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Admission monocyte to high density lipoprotein cholesterol ratio predicts amputation in patients undergoing embolectomy for acute lower extremity ischemia

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Abstract. – OBJECTIVE: Acute limb ischemia is a common clinical manifestation of embolism or thrombosis, which can lead to amputation. Increasing evidence suggests that various biomarkers can predict amputation at the time of admission. Identifying an easily obtainable and inexpensive indicator has always been a major objective. The aim of this study was to determine the predictive value of the admission monocyte count to the HDL-C ratio for a lower extremity amputation in patients undergoing embolectomy for acute limb ischemia.

PATIENTS AND METHODS: This retrospective, single-center study included 269 patients who underwent an emergent embolectomy. The study population was divided into two groups according to early amputation: the non-amputation group (n = 220) and the amputation group (n = 49). Two groups were compared based on various data.

RESULTS: According to the multivariate regression analysis, patients with a higher CRP and MHR have a significantly higher amputation rate (HR: 1.148; CI: 1.075-1.225; $p < 0.001$ and HR: 1.547; CI: 1.003-2.387; $p = 0.04$, respectively). Patients with arterial back bleeding have a significantly lower amputation rate (HR: 0.106; CI: 0.02-0.558; $p = 0.008$).

CONCLUSIONS: Our study demonstrated that preoperative CRP, MHR, and no arterial back bleeding after surgery were found to be independent predictors of amputation as a poor prognostic factor within 30 days after an embolectomy.

Key Words:
Amputation, Embolectomy, High density lipoprotein cholesterol, Monocyte count.

Introduction

Acute leg ischemia (ALI) is an important clinical manifestation that can occur due to embolism or thrombosis, causing ischemic changes in tissues that can lead to necrosis. Despite recent advances in both diagnosis and treatment, ALI-induced amputation and mortality rates are still high[1,2]. The risk stratification for ALI patients is becoming increasingly important in predicting the prognosis and determining the most appropriate treatment for patients, not only by identifying high-risk patients but also by defining which patients would benefit the most from the newer, less-invasive treatment. It is thus possible to potentially choose more appropriate treatments, improve perioperative management, and reduce complication rates by identifying patients at risk before an operation. Increasing evidence[3-6] suggests that advanced age, ischemic foot ulcer, sensorineural impairment and a high C-reactive protein (CRP) level at the time of admission are risk factors for amputation.

Serious inflammation occurs when ischemic tissue is damaged, a process in which monocytes play a critical role. As a resource of numerous cytokines and chemicals, circulating monocytes first interact with platelets and endothelial cells, aggravating pro-thrombotic and inflammatory pathways[7]. High-density lipoprotein cholesterol (HDL-C) prevents monocytes' prooxidant and proinflammatory actions by blocking the macrophage migration and oxidation of low-density lipoprotein molecules and facilitating the cholesterol outflow from these cells[8]. The monocyte count to HDL-C ratio (MHR) is a novel inflammation-based biomarker identified as a prognostic marker and predictor of cardiovascular disorders[9-11]. An important benefit of this new marker is that it is easily obtainable and inexpensive. The aim of this study was to determine the predictive value of admission MHR for lower extremity amputation in patients undergoing an embolectomy for acute limb ischemia.

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Patients and Methods

This retrospective, single-center study included 269 patients who underwent an emergent embolectomy between January 2012 and December 2017 with acute leg ischemia. The research team obtained preoperative data (medical records, demographic characteristics, and laboratory test results), operational registers, and outcomes from medical files.

A total of 457 patients were admitted to our emergency department for ALI during the study period. One-hundred forty-eight patients were treated with medical therapy or endovascular methods. A total of 309 patients underwent an embolectomy for ALI. Twenty-four patients were excluded due to insufficient data. Unstable coronary artery disease (n = 4), patients with active cancer and/or under treatment of cancer (n = 3), corticosteroid therapy (n = 5), and infected wounds (n = 4) were eliminated from the study according to the exclusion criteria.

Hematopoietic system diseases, active glucocorticoid use, coronary revascularization in the previous six months, infection, cancer and a history of anticancer drug use, metabolic syndrome, and severe renal and liver disease all affect the total and the differential white blood cell (WBC) count. Due to the significant levels of leukocyte subtype changes in these patient groups, MHR would be increased. As a result, each of these factors was accepted as exclusion criteria. In the final analyses, 269 patients were included in the study (Figure 1).

Acute limb ischemia is defined as a rapid decline in limb perfusion that poses a risk to limb viability in patients who present within two weeks of the initiation of the acute event, according to the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II)[12]. In all our cases, sudden pain, pallor, coldness, and lack of pulse were present, while in some late cases, there was also a sense defect, limb fatigue, and less paralysis. The diagnosis was made by

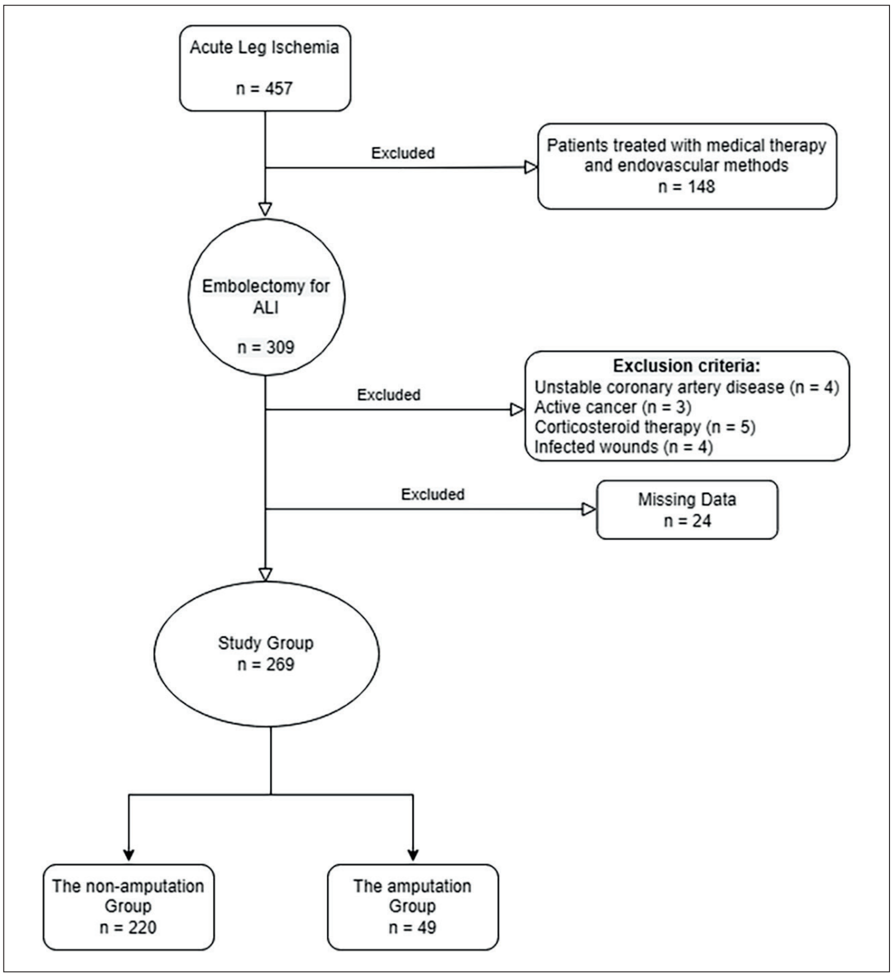

Figure 1. Flowchart diagram of the study population.

physical examination, doppler ultrasonography, computed tomography angiography, and rarely, digital subtraction angiography. In particular, in cases where acute leg ischemia is thought to have developed on an arteriosclerosis basis, an emergency angiography is preferred. To investigate the origin of acute leg ischemia, all patients were examined using abdominal ultrasonography and cardiac echocardiography following the embolectomy.

Baseline characteristics, laboratory results, computerized tomography scans, echocardiography, and peri/post-operative details were obtained from the hospital records. All laboratory data were obtained from venous blood samples at emergency department admission. The Siemens ADVIA 2120 analyzer (Siemens Healthcare, Erlangen, Germany) was used to calculate the WBC count, neutrophils, lymphocytes, and hemoglobin (Hb). The admission biochemical parameters, such as urea, creatinine, aspartate aminotransferase, glucose, CRP, and HDL-C, were also noted for all patients. The MHR was calculated by dividing the absolute monocyte count by the absolute HDL-C level. The neutrophil-lymphocyte ratio (NLR) was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count. The patients were contacted for follow-up at weeks 1 and 4 following discharge.

Surgical Procedure

All patients were planned to undergo the operation under local anesthesia; however, general anesthesia was required in some patients who developed complications during the procedure or decided to have revascularization with a distal bypass. Common, superficial and profunda femoral arteries were explored following groin incision. After heparinization, a transverse arteriotomy was performed, and an appropriate size Fogarty catheter was used for the embolectomy. All the patients had a femoral embolectomy, but some also underwent endarterectomy, patchplasty, and/or fasciotomy procedures. Back bleeding from the distal arterial tree upon embolectomy was utilized to evaluate the procedure's efficacy as a practical approach for all patients. Following embolectomy, evaluation of the distal arterial patency and satisfactory thrombus removal can be predicted by back bleeding from the target artery. Although intraoperative imaging in the hybrid room following embolectomy is the optimal choice, our clinic did not have this capability at the time of the study. As a result, we favored back bleeding, which is a conventional technique, to assess adequate thrombus removal. All post-operative patients were administered intravenous heparin and continued maintenance treatment with an oral anticoagulant if necessary.

The local ethics committee approved the study protocol. All patients gave informed consent.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation for normally distributed variables, while median and interquartile ranges were used for data with a non-normal distribution. Nominal variables were given as a number and a percentage. A normality analysis was performed using the Kolmogorov Smirnov test. The difference of the normally distributed variables between groups was evaluated with the Student's *t*-test. The Mann-Whitney U test was used for the comparison of non-normally distributed data between groups. The chi-squared or Fisher's exact test was used to compare categorical data. The cut-off points of NLR and MHR on early amputation were evaluated by a receiver operating characteristic (ROC) analysis and the area under the curve (AUC). With a multivariable logistic regression model and a backward stepwise technique, risk adjustment was utilized to discover independent predictors of early amputation, incorporating factors with $p = 0.05$ for the univariate analysis. To demonstrate the strength of the association, odds ratios and 95% confidence intervals were provided. A *p*-value of < 0.05 was considered significant.

Results

Baseline demographic characteristics and laboratory data of the patients are given in Table I. Of the 269 patients who underwent emergency embolectomy, 35.7% were female (n = 96), and 64.3% were male (n = 173). The mean age of all patients was determined to be 67.52 ± 12.37 years. Patients were also examined for other accompanying diseases. Most of the patients were current smokers (65.4%, n = 176), and hypertension (50.6%, n = 136), coronary artery disease (26.8%, n = 72), and atrial fibrillation (19%, n = 51) were diagnosed preoperatively (Table I). Amputations within the first 30 days following

Table I. Baseline demographic characteristics and the laboratory data of the patients.

	All patients (n = 269)	Non-amputation group (n = 220)	Amputation group (n = 49)	*p*
Age (years)	67.52 ± 12.37	67.5 ± 12.26	67.59 ± 12.95	0.963
Gender				0.1
Male	173 (64.3%)	136 (61.8%)	37 (75.5%)	
Female	96 (35.7%)	84 (38.2%)	12 (24.5%)	
Current smoker	176 (65.4%)	140 (63.6%)	49 (73.5%)	0.253
Hypertension	136 (50.6%)	116 (52.7%)	20 (40.8%)	0.177
Diabetes mellitus	64 (23.8%)	54 (24.5%)	10 (20.4%)	0.667
Atrial fibrillation	51 (19%)	44 (20%)	7 (14.3%)	0.471
Previous cerebrovascular event	10 (3.7%)	7 (3.2%)	3 (6.1%)	0.396
Previous coronary artery disease	72 (26.8%)	59 (26.8%)	13 (26.5%)	ns
Previous vascular operations				
Femoropopliteal bypass	15 (5.6%)	10 (4.5%)	5 (10.2%)	0.16
Aorto-bi/femoral bypass	16 (5.9%)	13 (5.9%)	3 (6.1%)	ns
Femorofemoral crossover	8 (3%)	5 (2.3%)	3 (6.1%)	0.162
Previous embolectomy	6 (2.2%)	3 (1.4%)	3 (6.1%)	0.076
Previous percutaneous intervention	7 (2.6%)	2 (0.9%)	5 (10.2%)	**0.003**
Preoperative hemoglobin	13.56 ± 2.49	13.77 ± 2.32	12.61 ± 3.01	**0.014**
Preoperative white blood cells (10^9/µl)	9,200 (7,600-11,150)	9,110 (7,432-10,900)	9,780 (8,800-11,550)	0.061
Preoperative neutrophil (10^9/µl)	6,360 (4,860-9,070)	6,060 (4,630-8,110)	9,070 (6,420-13,715)	**< 0.001**
Preoperative lymphocyte (10^9/µl)	1,580 (1,150-2,175)	1,640 (1,177.5-2,187.5)	1,360 (970-2,015)	0.075
Preoperative monocyte (10^9/µl)	580 (445-740)	540 (430-707.5)	790 (705-910)	**< 0.001**
Preoperative platelet (10^3/L)	231 (181.5-280.5)	231 (177-285.75)	223 (182.5-273)	0.838
Preoperative creatinine	1.02 ± 0.37	1 ± 0.31	1.08 ± 0.57	0.38
Preoperative urea	41 (29-56.5)	40 (29-56)	47 (29.5-60)	0.612
Preoperative aspartate aminotransferase	41 (26.5-53)	39 (27-52)	45 (23-80)	0.158
HDL	42 (36-47.5)	42.5 (36-48)	39 (35.5-44)	0.104
Preoperative C-reactive protein	35.6 (25.85-60.75)	32.1 (23.75-43.6)	88.4 (77.05-97.3)	**< 0.001**
Preoperative NLR	3.74 (2.56-6.63)	3.49 (2.43-6.27)	6.15 (3.41-12.64)	**< 0.001**
Preoperative MHR	14.34 ± 5.12	13 ± 4.08	20.35 ± 5.01	**< 0.001**
NLR ≥ 4.71	112 (41.6%)	81 (36.8%)	31 (63.3%)	**0.001**
MHR ≥ 15.8	92 (34.2%)	55 (25%)	37 (75.5%)	**< 0.001**

surgery were considered early amputations. The study population divided into two groups according to early amputation: the non-amputation group (n = 220) and the amputation group (n = 49). Two groups were compared according to various data. Previous percutaneous intervention ($p = 0.003$), preoperative hemoglobin ($p = 0.014$), preoperative neutrophil ($p < 0.001$), preoperative monocyte ($p < 0.001$), preoperative CRP ($p < 0.001$), preoperative NLR ($p < 0.001$), NLR≥4.71 ($p = 0.001$), preoperative MHR ($p < 0.001$), and MHR≥15.8 ($p < 0.001$) for patients who had amputations differed significantly from that of patients who did not have amputations.

Operative and postoperative characteristics of the patients are given in Table II. Patients admitted to the emergency department with acute limb ischemia were diagnosed with iliac artery embolism in 12.6%, femoropopliteal artery embolism in 85.1%, and graft embolism in 12.6%. In 81% of patients, arterial back bleeding was present after the embolectomy. Twelve patients underwent a distal bypass within 48 hours after the initial embolectomy. After the embolectomy, 43 patients (16%) required iloprost infusion. Patients who received iloprost treatment were individuals who were no longer eligible for surgery. The amputation and non-amputation groups were compared according to operative and postoperative data. The arterial occlusion site as a graft ($p = 0.041$), arterial back bleeding after the embolectomy ($p < 0.001$), postoperative iloprost infusion ($p < 0.001$), early distal bypass following the embolectomy ($p = 0.047$), and hospital mortality ($p < 0.001$) differed significantly between the two groups.

According to the univariate analysis, previous percutaneous intervention, preoperative hemoglobin level, preoperative neutrophil count, preoperative monocyte count, preoperative CRP, NLR, NLR≥4.71, MHR, MHR≥15.8, arterial back bleeding after embolectomy, and postoperative iloprost infusion were all significantly associated with early amputation. Based on the multivariate regression analysis, preoperative

Table II. Operative and postoperative characteristics of the patients.

	All patients (n = 269)	Non-amputation group (n = 220)	Amputation group (n = 49)	p
Arterial occlusion site				
Femoropopliteal	229 (85.1%)	190 (86.4%)	39 (79.6%)	0.326
Iliac	34 (12.6%)	27 (12.3%)	7 (14.3%)	0.884
Graft	34 (12.6%)	23 (10.5%)	11 (22.4%)	0.041
Arterial back bleeding after embolectomy	218 (81%)	202 (91.8%)	16 (32.7%)	< 0.001
Postoperative heparin infusion	70 (26%)	52 (23.6%)	18 (36.7%)	0.087
Postoperative iloprost infusion	43 (16%)	15 (6.8%)	28 (57.1%)	< 0.001
Early distal bypass following embolectomy	12 (4.5%)	7 (3.2%)	5 (10.2%)	0.047
Postoperative medications				
ASA	257 (95.5%)	210 (95.5%)	47 (95.9%)	ns
Warfarin	126 (46.8%)	107 (48.6%)	19 (38.8%)	0.275
Statin	64 (23.8%)	48 (21.8%)	16 (32.7%)	0.154
Cilostazol	127 (47.4%)	104 (47.5%)	23 (46.9%)	ns
Hospital mortality	11 (4.1%)	2 (0.9%)	9 (18.4%)	< 0.001

CRP, MHR, and no arterial back bleeding after the embolectomy were found to be independent predictors of amputation within 30 days after the embolectomy. According to this analysis, patients with higher CRP and MHR have a significantly higher amputation rate (HR: 1.148; CI: 1.075-1.225; $p < 0.001$ and HR: 1.547; CI: 1.003-2.387; $p = 0.04$, respectively). Patients with arterial back bleeding have a significantly lower amputation rate (HR: 0.106; CI: 0.02-0.558; $p = 0.008$) (Table III).

ROC curves were examined to explore the relationship between preprocedural NLR and amputation (Figure 2). For early amputation, the area under the curve was 0.69 (95% confidence interval [CI]: 0.609-0.77). Using a cut-off point of 4.71, the preprocedural NLR predicted amputation with a sensitivity of 63.3% and a specificity of 63.2% ($p < 0.001$). NLR was assumed to be a categoric variable according to this cut-off point (NLR≥4.71). ROC curves were used to explore the relationship between preprocedural MHR and amputation (Figure 3). For early amputation, the area under the curve was 0.868 (95% confidence interval [CI]: 0.818-0.918). Using a cut-off point of 15.8, preprocedural MHR predicted amputation with a sensitivity of 75.5% and a specificity of 75% ($p<0.001$). MHR was assumed to be a categoric variable according to this cut-off point (MHR≥15.8).

Table III. Independent predictors of amputation in univariate and multivariate analysis.

Variable	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Previous percutaneous intervention	12.386	(2.328-65.898)	**0.003**	4.223	(0.113-158.45)	0.436
Preoperative hemoglobin	0.832	(0.734-0.942)	**0.014**	0.981	(0.691-1.392)	0.914
Preoperative neutrophil	1.201	(1.112-1.298)	**< 0.001**	0.968	(0.655-1.43)	0.87
Preoperative monocyte	3.345	(1.646-6.798)	**0.001**	1.028	(0.121-8.692)	0.98
Preoperative C-reactive protein	1.181	(1.118-1.248)	**< 0.001**	1.148	(1.075-1.225)	**< 0.001**
NLR	1.116	(1.049-1.187)	**0.001**	1.185	(0.874-1.608)	0.275
NLR ≥ 4.71	2.955	(1.555-5.617)	**0.001**	0.337	(0.025-4.45)	0.408
MHR	1.432	(1.294-1.585)	**< 0.001**	1.547	(1.003-2.387)	**0.04**
MHR ≥ 15.8	9.25	(4.507-18.986)	**< 0.001**	0.086	(0.004-2.034)	0.128
Arterial back bleeding after embolectomy	0.043	(0.02-0.093)	**< 0.001**	0.106	(0.02-0.558)	**0.008**
Postoperative iloprost infusion	18.222	(8.426-39.408)	**< 0.001**	1.494	(0.283-7.883)	0.636

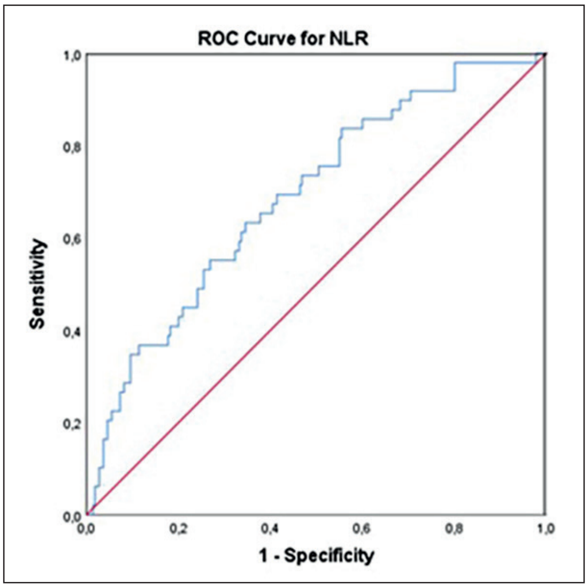

Figure 2. Receiver operating characteristic for neutrophil/lymphocyte ratio vs. early amputation.

Discussion

In this study, the clinical characteristics and laboratory parameters of patients who underwent an embolectomy due to acute leg ischemia were retrospectively examined. The results of the current study revealed that a simple ratio (MHR) derived from a low-cost and universally available test (complete blood cell count) provides relevant data concerning the amputation risk of patients who have had an embolectomy. To the best of our knowledge, this is the first study in the literature to have demonstrated a numerical risk of early term amputation following an embolectomy in association with MHR, confirming that this ratio is a new inflammation-based marker.

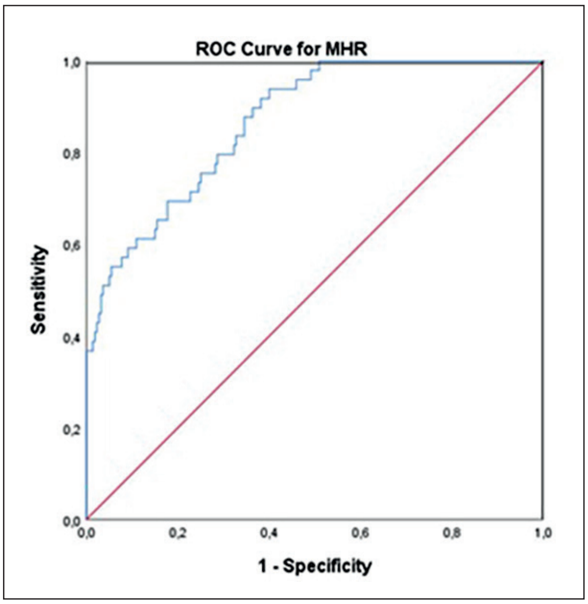

Figure 3. Receiver operating characteristic for monocyte/HDL-C ratio vs. early amputation.

Acute leg ischemia should be evaluated in the emergency department due to its poor prognosis with high mortality and amputation rates and should be treated immediately[1]. Both the physician and the patient must be aware of the disease's prognosis during the emergency treatment procedure. Thus, the purpose of this study was to identify the predictors of amputation as a prognostic factor in patients who underwent embolectomy for ALI. In clinical practice, an amputation is considerably linked with mottling, muscle tenderness, motor loss, sensory loss, and missing ankle Doppler; however, none gives quantitative evidence for predicting amputations in individuals with ALI. Contrary to the categorical nature of these clinical findings, MHR presents an objective numerical option of amputation risk. According to our findings, an increased risk of amputation is associated with increasing MHR. As a result of this study, MHR can be used as a valuable prognostic tool, allowing physicians to quantify the probability of an amputation prior to an embolectomy.

Previously published reports identified numerous significant amputation associations based on clinic findings, risk factors, and laboratory data, such as history of myocardial infarction, ischemia, diabetes, previous vascular surgery, increased age, long time from the onset of symptoms to the operation, sensorineural deficit, presence of a foot ulcer, increased creatine kinase, high CRP, elevated NLR, anemia, and absence of ankle Doppler signals[13-19]. To date, no study has analyzed the association of MHR and amputations in patients who underwent an emergency embolectomy. It became possible to demonstrate in this study, for the first time in the literature, that MHR is an independent risk factor for an amputation following an embolectomy in individuals with ALI.

MHR was identified as a new inflammation marker and was used in several studies to predict clinical outcomes. Furthermore, in many cardiovascular disorders, MHR has proved to be predictive for morbidity and mortality, including stent thrombosis in ST-segment elevation myocardial infarction and in asymptomatic abdominal aortic aneurysm patients[20,21].

Atherogenesis is not simply passive damage with lipid infiltration but an aggressive, inflammatory process. Experimental models demonstrate the function of inflammation in atherosclerosis initiation, progression, and complications[22]. High monocyte counts and low levels of HDL-C have been shown to be important for inflammation[23], and it has been shown that monocytes have a crucial pathophysiologic role in the development of atherosclerotic plaque and the deposition of lipids therein[24]. The role of monocytes in atherogenesis is not limited to macrophage functions inside the arterial wall. In many biochemical mechanisms, monocytes mediate inflammatory responses, such as growth factors, cytokines, eicosanoids, platelet-derived activation products, and immune stimulatory agents. Monocytes in circulation produce a variety of substances, and their receptors interact with platelets and endothelial cells, resulting in inflammation, thrombosis, and atherosclerosis[20].

On the other hand, HDL-C produces a number of biological activities, including antithrombotic, antioxidant, anti-inflammatory, and anti-atherosclerotic effects, that improve endothelial function[25,26]. As a result, a low HDL-C level may result in diminished cardiovascular protection. Thus, when taken together, MHR is a more accurate marker of atherosclerosis and thrombosis than isolated monocyte counts or HDL levels. In view of these findings, we hypothesized that the MHR could be associated with a poor outcome in patients undergoing an embolectomy.

Previous studies[1,13,16] showed that delaying the treatment of ischemia, having considerable underlying atherosclerosis, and having inadequate arterial back bleeding after surgery all increase the risk of ALI-related amputations. In clinical practice, the adequacy of clot removal is determined routinely and accurately during surgery based on post-embolectomy back bleeding. When the surgeon is not satisfied with back bleeding, it is believed that distal patency was not ensured. According to the study by Tasoglu et al[19], inadequate back bleeding is associated with poor outcomes following an embolectomy. Consistent with the literature, our study demonstrates that the absence of arterial back bleeding after an embolectomy was found to be an independent predictor of amputation within 30 days following surgery.

Numerous systemic proinflammatory biomarkers were investigated for their predictive value in post-embolectomy amputations. As an acute phase reactant, C reactive protein serves as an excellent indicator of assessing systemic inflammatory responses. Saskin et al[27] evaluated the role of inflammatory markers in predicting amputations following thromboembolism surgery and revealed that the preoperative CRP level was an independent predictor of amputations. In our study, admission CRP, a traditional inflammatory marker, was revealed to be an independent predictor of amputation following an embolectomy in patients with ALI.

The major limitation of our study is its retrospective design. Another limitation of the study is that it was carried out in a single center. We also could not compare MHR to other cytokines and inflammatory markers, such as myeloperoxidase and interleukin-6. There is still the chance of residual confounding despite our best attempts to control for relevant clinical characteristics. Despite these limitations, our research is the first of its type to examine the link between MHR and early amputation after an embolectomy. To uncover all factors affecting post-embolectomy amputation, large-scale, multi-center, prospective studies are required.

Conclusions

In conclusion, acute limb ischemia is responsible for a high proportion of morbidity and mortality. Our results indicate that preoperative MHR – a simple ratio derived from a low-cost and universally available test – is an independent predictor of amputations in ALI patients following an embolectomy as a novel inflammation marker. The routine use of MHR in clinical practice may be considered a prognostic indicator for ALI patients in the near future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

Institutional review board (University of Health Sciences Konya City Hospital Medical Specialty Training Board) approved the study with the protocol number TUEK-2018/13-13..

Informed Consent

All patients provided written informed consent for their clinical records to be used for research purposes. The study was conducted in line with the Declaration of Helsinki.

Data Availability

The dataset used during the current study is available from the corresponding author, however it is not allowed to be shared publicly.

Authors' Contribution

MCÇ designed, carried out the study and wrote the article. ISY and ANB made data collection. The data was interpreted by MD. KD drafted the article. The manuscript was reviewed and edited by all authors. Each author contributed to the manuscript's intellectual content.

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