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# Can monocyte/HDL ratio predict the mortality in acute pulmonary embolism?

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**ABSTRACT**

In recent times, monocyte/high-density lipoprotein cholesterol (HDL) ratios (MHR) surfaced as novel markers of inflammation and oxidative stress. This study aims to investigate the short-term prognostic role of the MHR ratios in patients who suffer from acute pulmonary embolism (PE).

Two hundred patients who suffered from pulmonary embolism were included retrospectively in the current study. The demographic data along with the laboratory parameters of the patients were obtained from the digital archive system of the facility.

Mortality was seen in 42 (21%) of 200 patients with PE. It was determined that the mean age, mean troponin level, pulmonary artery pressure, monocyte value, and MHR ratios were statistically higher in exitus group compared to the survivor group. The mean MHR value was higher in patients with exitus in 1st month than patients with exitus between 1-6 months (p=0.009). 132 (66%) patients with acute PE had sPESI ≥1, while mean MHR was statistically higher in high-risk patients compared to low-risk PE patients (17.95±12.67, 11.54±5.66, p= 0.001, respectively). For the MHR ratio, when the cut-off value was considered 16.03 in the prediction of PE cases for survival, the sensitivity was 81% and the specificity was 62% (AUC=0.793, p=0.001, CI%= 0.722-0.865)

The fact that MHR was higher in exitus group, in high-risk patients and in those patients with exitus in the first 1 month suggested that it may be an important factor in predicting mortality in patients with PE.

**Keywords**: Monocyte/HDL ratio, Pulmonary embolism, PESI, Mortality

## Introduction

After myocardial infarction and stroke, pulmonary embolism (PE) is the third most frequent cause of cardiovascular mortality. PE's annual incidence rates have risen in last years (1). Its mortality remains between 8% and 30%, despite the recent advances in diagnosis and treatment methods. Studies are conducted on serum markers as simple-to-use tools for early diagnosis (2). If PE is correctly diagnosed and treated at an early stage, the mortality rate drops below 10% (3). Monocyte-to-HDL-cholesterol ratio (MHR) is one of the most recently suggested metrics for identifying systemic inflammation. Monocytes interact with circulating platelets and endothelial cells as a source of various cytokines and molecules, leading to the accumulation of inflammatory and pro-thrombotic pathways (4). High-density lipoprotein cholesterol (HDL) particles have also been linked to effects on monocytes, including mediating cholesterol efflux from macrophages and inhibiting endothelial cells against oxidation and inflammation (5,6). HDL prevents monocyte emigration into the arterial wall by reducing the exposure of endothelial adhesion molecules (7,8). By inhibiting LDL oxidation and ensuring the consistent efflux of cholesterol in these cells, HDL also counteracts the pro-oxidant effects of already active macrophages (9). MHR may even be more accurate at predicting clinical outcomes compared to independent measures of HDL and monocyte count (10).

MHR is a new cardiovascular prognostic marker, has recently come into the spotlight (5, 9). Additionally, a significant amount of study was later conducted to assess the relationship between MHR and prognosis in the context of specific diseases, particularly acute coronary syndrome (6).

Accordingly, this study aimed to investigate the MHR levels, which is a new inflammatory marker, in acute PE cases. Furthermore, identifying the link between MHR and the 1st-month and between 1-6 months mortality rates was another goal.

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## Materials and Methods

**Patients:** In this single-center study, the patients who were hospitalized at the Firat University Chest Diseases Clinic, Turkey, between January 2018 and March 2020 with the diagnosis of PE were included. The patient's demographic data, radiological results, and laboratory parameters were obtained. In all patients, the thorax computerized tomography (CT) angiography method was utilized for the diagnosis of PE. Patients with pulmonary embolism over the age of 18 with complete file records and radiological reports were included in the study. The records of 298 patients with pulmonary embolism were evaluated. Having a pediatric age range (younger than 18 years), having insufficient information in patient files, declining treatment and leaving the hospital, not having radiological reports, and dying before the establishment of a confirmed pulmonary embolism diagnosis were the exclusion criteria for all the patients. Accordingly, the study excluded 98 patients in total who met the exclusion criteria. Based on data from the Medulla-E-Pulse and Death Notification System, mortality rates for the 1st-month and the first 1-6 months were calculated.

The severity of acute PE was defined according to the European Society of Cardiology Guidelines that was based on the systemic systolic blood pressure on admission and detection of RV dysfunction at echocardiography and elevated plasma troponin levels. The prognostic scoring systems called the Pulmonary Embolism Severity Index (PESI) and its simplified version is (sPESI). The patients with a sPESI risk score 0 were defined as low risk patients, and those with a sPESI score ≥1 were defined as high risk patients.

The ethical approval for the study was obtained from the institutional review board (date: March 17,2022, decision no: 2022/04-11).

**Laboratory Analysis:** venous blood samples were taken from the antecubital region, and hemogram and biochemistry parameters were noted for the analysis at the time of application. MHR was calculated by division of the count of monocytes by HDL levels. Complete blood count measurements were performed using theSysmex XN 10 (Sysmex, Kobe, Japan) automated analyzer. Biochemical parameters measurement were performed using the Siemens Advia 2400 automatic measurement device.

**Statistical Analysis:** IBM Statistical Product and Service Solutions version 22.0 (IBM SPSS Statistics 22 program, Armonk, NY, USA) software was used. Normality of the data was tested by Kolmogorow-Smirnow test. Parameters which had normal and non-normal distribution were expressed as mean±SD and median (min-max), respectively. Independent samples t test was used to compare survivor and exitus patients and groupings according to risk factors. Chi-square test was used to evaluate the difference between genders. Mann-Whitney U test was used to group according to exit times and expressed as minimum and maximum values. The level of statistical significance was regarded as $p<0.05$. The ROC curve analysis was used to establish the cut-off level of the MHR in terms of mortality.

## Results

The study consisted of 200 patients with PE. Mortality was seen in 42 (21%) of 200 patients with PE. Thirteen patients died within the first month, and 29 patients died between the first and sixth months. There was no statistically significant difference in gender between exitus patients and survivors ($\chi 2$: 1.337, $p=0.248$). The mean age, mean troponin levels, pulmonary artery systole pressure, monocyte value, and MHR ratio were all significantly higher, while the mean arterial oxygen saturation, lymphocyte and HDL values were significantly lower in exitus patients compared to survivors (Table 1). The demographic data and laboratory parameters of all patients were demonstrated in Table 1. Mean MHR were statistically higher in patients who died in 1st month than who died during 1-6 month ($p=0.009$) (Table 2). 132 (66%) patients with acute PE had sPESI ≥1, while mean MHR was statistically higher in high-risk patients compared to low-risk PE patients (17.95±12.67, 11.54±5.66, $p= 0.001$, respectively) (Table 3). When the MHR cut-off value of 16.03 was used to predict exitus and survivor PE cases, the sensitivity and specificity were 81% and 62%, respectively (AUC=0.793, $p=0.001$, CI%= 0.722-0.865) (Figure 1).

## Discussion

This study showed that patients with acute PE who died had a significantly higher MHR than survivors. Also, higher MHR values were found in patients who died in 1st month than who died 1-6 month. Furthermore, higher MHR values were found in high-risk patients according to the sPESI score. Based on these findings, one can speculate

**Table 1:** The Demographic Data and Laboratory Parameters of Patients with Pulmonary Embolism

| | PE (Exitus) n=42 (%21) | PE (Survivor) n= 158 (%79) | P |
|---|---|---|---|
| Age(Year)* | 76.66±13.65 | 65.5±17.29 | 0.000 |
| M/F (n)** | 22/20 | 67/91 | 0.248 |
| SaO2 (%)* | 87.07±8.36 | 89.91±6.41 | 0.020 |
| TnI (ng/mL)* | 1.3±7.7 | 0.1±0.46 | 0.049 |
| D-dimer (ng/mL)* | 5.13±5.69 | 4.21±5.99 | 0.073 |
| Neutrophil (x109/L)* | 7.39±3.92 | 6.45±3.02 | 0.094 |
| Lymphocyte(x109/L)* | 1.23±0.59 | 1.8±1.24 | 0.005 |
| Monocyte (x109/L) * | 920.00±430.66 | 495.90±206.48 | 0.000 |
| WBC (x109/L)* | 9.6±4.32 | 9.3±4.25 | 0.702 |
| Platelet (×109/L)* | 218.3±97.21 | 244.13±91.54 | 0.110 |
| HDL (mg/dL)* | 35.26±10.52 | 43.84±10.98 | 0.000 |
| MHR* | 28.59±15.53 | 12.36±6.38 | 0.000 |
| sPAP(mm Hg )* | 42.65±29.66 | 30.38±14.74 | 0.020 |

*Independent samples t test, ** Chi-square test
Abbreviations: SaO2; arterial oxygen saturation, HDL; high density lipoprotein cholesterol, MHR; monosit/HDL ratio, sPAP; pulmonary artery systole pressure

**Table 2.** The Monocytes, HDL values and MHR In Patients With Pulmonary Embolism Who Died Between The 1st and 1-6 Months

| | PE(Exitus 1stmonth) n=13 | PE (Exitus 1-6 month) n= 29 | p |
|---|---|---|---|
| Age (Year)* | 78.00 (36-98) | 75.00 (42-93) | 0.754 |
| Monocyte (x109/L)* | 1050 (310-1440) | 710.00 (120-1420) | 0.005 |
| HDL (mg/dL)* | 28 (24-74) | 37 (24.80-68.60) | 0.013 |
| MHR* | 33.66 (12.40-45.66) | 16.44 (3.13-50.71) | 0.009 |

* Mann Whitney U test ; Descriptive statistics are expressed as (minimum-maximum)
Abbreviations: **HDL**; High Density Lipoprotein Cholesterol, **MHR**; Monosit/HDL ratio

that increased MHR value may be associated with a poor prognosis.

Thrombogenesis, inflammation, endothelial cell dysfunction, and hemodynamic aberrations all play a role in the complicated pathophysiology of PE (11). Inflammation is the most frequently suggested mechanism to explain the association between PE and hematological parameters. Accordingly, a major factor in the pathophysiology of PE is inflammation (12). To properly direct clinical management, patients with acute PE should undergo a prognostic assessment. It was reported that several biomarkers were used in the diagnosis and risk classification of PE (13). In terms of management and decision-making, it is crucial to have a ready-made marker that can be accessed quickly (4,14).

The MHR is referred to as a biomarker for thrombosis caused by systemic inflammation in cardiovascular (15,16). and oncological events (16). As an immune-mediated process, atherosclerosis progresses as a result of monocytes' ability to bind to adhesion molecules expressed on the damaged vascular endothelium. Monocyte activation is crucial for both atherogenesis and atherothrombosis, as it occurs not only inside the arterial wall but also in the bloodstream. The development and rupture of atherosclerotic plaques are correlated with the accumulation of macrophages (5). Monocytes have an important role in the formation of inflammation and oxidative stress. It has been demonstrated that hypoxia could raise monocyte counts and their pro-inflammatory effects. A study revealed the anti-inflammatory and antioxidative effects of HDL cholesterol by suppressing cytokine expression and inhibiting monocyte activation and extravasation (17). Reduced HDL ratios promote the proliferation of

**Table 3.** The monocytes, HDL values and MHR in high and low risk PE patients according to sPESI

| sPESI | sPESI < 1 Low risk n: 68 | sPESI ≥ 1 High risk n:132 | P |
|---|---|---|---|
| Monocyte(x109/L)* | 479.90±184.24 | 654.60±350.66 | 0.001 |
| HDL (mg/dL)* | 43,25±11.70 | 41.42±11.26 | 0.283 |
| MHR* | 11.54±5.66 | 17.95±12.67 | 0.001 |

* Independent samples t test
Abbreviations: sPESI; simplified Pulmonary Embolism Severity Index, HDL; High Density Lipoprotein Cholesterol, MHR; Monosit/HDL ratio

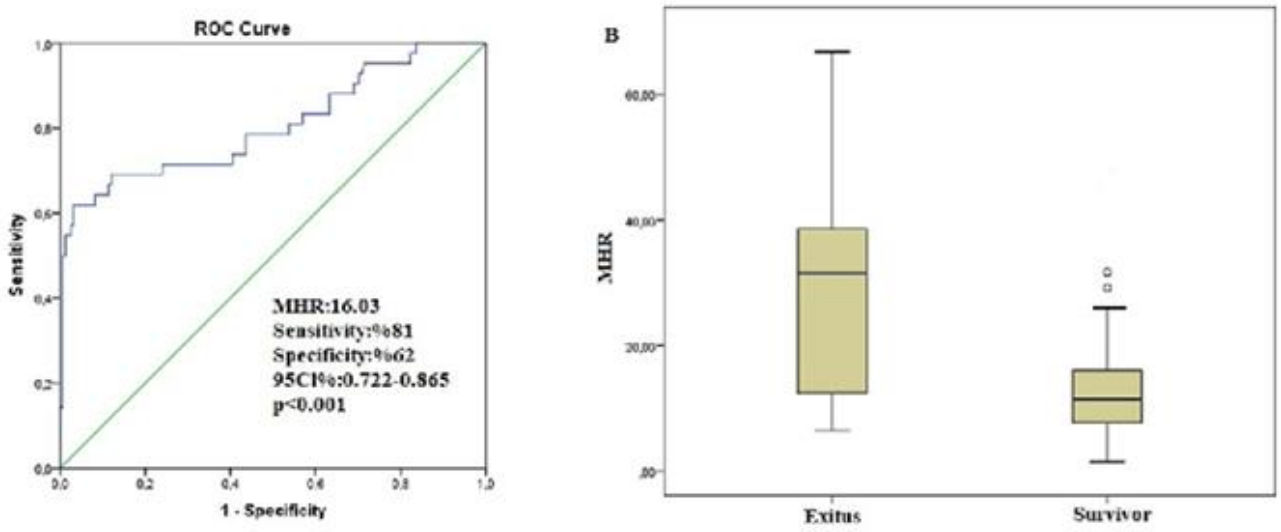


**Figure 1.** A) ROC (Receiver operating characteristic) curve showing sensitivity and specificity in predicting the exitus rate of MHR, B) Cut-off level of MHR in cases with PE with exitus and survivor

hematopoietic stem cells, particularly monocytosis. As a result of excessively produced inflammatory factors, low HDL levels may compromise the normal systemic response during the acute stage (18). Covering low HDL cases, Sarov-Blat et al. determined the pro-inflammatory activation of monocytes and monocyte-derived macrophages. According to this study, high expression levels of interleukin-1beta, interleukin-8, and tumor necrosis factor-alpha were shown in low HDL subjects (19). Multiple subgroups of HDL exist, each with a unique diameter, density, lipid, and protein composition. This heterogeneous structure provides it with a variety of biological activities. HDL has antioxidant, anti-inflammatory, anti-apoptotic, anti-thrombotic, and antiatherosclerotic properties in addition to reverse cholesterol transport (2). Murphy et al. demonstrated that HDL and the major protein that makes up it, apolipoprotein A-I (apo A-I), had an anti-inflammatory effect on human monocytes by preventing CD11b activation (20). According to Avcı et al., the group with mortality had significantly higher PESI, monocyte counts, and MHR levels compared to the group without mortality (2). According to Ganda et al., cases with mild renal dysfunction had elevated monocyte levels and more severe atherosclerosis. Overall, a decrease in serum HDL cholesterol concentration and an increase in the number of circulating monocytes were linked to renal dysfunction (21). According to the pioneering study of Kanbay et al., higher MHR was linked to a worse cardiovascular prognosis in chronic kidney disease (22). MHR was suggested to be a novel inflammatory-based diagnostic and prognostic marker in cardiovascular diseases while it was linked to systemic infection and endothelial dysfunction (22,23). After 48 hours of flow restriction, monocytes, which are known to express tissue factors, make up about 30% of the leukocytes in a venous thrombus (24). Rezende et al. discovered that venous thrombosis was linked to a higher peripheral blood monocyte count, even when it was within the reference range. Unexpectedly, a lower risk of venous thrombosis was linked to a low monocyte count (24). MHR is a recently discovered inflammatory status indicator (15). MHR was discovered to be higher among patients who experienced PE among postoperative outcomes in a study by Dolapoglu et al., examining the impact of MHR on

postoperative outcomes following coronary bypass surgery (25). Jiang et al. investigated the connection between MHR and overall cardiovascular mortality. Accordingly, the researchers discovered that the risk of cardiovascular mortality rose by 21% for every 1-fold increase in MHR (6).

Our study has a few significant limitations. One of them is the study's retrospective design. The single-center design of our study is another limitation. Also, we could not assess all potential factors that might disrupt the lipid table and worsen the prognosis such as body mass indexes, coronary heart disease, hyperlipidemia, hypertension and diabetes.

In conclusion, the results of our study demonstrated that a combination of a high circulating monocyte count and a low HDL concentration may predict mortality in PE patients. MHR may be used as a practical clinical tool for risk stratification and to direct clinicians' preventative and treatment strategies in routine clinical care thanks to being accessible and affordable. More centers can be included in prospective studies to provide more through information.

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