Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

Emergency Medicine

Red Cell Distribution Width in Predicting 30-Day Mortality in Acute Pulmonary Embolism Patients

Erkman SANRI[1*], Sinan KARACABEY[1], Arzu DENIZBASI[1]
Department of Emergency Medicine, Marmara University Pendik Education and Research Hospital, Istanbul, Turkey

Original Research Article

***Corresponding author**
Erkman SANRI

Article History
Received: 07.05.2018
Accepted: 15.05.2018
Published: 30.05.2018

DOI:
10.36347/sjams.2018.v06i05.027

Abstract: Risk stratification methods for guiding the diagnosis and prognosis of APE is essential for selecting treatment modalities. It was shown that RDW correlates with ischemic events. In this study, our primary aim is to investigate the predictive significance of RDW for 30-day mortality in APE patients. We also aim to investigate the diagnostic significance of RDW in patients with APE. We reviewed medical records of 237 patients including; red blood cell distribution width, hemoglobin, hematocrit, platelet distribution width values, platelet counts, *mean platelet volume* counts and pulmonary computed tomography scan results. Mortality was defined as mortality in 30 days after APE diagnosis and caused by APE. Two hundred twenty-nine patients were enrolled. The study population was consisted of 116 (50.3%) patients in APE group and 113 (49.3%) patients in control group. The AUC of RDW for mortality was 0.648 (95%CI, 0.566-0.730, p=.042). The sensitivity and the specificity for mortality were 78.85% and 41.81% respectively when the optimal cut-off value of RDW was set to 15%. We found that RDW is a simple and useful tool for predicting 30-day mortality in APE patients. We also found that RDW is a significant diagnostic tool for APE.
Keywords: Acute pulmonary embolism, Hemogram parameters, Computed tomography, RDW, MPV.

INTRODUCTION

Pulmonary embolism (PE) is a pulmonary circulation disorder caused by the occlusion of the pulmonary artery and the third most common cardiovascular cause of hospital admission [1]. Acute pulmonary embolism (APE) have high mortality rates despite improvements in diagnostic and treatment modalities [2]. Risk stratification methods for guiding the diagnosis and prognosis of APE is essential for selecting treatment modalities. Recent studies showed that presence of right ventricular dysfunction shows the risk classification for APE patients [3]. But echocardiography is not always available in the emergency departments (ED). In the literature, there are several studies about biochemical markers for diagnosis and assessment of prognosis in APE such as d-dimer, cardiac troponins and brain natriuretic peptide [3, 4]. These biomarkers reported to have poor sensitivity, and they are not available in all emergency departments. Hemogram parameters were studied for diagnosis of APE because it was inexpensive and faster.

Red cell distribution width (RDW) is one of the hemogram parameters that measures the variability in size of red blood cells [5]. In the literature, it was shown that RDW correlates with ischemic events [6]. Ozsu *et al*. [7] showed RDW can predict mortality in PE and Celik *et al.* [8] found that RDW can be considered as a diagnostic tool for acute APE. There are limited studies showed RDW for use in diagnosis and assessment of prognosis in APE.

In this study, we aimed to investigate the predictive significance of RDW for 30-day mortality in APE patients. We also aim to investigate the diagnostic significance of RDW in patients with APE.

METHODS

This retrospective cohort study was conducted in a tertiary care university hospital emergency department (ED). After obtaining the ethical committee approval (ID=09.2017.272), medical records of all patients between April 2015 and April 2017, who underwent contrast-enhanced thoracic computed tomography (CT) scans due to attending physician's pre-diagnosis for APE were analyzed. Written

informed consent was not necessary since institutional ethics committee waived the need for obtaining written informed consent from patients due to the retrospective nature of this study. All patients who were older than 18 years of age were included. Patients with missing data in their records were excluded. A total number of 237 patient records were reviewed, and 229 patients were enrolled. Enrolled patients were divided into two groups: APE group and Non-APE group (control group), depending on their final diagnosis. The definitive diagnosis was achieved according to both the ICD-10 (International Statistical Classification of Diseases and Related Health Problems-10th revision) codes and the results of contrast-enhanced thoracic CT scans. Patients who had both positive ICD-10 code and CT scan result for APE were enrolled into APE group. Patients with either negative ICD-10 code or negative CT scan result for APE were enrolled into the control group.

All demographics, blood count values, comorbidities and contrast-enhanced thoracic CT scan results were recorded. Blood count results were consisted of hemoglobin (Hgb) levels (g/dL), hematocrit (Hct) values (%), platelet counts (PC) counts ($x10^3$/uL), platelet distribution width (PDW) values (%), *mean platelet volume* (MPV) counts (fL) and red blood cell distribution width (RDW) values (%). All blood counts were measured by a hematology analyzer (Beckman Coulter -LH 780, Beckman Coulter Inc, and Brea, CA). The normal reference ranges for Hgb level, Htc value, *platelet volume*, *PDW*, MPV, RDW used were 12-17 g/dL, 36-50 %, 150-440 $x10^3$/uL, 9.0-17.9 %, 7.4-11.6 fL, 11.6-16.5 %, respectively. Contrast-enhanced thoracic CT scans were performed by a 128 Slice CT Scanner (Siemens Somatom Definition AS, Siemens AG, Germany). Mortality was defined as mortality in 30 days after APE diagnosis and caused by APE. All mortalities and the cause of mortalities were scanned and confirmed according to National Death Reporting System (NDRS). Deceased patients with other causes of death (e.g., trauma) were included, but they were not analyzed in mortality group.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to express the normality of the distribution of continuous variables. Continuous data are presented as median value and interquartile range (IQR), with non-parametric analyses being used to assess differences. Kruskal- Wallis test and $\chi 2$ test were used to assess differences. The analysis for prognostic and diagnostic cutoff value was based on receiver operating characteristic (ROC) curve and calculated by taking the maximum Youden's index (sensibility + specificity -1) as standard. The area under the curve (AUC) was calculated.

Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), negative predictive value (NPV) and positive predictive value (PPV) for APE diagnosis and mortality were calculated for chosen cut-off values. Univariate regression analysis was performed to estimate the relationship between RDW and APE. SPSS 20.0 for Windows (SPSS, Chicago, IL, USA) was performed for statistical analysis. $P<0.05$ was considered as significant.

RESULTS

A total number of 237 patients were included in this study. Eight patients were excluded due to the missing data in their medical records, and 229 patients were enrolled. The final study population consisted of 116 (50.3%) patients in APE group and 113 (49.3%) patients in control group. Hundred and fifteen (50.2%) of all the study population was female, and the median (IQR) age was 66.0 (54.0, 74.0). Both groups were similar regarding baseline demographic characteristics including age, gender and comorbid diseases (Table 1).

The comparison of laboratory characteristics of the study population is shown in Table 1. The median (IQR) RDW value was 15.7 (14.3, 18.2). The median RDW value of APE group was significantly higher than control group (16.0; 15.1, p=.009, respectively). The differences of Hgb, Hct, Plt, MPV, and PDW values between two groups were insignificant.

In table 2, the difference of hemogram parameters for 30-day mortality is presented. The median (IQR) RDW value of deceased patients was 17.0 (15.1, 19.8) and 15.3 (14.1, 17.4) in not deceased patients. The difference between two groups was statistically significant (p=.001). We found no significant difference in other hemogram parameters between these two groups.

ROC curves of RDW values for predicting APE diagnosis and mortality were analyzed (Fig. 1 and 2). The AUC of RDW for APE diagnosis was 0.599 (95%CI, 0.526-0.673, p=.009) and 0.648 (95%CI, 0.566-0.730, p=.042) for mortality. The optimal cut-off value of RDW for 30-day mortality was set as 15%, and for APE diagnosis it was set as 14.8%. Sensitivity, specificity, PLR, NLR, NPV and PPV for APE diagnosis and mortality were calculated for chosen cut-off values (Table 3). And in table 4, the univariate logistic regression analysis of RDW for the diagnosis and mortality of APE is shown.

Table-1: Characteristics of the patients with APE and without APE

1. Index	2. APE (n=116)	3. Non-APE (n=113)	4. Total (n=229)	5. P
Age, median (IQR)	6. 68.0 (55.3, 74.8)	7. 64.0 (53.0, 73.0)	8. 66.0 (54.0, 74.0)	9. .055
Female, n (%)	10. 56 (47.9)	11. 59 (52.7)	12. 115 (50.2)	13. .466
Comorbidities, n (%)	14.	15.	16.	17.
Any comobidity	18. 100 (86.2)	19. 98 (86.7)	20. 198 (86.5)	21. .909
HT	22. 39 (33.3)	23. 25 (22.3)	24. 64 (27.9)	25. .063
DM	26. 26 (22.2)	27. 15 (13.4)	28. 41 (17.9)	29. .081
CAD	30. 17 (14.5)	31. 17 (15.2)	32. 34 (14.8)	33. .890
CHF	34. 18 (15.4)	35. 10 (8.9)	36. 28 (12.2)	37. .136
CRF	38. 8 (6.8)	39. 4 (3.6)	40. 12 (5.2)	41. .268
Ischemic Stroke	42. 9 (7.7)	43. 3 (2.7)	44. 12 (5.2)	45. .089
COPD	46. 27 (23.1)	47. 15 (13.4)	48. 42 (18.3)	49. .058
DVT	50. 0 (0.0)	51. 1 (0.9)	52. 1 (0.4)	53. .306
Operation	54. 17 (14.5)	55. 8 (7.1)	56. 25 (10.9)	57. .073
Malignency	58. 25 (21.4)	59. 34 (30.4)	60. 59 (25.8)	61. .120
62. Laboratory Values, Median (IQR)		63.	64.	65.
Hgb (g/dL), n=229	66. 11.5 (9.9, 13.1)	67. 12.0 (10.3, 13.7)	68. 11.8 (10.1, 13.2)	69. .472
Hct (%), n=229	70. 36.0 (31.7, 40.5)	71. 36.7 (32.0, 41.5)	72. 36.2 (31.8, 41.0)	73. .645
Plt (x10^3/uL), n=229	74. 227.5 (173.3, 288.3)	75. 245 (192, 313.5)	76. 236.0 (181.5, 293.0)	77. .322
RDW (%), n=229	78. 16.0 (14.8, 18.5)	79. 15.1 (14, 17.4)	80. 15.7 (14.3, 18.2)	81. .009
MPV (fL), n=229	82. 8.2 (7.6, 9.0)	83. 8.3 (7.5, 9.0)	84. 8.3 (7.5, 9.0)	85. .664
PDW (%), n=229	86. 17.1 (16.7, 18.0)	87. 17.1 (16.7, 17.6)	88. 17.1 (16.7, 17.7)	89. .379

QR: Interquartile range, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary arterial disease, CHF: Congestive heart failure, CRF: Chronic renal failure, COPD: *Chronic Obstructive Pulmonary Disease, DVT: Deep venous trombosis*, Hgb: Hemoglobin, Hct: Hematocrit, Plt: Platelet, RDW: Red blood cell distribution width, MPV: *Mean platelet volume, PDW: Platelet distribution width*

Table-2: Comparison of the Laboratory Characteristics of the patients for 30-day Mortality

Laboratory Values 90. Median (IQR)	**91. Deceased (n=52)**	**92. Not-Deceased (n=177)**	**93. P**
Hgb (g/dL), n=229	94. 11.2 (9.5,13.0)	95. 12.1 (10.4, 13.5)	96. .061
Hct (%), n=229	97. 34.0 (29.7,39.4)	98. 37.0 (32.3, 41.6)	99. .089
Plt (x10^3/uL), n=229	100. 212.0 (150.0, 286,8)	101. 240.0 (189.0, 295.5)	102. .452
RDW (%), n=229	103. 17.0 (15.1, 19.8)	104. 15.3 (14.1, 17.4)	**105. .011**
MPV (fL), n=229	106. 7.9 (7.3, 8.7)	107. 8.3 (7.7, 9.0)	108. .192
PDW (%), n=229	109. 17.2 (16.8, 18.2)	110. 17.1 (16.7, 17.6)	111. .347

IQR: Interquartile range, Hgb: Hemoglobin, Hct: Hematocrit, Plt: Platelet, RDW: Red blood cell distribution width, MPV: *Mean platelet volume, PDW: Platelet distribution width*

Table-3: The Optimal Cutoff Values of RDW for the Diagnosis and 30-day Mortality of APE

	RDW>14.8 for Diagnosis		RDW>15.0 for 30-day Mortality	
Index	Value	95% CI	Value	95% CI
Sensitivity	76.72%	67.97-84.07 (%)	78.85%	65.30-88.94 (%)
Specificity	41.59%	32.40-51.24 (%)	41.81%	34.45-49.44 (%)
Positive LR	1.31	1.09-1.58	1.35	1.12-1.64
Negative LR	0.56	0.38-0.83	0.51	0.29-0.88
Positive PV	57.42%	52.84-61.87 (%)	28.47%	24.80-32.45 (%)
Negative PV	63.51%	53.95-72.12 (%)	87.06 %	79.47-92.12 (%)

CI: Confidential interval, LR: Likelihood ratio, PV: Predictive value, RDW: Red blood cell distribution width

Table-4: Univariate Logistic Regression Analysis for the Diagnosis and Mortality of APE

Index	Regression Coefficient	Wald	P	OR	95% CI
RDW for Diagnosis	0.082	3.566	.059	1.085	0.997-1.181
RDW for Mortality	0.127	7.545	**.006**	1.135	1.037-1.243

OR: Odds ratio, CI: Confidential interval, RDW: Red blood cell distribution width

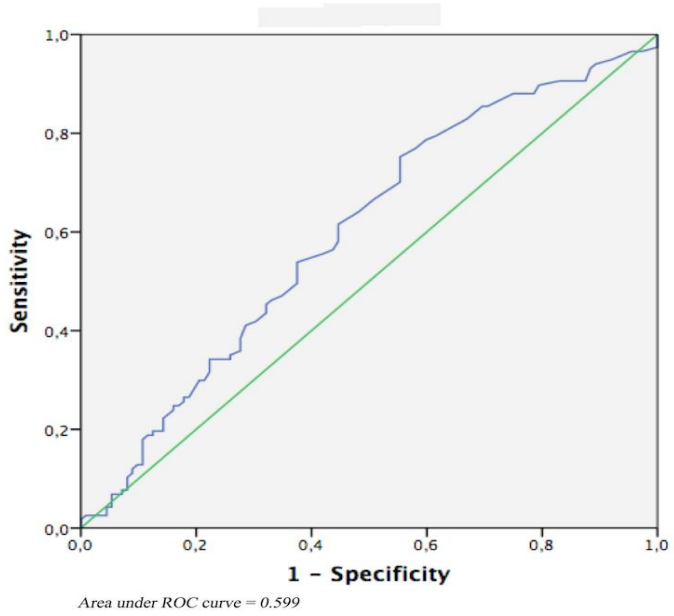

Fig-1: ROC for RDW predicting APE diagnosis

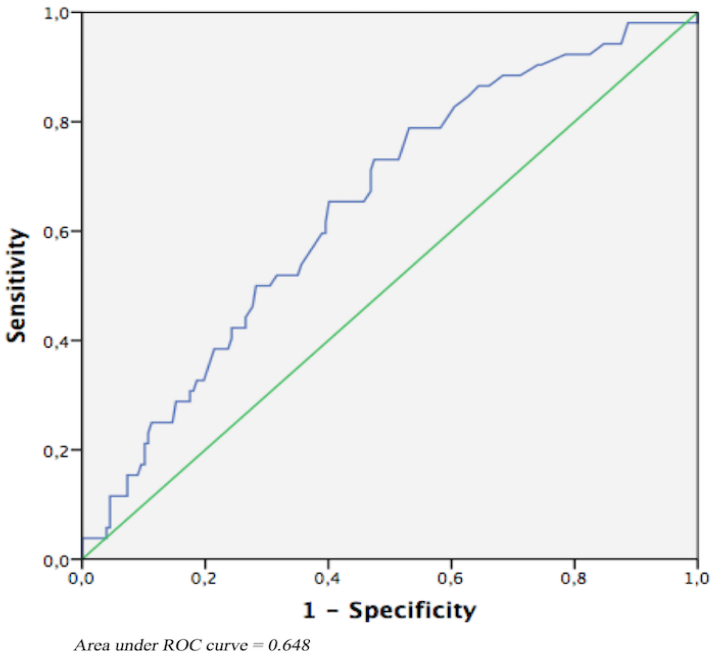

Fig-2: ROC for RDW predicting 30-day mortality in APE patients

DISCUSSION

Acute pulmonary embolism (APE) is a serious disease with a mortality rate of %15-20, and early diagnosis and management of APE are essential [2, 9]. In recent years, there has been a search for a simple and fast diagnostic and prognostic tool. Recent studies have evaluated RDW values for its significance in predicting the diagnosis and/or the prognosis of pulmonary embolism [7, 8, 10-14]. These studies reported that increased RDW values are associated with higher significance in predicting diagnosis and/or prognosis of APE.

In this study, we found that RDW values were significantly higher in deceased patients when compared to non-deceased patients. According to our results, RDW is a useful indicator in predicting 30-day mortality in patients with APE, with an AUC of 0.648 (95%CI, 0.566-0.730, p=.042) and an optimal cut-off value of RDW for predicting mortality of 15%. Ozsu *et al*. [7] also stated that high RDW levels to be an

independent predictor of in-hospital mortality in patients with APE, with an AUC of 0.649 (95% CI, 0.584-0.715). The cutoff value of RDW was 15%. The results of this study were similar to our findings.

In recent studies, Zhou *et al*. [10], Sen *et al*. [11] and Zorlu *et al*. [12] also found that high RDW values associated with higher mortality rates in APE patients, with an AUC of 0.6646 (95% CI, 0.5585-0.7518), 0.646 (95% CI, 0.557-0.736) and 0.734 (95%CI, 0.646-0.822), respectively. The reported sensitivity and specificity values of RDW for predicting mortality in these studies were 52.2%, 79.2%, 95.2% and 87.8%, 55.6%, 53% respectively. Our results were similar to these studies. But the definition of mortality (30-day, 100-day, 40-day, respectively) and the cut-off values of RDW for predicting mortality (16%, 16.25%, 14.6%, respectively) differed between our study and these three studies which explain the differences in sensitivities and the specificities between these studies and our study.

Our secondary objective was to evaluate RDW values in predicting the diagnosis of APE. We found that the median RDW value was significantly higher in APE group when compared to non-APE group (16.0, 15.1, p=.009). According to our findings, RDW is a useful indicator for predicting APE diagnosis, with an AUC of 0.648 (95%CI, 0.566-0.730, p=.042). Wang *et al*. [13] stated that increased RDW values can be used as a diagnostic tool in chronic pulmonary embolism (CPE), with an AUC of 0.815 (95CI, 0.734–0.895, p = 0.000) for RDW. They reported 82.1% sensitivity and 71.4% specificity with a cut-off value of 13.05% for RDW in diagnosing CPE. Although the Wang *et al*. set a lower cutoff value, they reported higher values of sensitivity and specificity when compared to our study. This difference may be that they evaluated RDW values in diagnosing CPE patients, whereas we assessed APE patients. In their recent study, Celik *et al*. [8] also found RDW to be a useful diagnostic tool for APE patients. They reported an AUC of 0.559 (95CI, 0.495–0.622, p = 0.1091), 20.7% sensitivity and 93.4% specificity in predicting the diagnosis of APE with a cut-off value of 18.9% for RDW. Our results were similar to their findings, but Celik *et al*. set a higher cutoff value of RDW, which explains the differences in sensitivity and specificity between the two studies.

In recent studies, other hemogram parameters were also evaluated regarding their significance for diagnosis and prognosis in APE [15-18]. In our study, we found that MPV, Hgb, Hct, and PDW are insignificant tools for predicting diagnosis and/or mortality in APE patients (Table 1,2).

All our findings and all the data reported by these studies support that RDW is a useful indicator for predicting mortality and diagnosis in APE. But the potential mechanisms that can be held responsible for the relation between increased RDW values and APE are unknown. On the other hand; RDW was reported to be in association with the inflammatory process of inflammation in pulmonary arterial hypertension (IPAH) [19]. It has also been shown that increased levels of inflammatory molecules are independent predictors for survival in IPAH[20]. Therefore, inflammation is one of the potential mechanisms responsible for the relation between the increased RDW values and APE. In addition to this; oxidative stress, which leads to increased RDW values by increasing anisocytosis, may be the potential mechanism[21]. Nonetheless, the pathophysiological mechanisms remain unknown.

LIMITATIONS

All patient comorbidities were analyzed from medical records. Since this is a retrospective study, we didn't have the chance to determine whether the patients with those comorbidities were under treatment or not, prior to their admission to ED. If there were any comorbidities which were not treated, the mortality rate might have increased in APE patients. But we don't think that this limitation affects our results since evaluating comorbidities was not our objective.

CONCLUSIONS

APE is a severe disease with the high mortality rate, and early diagnosis and management are vital in most cases. We found that RDW is a simple and useful tool and it is an independent predictor for 30-day mortality in APE patients. We also found that RDW is a significant diagnostic tool for APE. The mechanisms responsible for the relation between increased RDW values and APE is unclear. Further prognostic studies are needed to be established.

REFERENCES

1. Giuntini C, Di Ricco G, Marini C, Melillo E, Palla A. Epidemiology. Chest. 1995;107(1):3S-9S.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). The Lancet. 1999 Apr 24;353(9162):1386-9.
3. Torbicki A. (Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology) Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J. 2008;29:2276-315.
4. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based

clinical practice guidelines. Chest. 2008;133(6):454S-545S.
5. Evans TC, Jehle D. The red blood cell distribution width. The Journal of emergency medicine. 1991;9:71-4.
6. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. The American journal of cardiology. 2010;105(3):312-7.
7. Ozsu S, Abul Y, Gunaydin S, Orem A, Ozlu T. Prognostic value of red cell distribution width in patients with pulmonary embolism. Clin Appl Thromb Hemost. 2014;20(4):365-70.
8. Celik A, Ozcan IT, Gündes A, Topuz M, Pektas I, Yesil E, Ayhan S, Kose A, Camsari A, Cin VG. Usefulness of admission hematologic parameters as diagnostic tools in acute pulmonary embolism. The Kaohsiung journal of medical sciences. 2015 Mar 1;31(3):145-9.
9. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107(23 Suppl 1):I22-30.
10. Zhou XY, Chen HL, Ni SS. Red cell distribution width in predicting 30-day mortality in patients with pulmonary embolism. J Crit Care. 2017;37:197-201.
11. Sen HS, Abakay O, Tanrikulu AC, Sezgi C, Taylan M, Abakay A, Kaya H, Senyigit A. Is a complete blood cell count useful in determining the prognosis of pulmonary embolism? Ist ein komplettes Blutbild bei der Beurteilung der Prognose einer Pulmonalembolie nützlich?. Wiener klinische Wochenschrift. 2014 Jun 1;126(11-12):347-54.
12. Zorlu A, Bektasoglu G, Guven FM, Dogan OT, Gucuk E, Ege MR, Altay H, Cınar Z, Tandogan I, Yilmaz MB. Usefulness of admission red cell distribution width as a predictor of early mortality in patients with acute pulmonary embolism. American Journal of Cardiology. 2012 Jan 1;109(1):128-34.
13. Wang W, Liu J, Yang YH, Zhai ZG, Wang C, Wang J. Red cell distribution width is increased in chronic thromboembolic pulmonary hypertension. Clin Respir J. 2016;10(1):54-60.
14. Yazıcı S, Kırış T, Sadık Ceylan U, Terzi S, Uzun AO, Emre A, Yeşilçimen K. Relation between dynamic change of red cell distribution width and 30-day mortality in patients with acute pulmonary embolism. The clinical respiratory journal. 2018 Mar;12(3):953-60.
15. Hilal E, Neslihan Y, Gazi G, Sinan T, Zeynep Ayfer A. Does the mean platelet volume have any importance in patients with acute pulmonary embolism? Wien Klin Wochenschr. 2013;125(13-14):381-5.
16. Huang J, Chen Y, Cai Z, Chen P. Diagnostic value of platelet indexes for pulmonary embolism. Am J Emerg Med. 2015;33(6):760-3.
17. Varol E, Icli A, Uysal BA, Ozaydin M. Platelet indices in patients with acute pulmonary embolism. Scand J Clin Lab Invest. 2011;71(2):163-7.
18. Araz O, Albez FS, Ucar EY, Kerget B, Yilmaz N, Akgun M. Predictive Value of Mean Platelet Volume for Pulmonary Embolism Recurrence. Lung. 2017;195(4):497-502.
19. Rhodes CJ, Wharton J, Howard LS, Gibbs JS, Wilkins MR. Red cell distribution width outperforms other potential circulating biomarkers in predicting survival in idiopathic pulmonary arterial hypertension. Heart. 2011;97(13):1054-60.
20. Soon E, Holmes AM, Treacy CM, Doughty NJ, Southgate L, Machado RD, Trembath RC, Jennings S, Barker L, Nicklin P, Walker C. Elevated levels of inflammatory cytokines predict survival in idiopathic and familial pulmonary arterial hypertension. Circulation. 2010 Aug 31;122(9):920-7.
21. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. Arch Intern Med. 2009;169(5):515-23.