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Role of Systemic Inflammatory Markers in Pulmonary Embolism Severity and Mortality

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Abstract

Pulmonary embolism is a thromboembolic disease with high morbidity and mortality rates. Ratio of Monocyte-to-HDL cholesterol (MHR) could be present the inflammatory status of patients. The aim of this study was to research the association of MHR, which is a new marker in predicting the prognosis of patients with pulmonary embolism. Patients who were followed up in our hospital with the diagnosis of pulmonary embolism between October 2016 and June 2020 were included in the study. Patients' demographic data such as age and gender, vital findings, comorbid diseases, lipid profiles, renal function tests, hemogram outcomes at admission, electrolyte values and cardiac markers were recorded and analyzed. Patients' pulmonary embolism (PE) clinical classes were determined. The correlations between monocyte/HDL-cholesterol ratio and PE severity were analyzed. A total of 160 patients followed up in our hospital due to PE were included in the study. Of all patients 38.2% (n=60) were diagnosed with massive and 61.8% (n=100) non-massive PE. There were statistically differences between Non-massive and massive PE in terms of Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, Monocytes/ HDL ratio, sPAB and Survive status (p=0.035, p=0.004, p=0.046, p=0.000, p=0.008, p=0.031, p=0.001, p=0.000, p=0.000, and p=0.000, respectively). There was a positive correlation between PE severity and Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, MHR, sPAB and Survive status. Of all patients included in this study, 43 patients (71.2%) died in the massive group and 16 patients (15.5%) were died in the non-massive group. However, MHR was higher in patients who died (0.092±0.17) compare to survivor (0.015±0.00) (p=0.000). Monocyte-to-HDL-cholesterol ratio, which is an inexpensive marker easily available in all centers, can be used in acute pulmonary embolism for PE severity status and mortality status.

Key words: *Pulmonary embolism, Prognosis, Monocyte–HDL, Mortality.*

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Introduction

Pulmonary embolism (PE) is an acute thromboembolic disease with high rates of morbidity and mortality (1, 2). According to a study from the USA, 42 million deaths occurred within 20 years with 600.000 (1.5%) of these being due to PE (3). As in many emergencies, an early and correct diagnosis is vital in PE. However, since clinical features of PE are not specific, it is not easy to establish the diagnosis of PE. The rate of mortality decreases below 10% if the diagnosis is established correctly and in an early stage in PE (2, 4).

Venous thromboembolism resulting in PE causes a series of inflammatory reactions in the pulmonary artery wall with increased cell flow and release of cytokines and chemokines (5). Therefore, studies are investigating the effectiveness of various inflammatory markers in determining vascular inflammation. Studies have reported that systemic inflammation from PE will be determined by the neutrophil to lymphocyte ratio (NLR) in the near future and NLR will be used to predict mortality in PE (6, 7). One of the recently proposed parameters for the determination of systemic inflammation is the monocyte-HDL-cholesterol ratio (MHO). Monocytes, as a source of various cytokines and molecules, interact with circulating platelets and endothelial cells, resulting in the accumulation of inflammatory and pro-thrombotic pathways (8). HDL-C, on the other hand, abolishes these proinflammatory and pro-oxidant effects of monocytes by inhibiting the migration of macrophages. Therefore, MHO can indicate a patient's inflammatory state. It has been stated in previous studies that MHO may be a new cardiovascular prognostic marker (9, 10). However, the number of studies investigating the efficacy of MHO in predicting the prognosis and severity of PE is limited.

The aim of this study is to investigate the relationship of MHO, a new marker, in predicting the prognosis of patients with pulmonary embolism.

Materials and methods

This study was designed as a retrospective cohort study. Before the start of the study, the study protocol was approved by the local ethics committee of our hospital (Approval no: 2020.09.1.10.127). Patients followed-up and treated with the diagnosis of PE in our hospital between January 2016 and December 2020 were included in the study. Patient files were screened via the hospital registry system and patient's data were retrospectively screened and recorded. Patients' demographic data such as age and gender, vital findings, hemogram outcomes at admission (hemoglobin, neutrophil, platelets, lymphocytes, monocytes), lipid profiles (triglycerides, HDL, LDL), liver function tests (ALT, AST, albumin), renal function tests (urea, creatinine), electrolyte values (magnesium, calcium, phosphorus) and cardiac markers (troponin I) were recorded and analyzed. In addition, echocardiography (ECG) findings, blood gas values and patient outcomes at follow-up (follow-up in ward, referral to intensive care, exitus) were also recorded. Patients' pulmonary embolism (PE) clinical classes were determined and PESI test values were calculated. PE severity was determined in accordance with the Turkish Thoracic Society Thromboembolism Guidelines and classified based on ECG findings as massive (high risk), sub-massive (moderate risk) and non-massive (low risk) (13). Accordingly; patients with hypotension refractory to treatment were considered as

massive PE, those with normal systemic blood pressure, but right ventricular dysfunction on echocardiography as submassive PE, and patients with normal systemic blood pressure and right ventricular function as non-massive PE.

The data obtained in this study were analyzed using the statistical program SPSS v.25 (SPSS, Chicago, USA). Descriptive statistics such as frequency distribution, mean and standard deviation were used to evaluate the data. The normality control of the data was done with the Shapiro Wilk test. The difference between the means of two independent groups was compared with Student's t test, and the differences between more than two groups were compared with analysis of variance and parametric test. Mann-Whitney U and Kruskal-Wallis tests, which are non-parametric alternatives of these tests, were used when parametric test assumptions were not met. ROC analysis was used to determine the cut-off point, the area under the curve (AUC), the sensitivity (sensitivity) and the specificity (specificity) of the data. Categorical data were analyzed with Chi-square or Fisher's Exact test. $p < 0.05$ values were considered statistically significant at the 95% confidence interval.

Results

The comparison of patients' socio-demographic, clinical and laboratory parameters was shown in Table 1. Of all patients 38.2% (n=60) were diagnosed with massive and 61.8% (n=100) non-massive PE. There were statistically differences between Non-massive and massive PE in terms of Chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, Monocytes/ HDL ratio, sPAB and Survive status (p=0.035, p=0.004, p=0.046, p=0.000, p=0.008, p=0.031, p=0.001, p=0.000, p=0.000, and p=0.000, respectively).

The correlation analysis between MHR and other variables was shown in Table 2.

There was a positive correlation between PE severity and chronic renal failure, Troponin, D-dimer, HDL, creatinine, White Blood Cell, Monocytes, MHR, sPAB and survival status.

As a result According to ROC analysis for massive PE, MHR was significant prognostic factor (AUC: 0.751, p=0.001, min-max: 0.660-0.842) (Figure 1).

Of all patients included in this study, 43 patients (71.2%) died in the massive group and 16 patients (15.5%) were died in the non-massive group. However, MHR was higher in patients who died (0.092±0.17) compare to survivor (0.015±0.00) (p=0.000) (Figure 2).

Table 1: Comparison of patients' socio-demographic, clinical and laboratory parameters.

Parameters	Non-massive (N = 100, 61,8 %) Mean ± SS (min-max), n (%)	Massive (N = 60, 38,2 %) Mean ± SS (min-max), n (%)	P
Age (year)	67.0 (21-91)	71.50 (31-88)	0.106
Gender			0.495
Male	34 (% 34.5)	24 (% 40.4)	
Female	66 (% 65.5)	36 (% 59.6)	
Coronary artery disease	21 (% 21.4)	14 (% 23.1)	0.823
Heart failure	5 (% 4.8)	4 (% 5.8)	0.798
Cancer	19 (% 19.0)	15 (% 25.0)	0.414
Hypertension	64 (% 64.3)	45 (% 75.0)	0.194
Hyperlipidemia	7 (% 7.1)	5 (% 7.7)	0.906
Diabetes mellitus	37 (% 36.9)	27 (% 44.2)	0.400
Cerebrovascular disease	12 (% 11.9)	10 (% 17.3)	0.381
Atrial fibrillation	7 (% 7.1)	7 (% 11.5)	0.384
Chronic renal failure	15 (% 15.5)	18 (% 30.8)	0.035
COPD	15 (% 15.5)	12 (% 19.2)	0.574
Deep vein thrombosis	58 (% 58.3)	31 (% 51.9)	0.468
Hemoglobin (g/dL)	11.83±1.7 (7.0-15.4)	11.95±2.1 (8.1-16.0)	0.715
troponin (pg/mL)	100.5±194.3 (0.0-920.0)	224.3±391.6 (4.3-1933.0)	0.004*
D-dimer (pg/dL)	5.42±3.5 (0.1-14.2)	7.11±3.8 (0.1-15.8)	0.046
HDL (mg/dL)	43.3±12.1 (9.0-82.0)	31.5±10.1 (12.0-64.0)	0.001*
LDL (mg/dL)	127.2±41.2 (25.0-253.0)	124.1±44.4 (37.0-252.0)	0.698
Total cholesterol (mg/dL)	198.5±52.9 (74.0-337.0)	191.6±55.2 (71.2-338.0)	0.492
Triglycerides (mg/dL)	157.1±79.4 (48.0-565.0)	155.6±75.0 (59.0-483.0)	0.922
CRP (mg/dL)	64.53±70.7 (1.7-401.0)	74.92±84.8 (4.1-364.8)	0.443
Creatinine (mg/dL)	1.00±0.8 (0.3-7.4)	1.24±1.0 (0.5-7.0)	0.008*
Albumin (g/dL)	3.50±0.7 (1.7-4.8)	3.41±0.6 (2.1-4.8)	0.461
White Blood Cell (103/µL)	10.26±4.7 (1.0-29.3)	12.48±1.0 (4.8-45.7)	0.031
Neutrophils (109/L)	6.87±4.8 (0.1-27.0)	7.85±5.8 (0.1-32.3)	0.294
Lymphocytes (109/L)	3.98±6.1 (0.3-42.0)	3.54±4.8 (0.2-25.0)	0.667
Platelets (109/L)	244.47±89.7 (56.0-562.0)	243.64±112.6 (4.7-603.0)	0.962
Monocytes (109/L)	0.73±0.31 (0.0-1.9)	2.06±3.9 (0.3-27.0)	0.001*
Platelet / lymphocyte ratio	149.44±130.6 (5.6±661.4)	157.77±179.3 (1.6-1162.5)	0.757
Neutrophil / lymphocyte ratio	4.79±5.5 (0.0-28.6)	6.50±9.7 (0.0-54.5)	0.200
Monocyte / HDL ratio (MHR)	0.019±0.01 (0.00-0.06)	0.083±0.17 (0.00-1.22)	0.001*
sPAB (mmHg)	34.47±7.6 (20-55)	54.45±11.8 (30-90)	0.001*
Survival status			0.001*
Yes	84 (% 84.0)	17 (% 28.8)	
No	16 (% 16.0)	43 (% 71.2)	

*: Mann–Whitney U was applied. COPD: Chronic obstructive pulmonary disease, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, CRP: C-reactive protein, sPAB: Systolic pulmonary artery pressure.

Table 2: Correlation analysis between MHR and other variables.

	Correlation coefficient (r)	**P**
Massive PE	0.423**	0.001
Death rate	0.561**	0.001
Chronic renal failure	0.225**	0.008
Troponin	0.136	0.138
D-dimer	0.160	0.143
HDL	-0.753**	0.001
LDL	-0.234**	0.010
Total cholesterol	-0.235**	0.010
Creatinine	0.130	0.132
White blood cell	0.407**	0.001
Neutrophils	0.275**	0.001
Monocytes	0.898**	0.001
CRP	0.309**	0.001
Albumin	-0.245**	0.004
Neutrophil / lymphocyte ratio	0.186**	0.032
sPAB (mmHg)	0.357**	0.001

HDL: High-density lipoprotein. sPAB: Systolic pulmonary artery pressure.

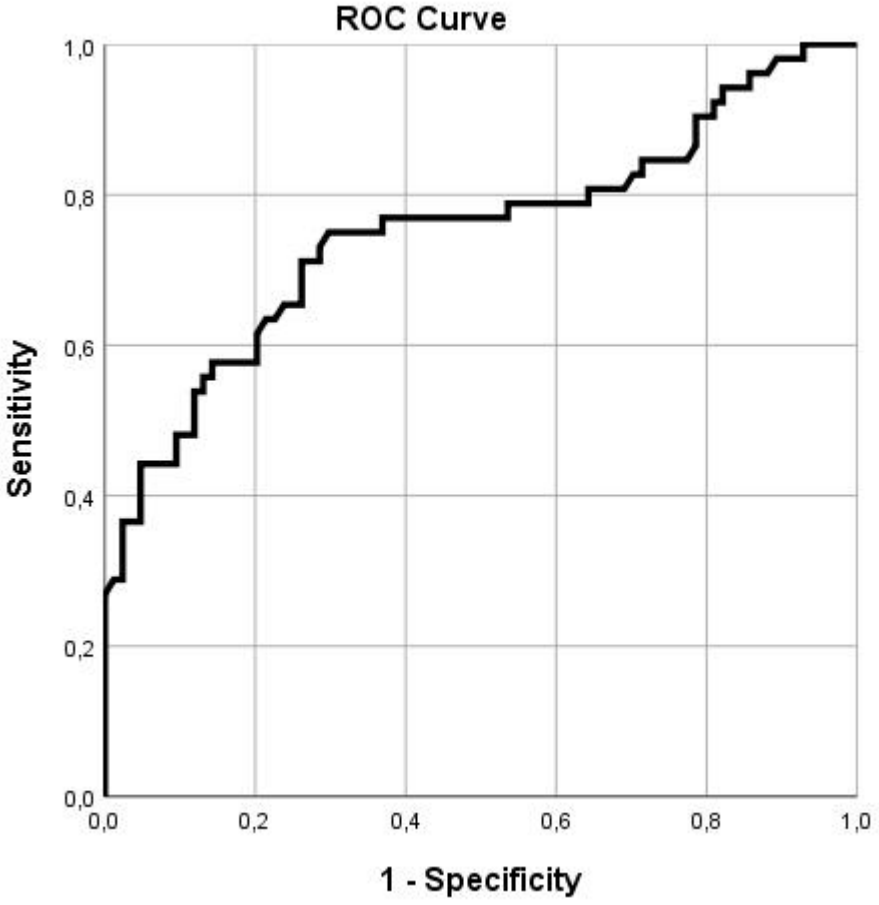

Figure 1: ROC analysis results in patients with massive pulmonary embolism. Diagonal segments are produced by ties.

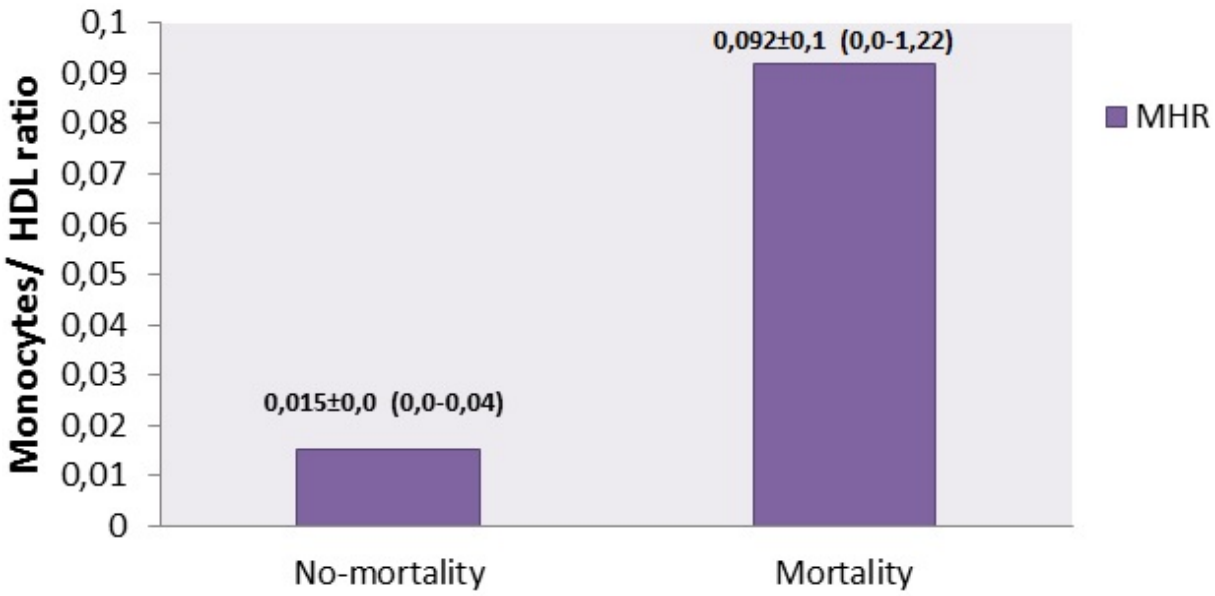

Figure 2: Comparison of MHR values between patients with and without PE mortality. Monocytes/HDL ratio seems influentially to be predicting survivability.

Discussion

In this study, we investigated the relationship between MHR, which is among readily available laboratory markers, and the severity of PE. Acute PE is a disease with significant morbidity and mortality. Studies have reported the rate of mortality due to PE between 8% and 30%. In our study, 59 (36.8%) patients died in the hospital. 43 (71.2%) of the deceased patients were massive PE patients. We think that a higher rate of mortality in our study compared to the literature resulted from the larger number of patients with massive PE.

The most widely recommended mechanism in order to explain the relationship between PE and hematological parameters is inflammation. Inflammation plays a primary role in the pathophysiology of PE. In inflammatory diseases, monocytes counts increase, while HDL-C levels decrease. Monocytes are a distinct type of leukocytes, migrate to the tissue macrophages and initiate inflammation. Previous studies have found that monocyte count is associated with the prediction of coronary artery Disease (11). On the other hand, HDL-C inhibits the activation of monocytes, prevents the transformation of monocytes to macrophages and decreases inflammation. In conclusion, the combination of these two parameters as MHR is thought to represent an inflammatory process. This relationship between monocytes and HDL-C has led researchers to investigate whether MHR is more effective than monocyte count or HDL-C alone in predicting cardiovascular events. Kanbay et al. reported that MHR acts as an independent predictor for cardiovascular events and increases in parallel with the decrease in eGFR in patients with chronic kidney disease (12).

It has been proposed that MHR is associated with systemic infection and endothelial dysfunction, and it can be used as a novel inflammation-based diagnostic and prognostic marker in cardiovascular diseases. In a study by Pamukcu, MHR was associated with mitral annulus calcification (13). In a study by Zhu et al. preoperative MHR value was significantly

higher in patients who developed acute deep vein thrombosis following total joint arthroplasty (14). In our study, there was a positive correlation between MHR values and cancer, Deep vein thrombosis, and chronic renal failure. However, there wasn't any correlation between MHR values and coronary artery disease, heart failure, hypertension, hyperlipidemia, diabetes mellitus, cerebrovascular disease, atrial fibrillation, and COPD. In a study investigating prognostic value of MHR in predicting short term mortality in patients with acute PE, 26 of 99 patients (25.2%) died within the first month of the diagnosis and MHR was found to be significantly higher in these patients. The authors found that MHR was an independent predictor of mortality in patients with acute PE (15). In our study, 59 of 160 patients (36.8%) died after diagnosis of PE and MHR was found to be significantly higher in these patients. However, MHR was an independent predictor of mortality in patients with acute PE (B: 1.393, 95% CI (0.707-2.079), p=0.000) in our study. In the present study, we evaluated the correlations of MHR with the severity of PE and other variables. We found that the severity of PE, HDL, LDL, Total cholesterol, White Blood Cell, Neutrophils, Monocytes, CRP, Albumin, Neutrophil/lymphocytes ratio, and sPAB increased as MHR increased. Nevertheless, because the number of studies investigating the predictive value of MHR in acute PE is limited, our findings should be evaluated with further multicenter comprehensive studies.

Limitations of Study

This study has several limitations. The study was designed as an observational, retrospective and single-center study. In addition, repeating MHR measurements with certain intervals possibly would affect the results. We could not compare MHR with the other markers used in pulmonary embolism. Finally, we could not make a comparison between the patients using statins and those not using in order to avoid the confounding effect of statins on HDL-C values. Further comprehensive studies are needed to better clarify this relationship.

Conclusion

In conclusion, Monocyte-to-HDL-cholesterol ratio, which is an inexpensive marker easily available in all centers, can be used in acute pulmonary embolism for PE severity status and mortality status.

Conflict of interest

The authors declare that they have no competing interests with regards to authorship and/or publication of this paper.

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Authorship Contributions: Idea/Concept and design; SK, EO, control/supervision; SK, EO, data collection and/or processing; SK, EO, analysis and/or interpretation; SK, literature review; SK, EO, writing the article; SK, EO, critical reviewing; SK, EO. There are no funding sources.

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