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Retrospective Analysis of the Impact of Seasonal Factors, Laboratory Data, and Risk Scoring on The Prognosis of Patients With Pulmonary Thromboembolism

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Abstract: *New markers are still needed in the diagnostic and prognostic monitoring of pulmonary thromboembolism. The study was conducted retrospectively in a single center at a tertiary education and research hospital emergency clinic. We used clinical, demographic and laboratory data of the cases. Out of 541 cases, 234 (43.3%) were male, with a mean age is 64.6±15.8 years. It was observed that PTE cases were most frequent during the winter season. In 95.6% of the cases, embolism was present in the segmental branch. Low atmospheric pressure was significantly higher in PTE cases with mortality. Patients with hypotension at the admission time and during follow-up, as well as those with RV/LV >1, had significantly higher mortality rates. The rates of MPV and RDW were significantly higher in patients who ended up with mortality compared to those who survived. Our study revealed that PTE cases most commonly presented during the winter season, and low atmospheric pressure had an adverse effect on the prognosis. Besides hematological parameters such as MPV and RDW, hypotension at admission time and a right ventricular diameter greater than the left ventricular diameter were also identified as negative prognostic indicators.*

Keywords - *Pulmonary Thromboembolism, MPV, RDW, Hypotension, RV/LV Ratio*

I. INTRODUCTION

Pulmonary thromboembolism (PTE) is a serious cardiovascular disease with high mortality and morbidity rates. The annual death incidence of PTE is reported to be 60-70/100.000. (1) Currently, Spiral CT pulmonary angiography is stil used as the gold Standard for the diagnosis of PTE. However, considering the side effects related to radiation exposure and the cost implications, there is still a need for new parameters in the diagnosis and prognos is evaluation of PTE.

The RDW is a measure of erythrocyte size as well as an index of erythrocyte heterogeneity, typically combined with leukocyte volume, in determining the underlying cause of anemia. RDW is an easy, inexpensive, and routinely reported test, and its evaluation can provide important diagnostic and prognostic information in patients with cardiovascular and thrombotic disorders. (2)

In literature, MPV has been considered as an indicator of platelet functions and activation. (3-5) Due to the increased activity of larger platelets, MPV is regarded as an indicator of increased risk for cardiovascular disease in the general population. Some studies in the literature have reported that MPV is a good prognostic marker for thromboembolic diseases. (3-5)

The relationship between environmental factors and PTE is among the topics that attracted the interest of the literature recently. Inaddition to numerous studies demonstrating the association between PTE and seasonal variations, there are also studies investigating the impact of parameters such as atmospheric pressure, humidity, windspeed, and temperature on the occurrence and prognosis of the disease. (6-9)

In this study, the effects of meteorological, epidemiological, clinical, and laboratory parameters on PTE were investigated.

II. MATERYAL AND METHODS

Patients who underwent spiral computed tomography (CT) and spiral CT pulmonary angiography (CTPA) with a preliminary diagnosis of PTE at the Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Hospital were included in the study. The study was initiated after obtaining approval from the ethics committee. Following the ethical approval, data were retrospectively collected from the hospital automation system. Patients with missing data were partially or completely excluded from the study. Patients who were diagnosed with PTE based on the results of spiral CT angiography were evaluated within the scope of their search.

The study included adult patients who were diagnosed with PTE and under went both spiral CT and spiral CTPA. Patients with missing data, those diagnosed with a pathology other than PTE, those who did not undergo spiral CT and Spiral CTPA, those whose follow-up was not completed, and cases under the age of 18 were excluded from the study. Out of the initially identified 1045 patients, 181 patients were excluded from the study due to the lack of spiral CTPA results and/or the in ability to perform the test despite the request for examination. Additionally, 323 out of the remaining 864 patients were excluded from the study as they received a diagnosis other than PTE. The study was conducted with a total of 541 cases.

Application dates, addresses, age and gender, vital parameters, laboratory findings, and spiral CTPA results of the patients were recorded in the previously created study form. According to the addresses of the patients, the temperature, humidity, wind speed, and atmospheric pressure values on the admission date were obtained from the general directorate of meteorology. In the CTPA, the right ventricle (RV) and left ventricle (LV) diameters were measured by finding the longest distance perpendicular to the long axis of the heart between the endocardiumand the interventricularseptum. Then, the RV diameter was divided by the LV diameter to calculate the RV/LV ratio.

Serum D-dimer levels were studied by Siemens BCS-XP, with the immunoturbidimetric method. CT and CTPA examinations were performed by administering FOV: 35 cm, section thickness: 3 mm, pitch: 2 and i.v. 120 ml of contrast material.

Statistical Analysis

Data analysis was done with SPSS program version 15.0. Kolmogorov Smirnov test was used to evaluate whether the distributions of continuous and discrete variables were normal. Variables were expressed as mean ± standard deviation (SD) or median (min-max).

While the Student T Test was used to compare the quantitative variables between two different groups that did not fit the normal distribution; Mann Whitney U Test was used to compare the quantitative variables with normal distribution. Pearson Chi-Square and Fisher's Exact Test were used to compare two different groups.

ROC Curve analysis was used to determine the diagnostic value of MPV and RDW to determine mortality in PTE cases. In these patients, the optimum cut-off value and the sensitivity and specificity values obtained based on this value, together with the area under the curve (AUC) were determined.

The success of detecting the predictors of RDW and MPV on mortality in PTE cases was evaluated by Multiple Logistic Regression analysis after adjusting for all other comparator factors. Any variable with a univariate test p-value <0.25, along with all variables of known clinical significance, was considered a candidate for the multivariate model. Probability ratios and 95% confidence intervals were also calculated for each independent variable.

A p<0.05 value was accepted for statistical significance.

III. RESULTS

Out of the total 541 patients included in the study, 234 (43,3%) were male, with a mean age is 64.6±15.8 years, ranging from 18 to 91 years.

It was observed that 197 (36.4%) of the included patients applied most frequently during the winter season (December, January, and February). There was no significant relationship between temperature, wind, humidity, and PTE prognosis. However, low atmospheric pressure was significantly higher in PTE cases with mortality (p=0.020) (Table 1).

In spiral CTPA examinations, main pulmonary artery involvement was observed in 26 (4.8%) patients, segmental branch involvement in 517 (95.6%) patients, and subsegmental branch involvement in 136 (25.1%) patients. Mortality was observed in 35 (6.5%) of 541 patients. When comparing patients with mortality to those who survived, no significant differences were found in terms of age, gender, and the affected vessel (Table 2). However, when comparing the Wells scores calculated from the clinical and laboratory data of the cases, it was noted that patients with high Wells scores had significantly higher mortality rates compared to those with low and intermediate Wells scores (p<0.001) (Table 2).

Mortality was found to be significantly higher in patients with hypotension at admission and during follow-up, and in patients with RV/LV >1 (p<0.001 for both parameters). The rate of MPV and RDW was found to be significantly higher in patients who ended up with mortality compared to those who survived (p=0.007 and p=0.009, respectively) (Table 3).

The accuracy of the predictive power in predicting the prognosis for the 8.45 cut-off value of MPV in PTE cases was 58.4% (AUC=0.636, 95% CI=0.532-0.740, p=0.007). The accuracy of the predictive power of RDW in predicting prognosis for a cut-off value of 15.55 in PTE cases was 69.0% (AUC=0.632, 95% CI=0.517-0.747, p=0.009) (Table 4, Figure 2).

In the logistic regression analysis, where we examined the independent effects of all factors that could be effective in the prognosis, hypotension (p<0.001), MPV>8.45 (p=0.004), RDW>15.55 (p<0.001), and RV/LV>1 (p=0.004) parameters were statistically significant (Table 5).

IV. FIGURES AND TABLES

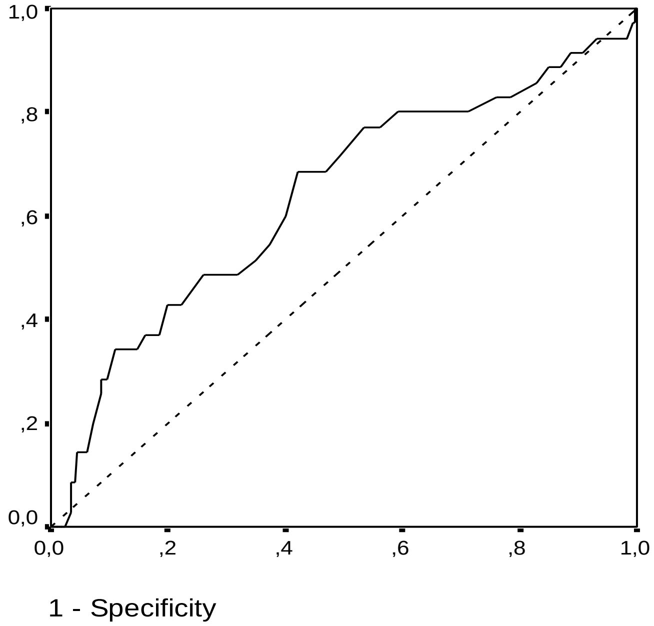

Figure 1. ROC Curve for MPV Measurements in Differentiating Survivors from Mortal PTE Cases

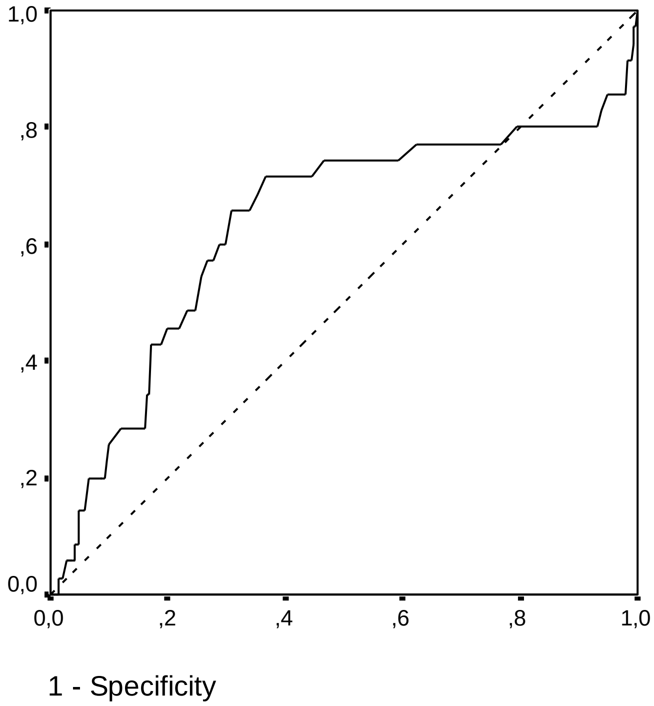

Figure 2.ROC Curve for RDW Measurements in Differentiating Survivors from Mortal PTE Cases

Table 1. Seasonal Characteristics by Prognosis in PTE Patients

Variables	Surviving(n:506)	Exitus (n:35)	p-value
Temperature	12 (-19 – 35)	17 (-9 – 35)	0,183
Wind	9 (0 – 44)	11 (2 – 30)	0,474
Humidity	55 (15 – 100)	51 (16 – 100)	0,286
Pressure	1015 (1000 – 1031)	1014 (1002 – 1029)	0,020
Season			0,272
Winter	187 (%37,0)	10 (%28,5)	
Spring	142 (%28,0)	8 (%22,9)	
Summer	105 (%20,8)	8 (%22,9)	
Autumn	72 (%14,2)	9 (%25,7)	

Table 2. Age, Gender, Involved Vessel Branch, D-dimer and Wells Scores by Prognosis in PTE Patients

Variables	Surviving (n:506)	Exitus (n:35)	p-value
Age	64,4±15,9	67,7±13,8	0,246
Gender			0,173
Male	215 (%42,5)	19 (%54,3)	
Female	291 (%57,5)	16 (%45,7)	
MainPulmonary	25 (%4,9)	1 (%2,9)	1,000
Segmental Branch	483 (%95,5)	34 (%97,1)	1,000
Subsegmental Branch	130 (%25,7)	6 (%17,1)	0,260
D-dimer	1705,5 (190,0-10000,0)	2864,7 (638,0-8320,6)	0,176
Wells			≤0,001
Low	90 (%17,8)	3 (%8,6)	
Medium	274 (%54,1)	11 (%31,4)	
High	142 (%28,1)	21 (%60,0)	

Tablo 3. Hypotension, Right VentricularWidth and CardiacTroponin Positivity, MPV and RDW Levels by Prognosis in PTE Patients

Variables	Surviving (n:506)	Exitus (n:35)	p-value
Hypotension	96 (%19,0)	20 (%57,1)	≤0,001
RV/LV >1	274 (%54,2)	30 (%85,7)	≤0,001
Troponin-I Positive	182 (%36,0)	17 (%48,6)	0,135
MPV	8,2 (5,7-15,8)	8,8 (6,0-10,8)	0,007
RDW	14,5 (10,1-30,3)	16,2 (10,1-21,3)	0,009

Table 4. ROC Analysis Results and Diagnostic Performance Levels of MPV and RDW Measurements in Differentiating Survivors and Exitus in PTE Patients

Indicators	Definitions	MPV	RDW
Area Under theCurve		0,636	0,632
%95ConfidenceInterval		0,532-0,740	0,517-0,747
p-value		0,007	0,009
Optimal cut-off value		>8.45	>15.55
Number of Cases	N	541	541
Sensitivity	TP/(TP+FN)	24/35 (%68,6)	23/35 (%65,7)
Specificity	TN/(TN+FP)	292/506 (%57,7)	350/506 (%69,2)
PPV	TP/(TP+FP)	24/238 (%10,1)	23/179 (%12,8)
NPV	TN/(FN+TN)	292/303 (%96,4)	350/362 (%96,7)
Accuracy	(TP+TN)/(N)	316/541 (%58,4)	373/541 (%69,0)
p-value		0,002	<0,001

TP: True Positive, FN: False Negative, TN: True Negative, FP: False Positive, PPV: Positive Predictive Value, NPV: Negative Predictive Value.

Table 5. Investigation of All Possible Risk Factors That May Be Effective in Differentiating Survivors and Exitus Cases in PTE Patients According to Multivariate Logistic Regression Analysis

Variables	Odds Ratio	%95 Confidence Interval		Wald	p-value
		Lower limit	*Upper limit*		
Age	1,001	0,975	1,028	0,005	0,945
Male Factor	1,257	0,567	2,788	0,316	0,574
Temperature	1,032	0,993	1,073	2,511	0,113
Pressure	0,924	0,853	1,001	3,715	0,054
D-dimer	1,000	1,000	1,000	1,277	0,259
Hypotension	4,662	1,830	11,875	10,412	<0,001
Wells – Medium	0,677	0,164	2,797	0,290	0,590
Wells – High	1,185	0,267	5,257	0,050	0,823
MPV>8.45	3,364	1,478	7,659	8,354	0,004

RDW>15.55	4,514	1,942	10,495	12,262	<0,001
RV/LV>1	4,504	1,618	12,535	8,304	0,004
Troponin-I Positive	1,454	0,664	3,180	0,877	0,349

V. DISCUSSION

In our study, it was found that the development of PTE showed variations according to seasons and months, and the prognosis was influenced by low barometric pressure, hypotension, right ventricular diameter, and hematological parameters such as MPV and RDW.

In our study, the prognostic significance of shock and hypotension in acute PTE was obtained primarily from observational publications such as ICOPER and the MAPPET registry. (10,11) Post hoc analysis of ICOPER data revealed that the 90-day all-cause mortality rate was 52.4% in patients with systolic blood pressure (SBP) <90 mmHg and 14.7% in normotensive patients. (10) Based on MAPPET data, a decrease in SBP of at least 40 mmHg lasting at least 15 minutes or systemic potency defined as SBP <90 mmHg is considered to carry a relatively lower risk compared to shock. (11) In our study, the incidence of hypotension was significantly higher in patients who had died.

In a meta-analysis study, patients with echocardiographic evidence of right ventricular dysfunction were found to be twice as likely to die from PTE. (12) Two studies have shown that the ecocardiography predicts risk in patients with normotensive PTE. (13,14) The sensitivity of right ventricular dysfunction in such patients is 56-61% and is associated with a 4-5% absolute increase in PTE-related early mortality. (12) Furthermore, in most reported series, mortality from PTE in patients with normal echocardiographic findings is less than 1%. (13) Use of spiral CT allows assessment of right ventricular size ratio, but does not provide direct information about RV function. Identifying the longest minoraxes of the RV and LV by CT requires visualization of the respective thoracic horizontal planes. Of 120 patients with confirmed PTE and stable at baseline, 58% had a RV/LV ratio of .1.0 and a positive predictive value (PPV) of 10% for PTE-related 30-day mortality. (15) In our results, RV/LV>1 was found in 85.7% (n=30) of patients who developed mortality, and this finding was statistically significant in predicting prognosis.

Ozsu et al.'s study with 702 patients investigated the relationship between high RDW levels and in-hospital mortality. When the cut-off value of >15% of RDW was taken as the optimal value in estimating in-hospital mortality, the negative predictive value was 93% and the AUC was 0.649. (16) Zorlu et al. With 136 patients, RDW was defined as an indicator of early mortality. When the optimal cut-off value was set to >14.6%, the sensitivity was 95.2% and the specificity was 53%. (17) In our study, when the cut-off value of 15.55 was taken to determine the prognostic predictor of RDW, the prognosis accuracy rate was found to be 69.0%. Our results supported the literature.

Hilal et al. It has been reported that high MPV values in 209 PTE patients are not significant in determining the diagnosis and severity of PTE. However, they obtained important results showing MPV as an indicator of mortality. (18) Kostrubiec et al. In 192 PTE patients, MPV was found to be an independent predictor of early mortality in PTE patients. They also found a significant relationship between MPV value and right ventricular dysfunction and myocardial damage. (19) In our study, the optimal cut-off value for MPV measurements was found to be 8.45, and the accuracy rate in predicting the prognosis was found to be 58.4%.

According to the meta-analysis results of Dentali et al., there was an increase in the frequency of venous thromboembolism in the winter season, especially in January. (6) In a study by Nimako et al. with 640 patients, the incidence of PE was found to be associated with low atmospheric pressure and increased temperature. (7) Oztuna et al.'s study with 206 patients showed a statistically significant positive correlation between the incidence of PTE and atmospheric pressure and humidity. (8) Staskiewiczet al. They found no seasonal distribution difference in 182 PTE patients, but observed a significant association between low atmospheric pressure and severe PTE. (9) Consistent with the literature, we observed the highest number of visits in our cases during the winter months. The effect of low atmospheric pressure on prognosis was found to be statistically significant. Masotti et al. In the study conducted by PTE, an increase in the number of PTE patients was observed during periods of low atmospheric pressure. (20) The results of these studies are consistent with our findings.

VI. CONCLUSION

In our study, it was found that the patients presenting with PTE mostly applied to medical care during the winter season and low atmospheric pressure adversely affected the prognosis. In addition to hematological parameters such as MPV and RDW, hypotension and an increased right ventricular diameter compared to left ventricular diameter were also identified as unfavorable prognostic indicators.

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