracotomy, were performed as required in patients for whom the pleural effusion etiology was not determined.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) and median. The mean differences of qualitative and quantitative variables were analyzed using a Chi-square test and an independent sample t-test in the data with normal distribution and a Mann–Whitney U-test in the data without normal distribution, respectively.

RDW was used to determine cut-off points to the highest possible level of accuracy and precision in a receiver operating characteristic (ROC) curve to assess the discriminating performance of RDW to separate exudative pleural effusions from transudative ones. Spearman's coefficient correlation was used to detect the correlation between the quantitative variables. The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0 (Chicago, IL, USA) and the parameters were considered significant if P-value ≤ 0.05.

RESULTS

We enrolled 223 patients with a mean age of 61.05 ± 16.83 years (ranging from 24 to 84 years) including 119 (53.4%) males and 104 (46.6%) females. The etiology of

pleural effusions is shown in Table 1. According to the Light's criteria, 100 patients (44.8%) had transudative pleural effusion and 123 patients (55.2%) had exudative pleural effusion.

Table 1. The baseline characteristics of biochemical markers

Variables	All patients	Transudate	Exudate	P value
P. Pro				
mean ± SD	3.38±0.83	2.53±0.39	6.23±25.54	<0.001
median	3.4	2.61	4.02	
S. Pro				
mean ± SD	5.16±0.74	5.38±0.76	5.02±0.70	0.001
median	3.4	5.45	5.2	
P/S Pro				
mean ± SD	0.66±0.15	0.47±0.03	0.77±0.05	<0.001
median	0.73	0.46	0.77	
P. LDH				
mean ± SD	364.59±292.13	152.89±22.97	493.38±305.21	<0.001
median	285	154	375	
S. LDH				
mean ± SD	503.69±375.21	355.54±325.02	607.38±367.57	<0.001
median	365	295	450	
P/ S LDH				
mean ± SD	0.71±0.43	0.50±0.06	0.84±0.51	<0.0001
median	0.75	0.52	0.80	
HB				
mean ± SD	12.54±2.10	12.57±1.59	12.52±2.44	0.86
median	12.4	12.3	12.6	
MCV				
mean ± SD	83.74±7.17	84.55±8.62	83.09±5.68	0.12
median	83	84	82	
RDW				
mean ± SD	13.23±2.01	13.15±1.76	13.30±2.20	0.59
median	13	13	12.80	
PLT *10^3				
mean ± SD	284±42	244.03±26	317.58±51	0.19
median	212	198.50	215	
MPV				
mean ± SD	11.26±1.24	11.32±1.27	11.22±1.22	0.59
median	11.8	11.80	11.70	
WBC*10^3				
mean ± D	9.78±5.10	7.43±4.57	11.69±4.70	<0.001
median	8.35	7.15	11.7	

P: Pleural; S, Serum; Pro: Protein; LDH: Lactate Dehydrogenase; HB: Hemoglobin; MCV: Mean Corpuscular Volume; RDW: Red Cell Distribution; WBC: Wight Blood Cell; PLT: Platelet; MPV: Mean Platelet Volume

The mean age difference was significant between the transudative (66.00 ± 16.9 years) and exudative (57.03 ± 15.67 years) groups ($P < 0.001$).

The baseline characteristics of biochemical markers are summarized in Table 1. In this study, we obtained the mean ± SD of the biochemical markers in serum and compared them in two types of pleural fluid. We found no significant differences concerning RDW between exudative pleural effusion and transudative effusion (Table 1).

Though, we detected high RDW levels above median in exudative pleural effusions. Figure 1 shows that the median RDW between first (Q_1) and third (Q_3) quartile the median value for RDW in all patients was 13% (Q_1-Q_3: 11.9-14.9%) in all the patients. The patients were divided into three groups based on RDW ranges (the lowest RDW range ≤ 11.9%, the middle 50% RDW range 12-14.8%, and the highest RDW range ≥ 14.9%). Table 2 shows the frequency distribution in different RDW ranges, separately in transudative and exudative pleural effusions. In this categorization, we noticed a significantly higher amount of RDW (14.9% ≤) in patients with exudative effusion than in those with transudative pleural effusion (66.7% vs. 33.3%; P=0.01).

Table 2. Frequency distribution in different RDW ranges

RDW ranges	All patients	Transudative PE	Exudative PE
Q_1 : ≤11.9	59	22(37.3%)	37(62.7%)
Q_2-Q_3: 12-14.8	107	59(55.1%)	48(44.9%)
Q_4 : 14.9≤	57	19(33.3%)	38(66.7%)

RDW: Red Cell Distribution Width; PE: Pleural Effusion; Q: Quarter

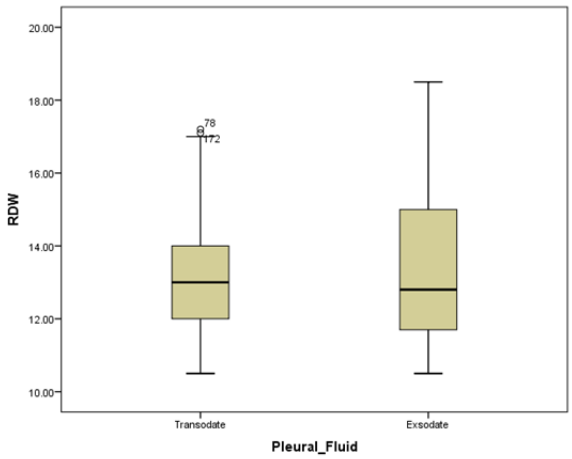

Figure 1. Median RDW values in transudate and exudate pleural effusion

In the exudative pleural effusion group, in terms of etiology, neoplastic conditions (76.3%), followed by pulmonary thromboembolism (PTE, 21.1%) and systemic lupus erythematosus (2.6%), were observed in patients with RDW≥14.9%, as shown in Figure 2. Of the 35 patients with neoplastic conditions, 82.9% had RDW ≥ 14.9% and the remaining 17.1% had RDW under 14.9%.

Even though, according to ROC curve analysis, the area under the curve for RDW was 0.50 (*P*=0.94, 95%CI=0.42-0.57, Figure 3), we noticed that RDW had no accuracy to distinguish exudative pleural effusion from transudative effusion.

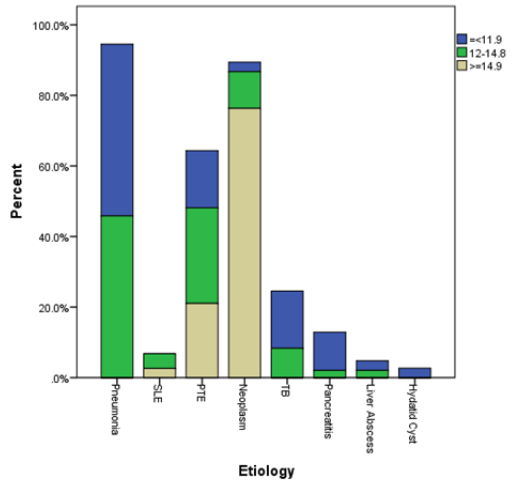

Figure 2. Stacked Bar Chart by RDW Quartile based on etiology in patients with Exudative pleural effusion

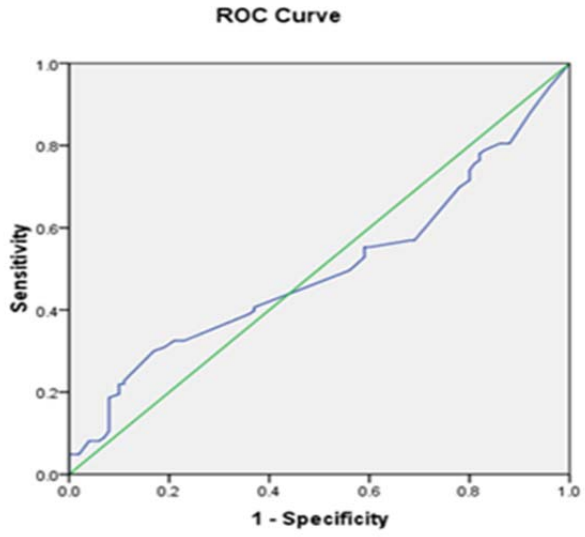

Figure 3. Receiver operating characteristic (ROC) curve and the area under curve (AUC) of RDW

We assessed the correlation between the laboratory blood parameters and the pleural fluid parameters and found significant correlation between RDW with S. LDH, P. LDH, and S. Pro (Table 3).

Table 3. The bivariate Spearman correlation between blood and pleural fluid parameters

Variables		HB	MCV	RDW	WBC	PLT	MPV
P. Pro	Correlation Coefficient	0.116	-0.04	-0.09	0.45	0.18	0.04
	P Value	0.10	0.57	0.18	<0.001	0.008	0.49
S. Pro	Correlation Coefficient	0.25	0.24	-0.24	-0.03	0.08	0.17
	P Value	<0.001	0.001	<0.001	0.62	0.24	0.01
P/S Pro	Correlation Coefficient	-0.04	-0.21	0.03	0.43	0.17	-0.03
	P Value	0.56	0.003	0.62	<0.001	0.01	0.63
S. LDH	Correlation Coefficient	-0.30	-0.24	0.28	0.31	-0.03	-0.15
	P Value	<0.001	0.001	<0.001	<0.001	0.63	0.02
P. LDH	Correlation Coefficient	-0.28	-0.28	0.25	0.39	0.03	-0.17
	P Value	<0.001	<0.001	<0.001	<0.001	0.61	0.01
P/S LDH	Correlation Coefficient	-0.01	-0.21	-0.02	0.44	0.17	0.01
	P Value	0.84	0.002	0.70	<0.001	0.01	0.87

P: Pleural; S, Serum; Pro: Protein; LDH: Lactate Dehydrogenase; HB: Hemoglobin; MCV: Mean Corpuscular Volume; RDW: Red Cell Distribution; WBC: Wight Blood Cell; PLT: Platelet; MPV: Mean Platelet Volume

DISCUSSION

RDW is a biomarker for variability in the size of red blood cells and has been used in the differential diagnosis of anemia, hemolysis, blood transfusion, or ineffective erythropoiesis. RDW is associated with several mechanisms that inhibit the maturation of erythrocyte in relation with erythropoietin and also inflammatory cytokines, especially in Interleukin-6 levels (27).

In this study, we hypothesized that RDW might be a noninvasive method for distinguishing exudative effusion from transudative pleural effusion. Since a complete blood count test is routinely performed on patients admitted to the hospital and is rather inexpensive, it might yield valuable information. Recently, high RDW has been considered as a biomarker of adverse outcomes in numerous acute and chronic conditions including thromboembolic events (28), cardiovascular diseases (29), and respiratory diseases (30). Thus, it was a good idea to

identify a novel marker and a noninvasive method that may improve clinical decision making in distinguishing exudates from transudates.

In a pulmonary setting, Rahimirad et al. (31) noticed that higher RDW values were associated with increased in-hospital mortality in patients with the acute exacerbation of COPD (odds ratio: 2.31).

Lee et al. (32) enrolled patients with pneumonia and reported that RDW was associated with 30-day mortality, the length of hospital stay, and the use of vasopressors in hospitalized patients. High RDW is correlated with an increased mortality rate and it is a better prognostic indicator than N-terminal–pro–B-type natriuretic peptide (NT-pro-BNP) in patients with pulmonary hypertension (21).

In a study on patients with acute PTE, the optimal cut-off value of RDW to predict early mortality was >14.6% and RDW appeared to help the risk stratification of patients with acute PTE (23). This cut-off is in accordance with our findings about high RDW (>14.9%) in patients with PTE as a cause of exudative pleural effusion, although the mortality rate of PTE was not the focus of the current study.

Koma et al. (20) reported that higher RDW values were significantly associated with higher clinical cancer stage and poorer prognosis compared to lower RDW values. Although we did not determine the correlation between tumor stage and prognosis with RDW, in line with Koma et al.'s study, we found an elevated RDW value in patients with the neoplastic condition as a prominent result of our study.

A large sample cohort study reported a non-significant correlation between RDW and venous thromboembolism in patients with newly cancer diagnosis but high RDW was found to be a significant predictor of mortality (33).

Ideal diagnostic markers should be highly specific, sensitive, inexpensive, and noninvasive. Thus, we attempted to find a quick and accurate biomarker to distinguish various types of pleural effusion. In other studies, RDW was used as an independent predictor of adverse outcomes. However, in the current study, RDW was used as a diagnostic marker, which is the major difference of our study with others.

This prospective cross sectional study had some limitations. We noticed that most of the patients in the higher quartile of RDW (Q_4) in exudative pleural effusion had neoplastic conditions probably due to inflammatory cytokines. However, we did not study other factors such as anemia, transfusion status, iron, vitamin B12, or folate deficiencies that may affect the RDW level. Thus, these findings encourage further studies with large sample sizes to examine the effect of RDW levels on various causes in this population.

CONCLUSION

Although this study's findings cannot demonstrate any correlation between RDW and the nature of pleural effusion, it appears that elevated RDW levels give suggestions to clinicians about the major role of RDW in predicting different aspects of conditions such as neoplastic diseases.

Acknowledgment

The authors would like to express their special thanks bronchoscopy ward staff.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Funding Support

No funding was received for this study.

REFERENCES

1. Karkhanis VS, Joshi JM. Pleural effusion: diagnosis, treatment, and management. ***Open Access Emerg Med*** 2012;4:31-52.
2. Porcel JM. Chest Tube Drainage of the Pleural Space: A Concise Review for Pulmonologists. ***Tuberc Respir Dis (Seoul)*** 2018;81(2):106-115.
3. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: the diagnostic separation of transudates and exudates. ***Ann Intern Med*** 1972;77(4):507-13.

4. Heffner JE, Brown LK, Barbieri CA. Diagnostic value of tests that discriminate between exudative and transudative pleural effusions. Primary Study Investigators. ***Chest*** 1997;111(4):970-80.
5. Dai Y, Konishi H, Takagi A, Miyauchi K, Daida H. Red cell distribution width predicts short- and long-term outcomes of acute congestive heart failure more effectively than hemoglobin. ***Exp Ther Med*** 2014;8(2):600-606.
6. Khaki S, Mortazavi SH, Bozorgi A, Sadeghian S, Khoshnevis M, Mahmoodian M. Relationship Between Red Blood Cell Distribution Width and Mortality of Patients with Acute Myocardial Infarction Referring to Tehran Heart Center. ***Crit Pathw Cardiol*** 2015;14(3):112-5.
7. Wonnerth A, Krychtiuk KA, Mayer FJ, Minar E, Wojta J, Schillinger M, et al. Red cell distribution width and mortality in carotid atherosclerosis. ***Eur J Clin Invest*** 2016;46(2):198-204.
8. Ye Z, Smith C, Kullo IJ. Usefulness of red cell distribution width to predict mortality in patients with peripheral artery disease. ***Am J Cardiol*** 2011;107(8):1241-5.
9. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. ***J Neurol Sci*** 2009;277(1-2):103-8.
10. Garbharran U, Chinthapalli S, Hopper I, George M, Back DL, Dockery F. Red cell distribution width is an independent predictor of mortality in hip fracture. ***Age Ageing*** 2013;42(2):258-61.
11. Lv H, Zhang L, Long A, Mao Z, Shen J, Yin P, et al. Red Cell Distribution Width as an Independent Predictor of Long-Term Mortality in Hip Fracture Patients: A Prospective Cohort Study. ***J Bone Miner Res*** 2016;31(1):223-33.
12. Wang D, Yang J, Zhang J, Zhang S, Wang B, Wang R, et al. Red cell distribution width predicts deaths in patients with acute pancreatitis. ***J Res Med Sci*** 2015;20(5):424-8.
13. Oh HJ, Park JT, Kim JK, Yoo DE, Kim SJ, Han SH, et al. Red blood cell distribution width is an independent predictor of mortality in acute kidney injury patients treated with continuous renal replacement therapy. ***Nephrol Dial Transplant*** 2012;27(2):589-94.
14. Vashistha T, Streja E, Molnar MZ, Rhee CM, Moradi H, Soohoo M, et al. Red Cell Distribution Width and Mortality in Hemodialysis Patients. ***Am J Kidney Dis*** 2016;68(1):110-21.
15. Weng CL, Wang CH, Chen IC, Hsiao KY, Chang KP, Wu SY, et al. Red cell distribution width is an independent predictor of mortality in necrotizing fasciitis. ***Am J Emerg Med*** 2014;32(10):1259-62.
16. Guray Y, Ipek EG, Guray U, Demirkan B, Kafes H, Asarcikli LD, et al. Red cell distribution width predicts mortality in infective endocarditis. ***Arch Cardiovasc Dis*** 2014;107(5):299-307.
17. Lorente L, Martín MM, Abreu-González P, Solé-Violán J, Ferreres J, Labarta L, et al. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. ***PLoS One*** 2014;9(8):e105436.
18. Kang C, Park IS, Kim DH, Kim SC, Jeong JH, Lee SH, et al. Red cell distribution width as a predictor of mortality in organophosphate insecticide poisoning. ***Am J Emerg Med*** 2014;32(7):743-6.
19. Warwick R, Mediratta N, Shackcloth M, Shaw M, McShane J, Poullis M. Preoperative red cell distribution width in patients undergoing pulmonary resections for non-small-cell lung cancer. ***Eur J Cardiothorac Surg*** 2014;45(1):108-13.
20. Koma Y, Onishi A, Matsuoka H, Oda N, Yokota N, Matsumoto Y, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. ***PLoS One*** 2013;8(11):e80240.
21. 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(6):868-72.
22. Abul Y, Ozsu S, Korkmaz A, Bulbul Y, Orem A, Ozlu T. Red cell distribution width: a new predictor for chronic thromboembolic pulmonary hypertension after pulmonary embolism. ***Chron Respir Dis*** 2014;11(2):73-81.
23. Zorlu A, Bektasoglu G, Guven FM, Dogan OT, Gucuk E, Ege MR, et al. Usefulness of admission red cell distribution width as a predictor of early mortality in patients with acute pulmonary embolism. ***Am J Cardiol*** 2012;109(1):128-34.

24. Hong N, Oh J, Kang SM, Kim SY, Won H, Youn JC, et al. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. ***Clin Chim Acta*** 2012;413(11-12):992-7.
25. Braun E, Kheir J, Mashiach T, Naffaa M, Azzam ZS. Is elevated red cell distribution width a prognostic predictor in adult patients with community acquired pneumonia? ***BMC Infect Dis*** 2014;14:129.
26. Seyhan EC, Özgül MA, Tutar N, Ömür I, Uysal A, Altin S. Red blood cell distribution and survival in patients with chronic obstructive pulmonary disease. ***COPD*** 2013;10(4):416-24.
27. Li N, Zhou H, Tang Q. Red Blood Cell Distribution Width: A Novel Predictive Indicator for Cardiovascular and Cerebrovascular Diseases. ***Dis Markers*** 2017;2017:7089493.
28. Bucciarelli P, Maino A, Felicetta I, Abbattista M, Passamonti SM, Artoni A, et al. Association between red cell distribution width and risk of venous thromboembolism. ***Thromb Res*** 2015;136(3):590-4.
29. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. ***J Thorac Dis*** 2015;7(10):E402-11.
30. Epstein D, Nasser R, Mashiach T, Azzam ZS, Berger G. Increased red cell distribution width: A novel predictor of adverse outcome in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease. ***Respir Med*** 2018;136:1-7.
31. Rahimirad S, Ghafari M, Ansarin K, Rashidi F, Rahimi-Rad MH. Elevated red blood cell distribution width predicts mortality in acute exacerbation of COPD. ***Pneumologia*** 2016;65(2):85-9.
32. Lee SM, Lee JH, Kim K, Jo YH, Lee J, Kim J, et al. The clinical significance of changes in red blood cell distribution width in patients with community-acquired pneumonia. ***Clin Exp Emerg Med*** 2016;3(3):139-147.
33. Riedl J, Posch F, Königsbrügge O, Lötsch F, Reitter EM, Eigenbauer E, et al. Red cell distribution width and other red blood cell parameters in patients with cancer: association with risk of venous thromboembolism and mortality. ***PLoS One*** 2014;9(10):e111440.