Introduction

Chronic total occlusion (CTO) is the total occlusion of the coronary arteries for more than three months. CTO is a clinical condition commonly detected during routine angiography and has a prevalence of 18-52% (1-3). According to the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, CTO is most commonly seen in the right coronary artery and least commonly in the circumflex artery. The incidence of CTO increases with age, with a reported incidence of 37% in patients aged less than 65 years, 40% in patients aged between 65-79 years, and 41% in patients aged over 85 years (4).

The development of CTO consists of multiple histological stages, with each stage containing different histopathological features. In most cases, CTO is triggered by thrombus caused by sudden rupture of an atherosclerotic plaque (5). The progression of coronary artery disease (CAD) and its evolution to a CTO lesion is caused by numerous conditions such as immunological upregulation, inflammatory markers (cytokines, leukocytes, high sensitivity C-reactive protein [CRP]), endothelial dysfunction, and cholesterol accumulation. In the intima layer of the vessel, macrophage activation often results from the proliferation of smooth muscle cells, thereby leading to lesion progression as a result of pathological thickening in the intima layer (6-7).

Monocytes have a pivotal role in the early stage of atherosclerosis (8). These cells bind to adhesion molecules expressed on damaged endothelial cells through immune-mediated mechanisms (9). Subsequently, they migrate to the subendothelial space and convert into macrophages and thereby internalize oxidized low-density lipoprotein (LDL) and class A scavenger receptors (10). Afterwards, they convert into foam cells, thereby causing the release of pro-inflammatory and pro-oxidant cytokines (11). Unlike monocytes, high-density lipoprotein (HDL) is a heterogeneous lipid and protein particle which has been shown to have

antioxidant, anti-inflammatory, antiapoptotic, antithrombotic and anti-atherosclerotic properties (12,13).

The monocyte to HDL ratio (MHR) has recently emerged as a novel, inexpensive, and accessible marker of inflammation and oxidative stress. MHR has also been associated with adverse cardiac outcomes in patients with acute myocardial infarction (AMI) (14), stable angina pectoris (SAP) (15), atrial fibrillation (AF) (16), coronary artery ectasia (CAE) (17), coronary slow-flow phenomenon (CSFP) (18), rheumatic mitral stenosis (RMS) (19), and hypertrophic cardiomyopathy (HCM) (20). Additionally, MHR is often associated with increased mortality, non-fatal adverse cardiac outcomes, and poor prognosis (21,22).

To our knowledge, there has been no study in the literature reporting on a definite relationship between MHR and long-term survival and mortality in CTO patients. The aim of this study was to investigate the relationship between MHR and long-term survival and mortality in CTO patients.

MATERIALS AND METHODS

Study population

The study was designed as an observational, single-center, retrospective study and included patients that had a diagnosis of SAP, unstable angina pectoris (USAP), non-ST-elevated myocardial infarction (NSTEMI), and ST-elevated myocardial infarction (STEMI) or were asymptomatic and were incidentally detected with CTO during routine angiography prior to cardiovascular surgery at Dicle University Medical School Cardiology clinic between January 2011 and December 2019. Patients with hematological diseases, systemic inflammatory diseases, malignancies, active infections, chronic liver or kidney disease, autoimmune

diseases, and a CTO vessel diameter <2 mm were excluded from the study. The study protocol was approved by the local ethics committee.

Definitions

Chronic total occlusion (CTO) was defined as a coronary occlusion with TIMI (thrombolysis in myocardial infarction) grade 0 flow for at least three months. During admission, a detailed medical history including cardiovascular risk factors was taken from each patient. Hypertension (HT) was defined as either systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mm Hg on two separate measurements or taking anti-hypertensive medication. Diabetes mellitus (DM) was defined as a fasting glucose level ≥126 mg/dL on two separate measurements or taking antidiabetic medication. Hypercholesterolemia was defined as serum total cholesterol of ≥200 mg/dl. Active smoking was accepted as smoker. A positive family history was accepted as the history of a cardiovascular event in first-degree family members before age 55 in males and before age 65 in females. Cerebral hemorrhage and ischemic stroke were accepted as cerebrovascular events. Chronic kidney disease was defined as having a glomerular filtration rate (GFR) of lower than 60 ml/min/1.73 m^2 over a period of more than three months with no renal impairment or as a structural and functional disorder in the kidney lasting for more than three months regardless of a decrease in GFR.

Biochemical and Hematological parameters

Hematological and biochemical tests were conducted on the venous blood samples taken from each patient immediately before routine coronary angiography. Determination of the counts and types of shaped elements of blood was performed for each patient using an automated

hematological analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, USA). Biochemical measurements were performed using the standard methods and MHR was calculated for each patient.

Follow-up

The follow-up period was defined as the time from the moment of admission to our clinic for angiography to death due to any cause or to the last clinical visit. Data on patients' death were accessed by telephone interviews or were retrieved from the civil registration records.

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (Armonk, NY: IBM Corp.). Normal distribution of data was analyzed using Kolmogorov-Smirnov test. Categorical variables were expressed as percentages (%) and were compared using Chi-square test. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and were compared using Student's t-test. Continuous variables with nonnormal distribution were expressed as median (25^{th}-75^{th} percentile) and were compared using Mann-Whitney U test. Independent predictors of mortality were determined using multivariate logistic regression analysis and the results were expressed with odds ratio (OR) and 95% confidence interval (CI). The optimum MHR cutoff for the prediction of mortality was determined using receiver operating characteristic (ROC) curve analysis. Correlations were analyzed using Spearman's correlation coefficient. Survival analysis was performed using Kaplan-Meier analysis. A p value of <0.05 was considered significant.

RESULTS

The study included 493 patients comprising 353 (71.6%) men and 140 (28.4%) women with a mean age of 63.03±10.88 years. Median follow-up period was 48 (interquartile range [IQR]: 26-73) months. Patients were divided into two groups: (I) MHR <17.68 (n=278) and (II) MHR ≥17.68 (n=215). Table 1 presents the demographic and clinical characteristics of patients in both groups. Of all patients, 254 (51.5%) underwent percutaneous coronary intervention (PCI), 104 (21.1%) underwent medical treatment alone, 61 (12.4%) had a failed CTO intervention, and 74 (15%) underwent coronary artery bypass grafting. A significant difference was found between the two groups with regard to gender, mortality, smoking status, and clinical symptoms (p=0.001, p<0.001, p=0.006, and p=0.035, respectively). Table 2 presents the hematological and biochemical parameters of both groups. White blood cell (WBC), red cell distribution width (RDW), lymphocyte, monocyte, and neutrophil counts, urea, creatinine, and total cholesterol were significantly higher and HDL level was significantly lower in group I (MHR <17.68) compared to group II.

On multivariate logistic regression analysis, MHR, albumin, and age were found to be independent predictors of long-term mortality (OR: 1.089, 95% CI: 1.055-1.124, p<0.001, OR: 0.332, 95% CI: 0.183-0.601, p<0,001, OR: 1.056, 95% CI: 1.029-1.083, p<0.001, respectively; Table 3). At a cutoff value of 17.68, MHR predicted long-term mortality in CTO patients with a sensitivity of 61% and specificity of 62% (ROC area under curve [AUC]: 0.679, 95% CI: 0.623-0.735; Figure 1). A positive correlation was found between MHR and the neutrophil-to-lymphocyte ratio (NLR) (r=0.103, p=0.22; Figure 2). The Kaplan-Meier analysis showed higher survival rates in group I (MHR <17.68) (log rank=14.66, p<0.001; Figure 3).

DISCUSSION

In addition to the risk models used in mortality estimation, practical, low-cost, and reliable novel markers are needed and could be beneficial in terms of treatment management and prognosis prediction. The present study aimed to investigate whether a simple and easily calculated parameter such as MHR could be used in predicting mortality and survival in CTO. The results indicated that MHR was associated with mortality and that the survival rate decreased as the MHR value increased. Additionally, MHR was found to be an independent predictor of long-term mortality.

High MHR has been shown to be a risk factor for CTO in CAD patients (23). A recent study indicated that MHR predicted mortality in patients with ischemic stroke (24). Similarly, Efe et al. showed the prognostic value of MHR in predicting early mortality in patients with acute pulmonary embolism (25). Another study reported that MHR predicted adverse cardiac outcomes in HCM patients (20). The same study, as in our study, found higher WBC, neutrophil, and lymphocyte levels in the group with higher MHR values. In a similar way, Wu et al. suggested that MHR could be a long-term prognostic marker in CAD patients undergoing PCI (26). Unlike that study, our study included CTO patients only and the treatment modalities other than PCI such as coronary artery bypass grafting, medical treatment, and failed CTO intervention.

The mechanism of the relationship between MHR and poor prognosis in CTO patients remains unclear. Monocytes have a key role in atherosclerosis development (8). These cells bind to adhesion molecules expressed on damaged endothelial cells (9). Subsequently, they migrate to the subendothelial space and convert into macrophages and thereby internalize oxidized LDL and class A scavenger receptors (10). Afterwards, they convert into foam cells, thereby causing the release of pro-inflammatory and pro-oxidant cytokines (11). In recent studies, HDL has been shown to act in the opposite direction in the development of atherosclerosis and to play an active role in monocyte activation, adhesion, and inflammation

and also to act as a natural protective barrier against the proinflammatory effects of monocytes by taking part in the control of the proliferation of progenitor cells that differentiate into monocytes (27-29). Low HDL value and high monocyte count appear to be indirect indicators of inflammation. Accordingly, using these two parameters in combination by calculating their ratios to each other provides more valuable information about the presence of inflammation and oxidation balance. On the other hand, heart failure could be a reason for the relationship between high MHR and poor prognosis in CTO patients. Wrigley et al. indicated that the monocyte count increased in patients with acute and stable heart failure (30). Another study showed that low HDL was associated with poor prognosis in patients with heart failure (31). In our study, in line with the literature, a significant correlation was found between higher MHR value and lower ejection fraction. Additionally, we suggest that cardiac arrhythmia could be a reason for the relationship between MHR and poor prognosis in CTO patients (20).

Both the studies abovementioned and our study found an association between high MHR value and mortality, which implicates that MHR could be a predictor of adverse cardiac outcomes in high-risk patients. Additionally, it was also revealed that MHR could be a novel marker, in addition to conventional parameter, for the prediction of long-term mortality in CTO patients.

Limitations

Our study was limited in several ways. First and foremost, the study was designed as a single-center retrospective study and had a limited number of patients. Second, the calculation of MHR was performed from the single blood sample taken prior to the procedure and the MHR value could have changed if it had been calculated from additional blood samples. Finally,

inflammatory markers including interleukin-6, thromboxane A2, and C-reactive protein (CRP) were not studied, and a correlation analysis was performed with NLR only.

Conclusion

Increased MHR (≥17.68) is associated with increased mortality risk and poor survival in CTO patients. Accordingly, MHR could be used as a practical biomarker of mortality and survival in CTO patients.

Authors' Note

All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and (3) final approval of the version to be published.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

'The Author(s) declare(s) that there is no conflict of interest'.

Prognostic Significance of Monocyte to High-density Lipoprotein Ratio in Patients With Coronary Chronic Total Occlusion

Objective: Monocyte to high-density lipoprotein ratio is a marker of inflammatory response. We investigate the relationship between MHR and mortality in CTO patients.

Methods: Study included 493 patients followed over a period of 73 months. Blood samples taken from patient before coronary angiography.

Results: Median follow-up was 48 months. Patients were divided into two groups: (I) MHR <17.68 (n=278) and (II) MHR ≥17.68 (n=215). Mortality was significantly higher in group II than in group I (n=70 vs. n=43; p<0,001). MHR was found to be an predictor of mortality (OR: 1.089, 95% [CI]: 1.055-1.124, p<0,001). Kaplan-Meier showed lower survival rates in group II than in group I (75.223±2.670 vs. 89.220±2.102, p<0,001).

Conclusion: MHR could be used as a biomarker of mortality in CTO patients

Key words: Chronic total occlusion, risk predictor, monocyte to high-density lipoprotein ratio, long-term mortality, inflammation

What's already known about this topic?

The association of MHR as an inflammatory marker with atherosclerotic diseases, various heart diseases, various inflammatory diseases and some types of cancer has been demonstrated in clinical studies.

What does this article add?

We have shown that high MHR were significant and independent predictor of long-term mortality in patients with CTO.MHR is a practical biomarker that may be useful for long-term cardiac risk stratification in patients with coronary chronic total occlusion.

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