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Diagnostic Efficacy of Monocyte Count and High-density Lipoprotein Ratio Combined with Cystatin C in the Diagnosis of Lower Extremity Atherosclerotic Disease in Patients with Essential Hypertension

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Abstract: *This study aims to investigate the efficacy of combining monocyte count and high-density lipoprotein ratio (MHR) with cystatin C in diagnosing lower extremity atherosclerotic disease (LEAD) in patients with essential hypertension (EH). A total of one hundred seventy-eight patients with EH were admitted to the Department of Family Medicine at the Second Affiliated Hospital of Guilin Medical College from July 2021 to December 2022. Among these patients, those who developed LEAD constituted the combined group (88 cases), while those who did not develop LEAD formed the control group (90 cases).A comparison between the two groups regarding age, history of coronary heart disease, white blood cell(WBC), red blood cell (RBC), hemoglobin(Hb), monocyte count, urea nitrogen, creatinine, cystatin C, total cholesterol(TC), and MHR revealed statistically significant differences ($P < 0.05$).Spearman rank correlation analysis revealed that the MHR was positively correlated with age, WBC,monocyte count, urea nitrogen , creatinine, uric acid, and TG . Conversely, MHR exhibited negative correlations with RBC, Hb , and HDL. Cystatin C was positively correlated with age, WBC, monocytes, urea nitrogen, creatinine, and uric acid. Additionally, cystatin C demonstrated negative correlations with RBC, Hb, and LDL. Furthermore, cystatin C was positively correlated with MHR. Multifactorial logistic regression analysis indicated that MHR and cystatin C are significant risk factors for the development of LEAD in patients with EH. The results of the receiver operating characteristic (ROC) curve analysis revealed that in patients with EH, the area under the ROC curve for MHR, cystatin C, and their combination in relation to the development of LEAD were 0.714 (95% CI: 0.639 - 0.788), 0.809 (95% CI: 0.745 - 0.873), and 0.834 (95% CI: 0.775 - 0.894), respectively. The optimal cut-off values were 0.398,1.275, 0.562, corresponding to sensitivities of 0.841, 0.693, 0.682,and specificities of 0.467, 0.800, 0.878, respectively. MHR and cystatin C are independent risk factors for the development of LEAD in patients with EH. Furthermore, there exists a positive correlation between these two factors, which holds predictive value for the onset of LEAD in this patient population.*

Keywords: *Essential Hypertension, Lower Extremity Atherosclerosis Disease, Monocyte Count and High-density Lipoprotein Ratio, Cystatin C*

1. Introduction

Essential hypertension (EH) is one of the common clinical cardiovascular diseases, and more than half of the patients are elderly. Survey data from 2018 indicated that the prevalence rates among individuals aged 60 to <70 years, 70 to <80 years, and ≥80 years were 54.4%, 65.2%, and 66.7%, respectively [1]. Lower extremity atherosclerosis disease (LEAD) is a common complication associated with EH, and its prevalence has been steadily increasing in recent years, significantly impacting patients' quality of life [2]. The monocyte count and high-density lipoprotein ratio (MHR) is a newly

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identified inflammatory marker that has been linked to cardiovascular disease [3-6]. Cystatin C, an inflammation-related indicator, plays a role in the formation and progression of atherosclerosis by facilitating the adhesion and phagocytosis of neutrophils [7]. Currently, there is a scarcity of domestic research reports on the relationship between MHR, cystatin C, and the incidence of LEAD in patients with EH. This article aims to investigate the correlation between peripheral blood MHR and cystatin C levels and the occurrence of LEAD in EH patients, thereby providing a theoretical basis for predicting the onset of LEAD in this population.

2. Methods

2.1 General materials

A total of 178 patients diagnosed with EH were admitted to the General Medicine Department of the Second Affiliated Hospital of Guilin Medical College between July 2021 and December 2022, forming the subjects of this study. The inclusion criteria encompassed patients diagnosed with EH for the first time, as well as those with a prior diagnosis, in accordance with the diagnostic criteria outlined in the "2018 Revised Version of the Chinese Guidelines for the Prevention and Treatment of Hypertension" [8]. Additionally, patients diagnosed with LEAD for the first time and those with a previous diagnosis were included, based on the criteria specified in the "Chinese Expert Recommendations on the Diagnosis and Treatment of Atherosclerotic Disease of the Lower Limbs (2007)" [9]. Exclusion criteria consisted of individuals with a history of drug abuse, secondary hypertension, adult mental stress-related hypertension, tumors, lower limb amputation, inflammation and fever, mental disorders, or those with incomplete information and lack of cooperation. Among the study participants, there were 85 females and 93 males, with ages ranging from 39 to 88 years (mean age 66.89 ± 11.29 years). This research protocol received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Guilin Medical College, and all participants provided written informed consent.

2.2 Data collection

Gender and age of the study participants were collected.

2.3 Blood pressure and physical measurements

After the study subjects rested for 15 minutes, professional nurses measured the blood pressure in both upper limbs using a standardized Omron blood pressure monitor. The side with the higher blood pressure was recorded as the measurement result. Each measurement was separated by a 5-minute interval, and the final result was determined by averaging the two measurements. If the difference in diastolic or systolic blood pressure between the two sides exceeded 5 mmHg, a third measurement was conducted, with the final result based on the average of all three measurements.

2.4 Blood tests and biochemical indicators

Fasting blood samples were collected from the cubital vein of all research subjects. The XN-9000 fully automatic blood analyzer, manufactured by Sysmex Company in Japan, was employed to measure white blood cell (WBC), red blood cell(RBC), hemoglobin(Hb), and monocyte counts. Additionally, the c702 automatic biochemistry instrument from Roche, a Swiss company, was utilized to assess levels of urea nitrogen, creatinine, and cystatin C, total cholesterol(TC), triglycerides(TG), low-density lipoprotein(LDL), and high-density lipoprotein(HDL).MHR was calculated as the monocyte count divided by the high-density lipoprotein level.

2.5 Ultrasound of lower extremity arteries

After instructing the patient to lie supine for 15 minutes, the common femoral artery, deep femoral artery, superficial femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery, peroneal artery, and dorsalis pedis artery of both lower limbs were evaluated. During this procedure, it is important to avoid applying pressure to the lower limbs, and the angle between the ultrasound beam and the blood flow should be maintained at less than 60° to accurately assess the presence of stenosis in the lower limbs. Based on this assessment, patients with EH who developed LEAD were classified into

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the combined group (88 cases), while EH patients who did not develop LEAD were designated as the control group (90 cases) during the same period.

2.6 Statistical analysis

SPSS version 26.0 statistical software was utilized for the analysis. Measurement data that conform to a normal distribution are expressed as (x±s), with comparisons between groups conducted using the two independent samples t-test. Count data are presented as [cases (%)], and group comparisons are performed using the chi-squared test. Additionally, Spearman rank correlation analysis was employed, and multivariate logistic regression analysis was conducted to identify the influencing factors of LEAD in patients with EH. The receiver operating characteristic (ROC) curve was utilized to evaluate the predictive value of MHR, cystatin C, and their combination for the occurrence of LEAD in EH patients. The value of $p < 0.05$ was considered to indicate statistical significance.

3. Results

3.1 Comparison of general clinical data and laboratory test indexes between the two groups of patients

Statistically significant differences were observed between the two groups concerning age, history of coronary heart disease, WBC, RBC, Hb, monocyte count, urea nitrogen, creatinine, cystatin C, TC, and MHR ($P < 0.05$). Specifically, the combined group exhibited higher levels of age, WBC, monocyte count, urea nitrogen, creatinine, cystatin C, and MHR compared to the control group. Conversely, the combined group demonstrated lower levels of RBC, Hb, and TC than the control group. No statistically significant differences were found in the comparison of gender, history of type 2 diabetes, smoking, alcohol consumption, uric acid, TG, HDL, and LDL ($P > 0.05$). (Table 1)

Table 1: Comparison of general clinical data and laboratory test indexes between the two groups of patients

variate	Combined group (n=88)	Control group(n=90)	$t/t'/\chi^2/z$	*P*
Age(years)	73.00±9.42	60.61±9.86	-7.420	0.000
gender(male/female)	53/35	40/50	4.442	0.055
history of coronary heart disease(n[%])	38(43.2)	10(11.1)	22.848	0.000
history of type 2 diabetes(n[%])	60(68.2)	56(62.2)	0.542	0.462
smoking(n[%])	10(11.4)	10(11.1)	0.001	0.979
alcohol consumption(n[%])	10(11.4)	12(13.3)	0.038	0.846
WBC($\times10^9$/L)	8.60±4.80	6.96±1.95	-2.648	0.008
RBC($\times10^9$ /L)	3.82±0.84	4.49±0.55	-6.388	0.000
Hb(g/L)	110.84±22.87	130.03±15.27	-6.083	0.000
monocyte count ($\times10^9$/L)	0.75±0.71	0.50±0.17	-4.665	0.000
Urea nitrogen (mmol/L)	8.28±4.94	5.67±1.79	-3.682	0.000
creatinine(umol/L)	128.51±109.99	76.20±18.47	-5.686	0.000
Cystatin C(mg/L)	1.76±0.97	1.06±0.27	-7.111	0.000
uric acid(umol/L)	359.49±134.45	335.09±115.20	-1.385	0.166
TC(mmol/L)	4.38±1.34	5.15±4.03	-2.159	0.031
TG(mmol/L)	2.03±1.81	2.33±2.13	-1.325	0.185
HDL(mmol/L)	1.09±0.28	1.18±0.35	-1.584	0.113
LDL(mmol/L)	2.65±1.02	3.20±3.18	-1.763	0.078
MHR	0.72±0.51	0.46±0.19	-4.924	0.000

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3.2 Correlation analysis of MHR, cystatin C and other indicators

Spearman rank correlation analysis revealed that MHR was positively correlated with age, WBC, monocyte count, urea nitrogen, creatinine, uric acid, and TG. Conversely, MHR exhibited a negative correlation with RBC, Hb, and HDL. Additionally, MHR showed no correlation with TC and LDL. Cystatin C was positively correlated with age, WBC, monocyte count, urea nitrogen, creatinine, and uric acid, while it displayed a negative correlation with RBC, Hb, and LDL. Furthermore, cystatin C showed no correlation with TG and HDL, but it was positively correlated with MHR.(Table 2)

Table 2: Correlation of MHR、cystatin C and other indicators

variate	age		WBC		RBC		Hb	
	r	P	r	P	r	P	r	P
Cystatin C	0.473	0.000	0.206	0.006	-0.484	0.000	-0.501	0.000
MHR	0.163	0.030	0.479	0.000	-0.158	0.035	-0.168	0.025
variate	monocyte count		urea nitrogen		creatinine		uric acid	
	r	P	r	P	r	P	r	P
Cystatin C	0.340	0.000	0.510	0.000	0.712	0.000	0.425	0.000
MHR	0.824	0.000	0.171	0.023	0.290	0.000	0.224	0.003
variate	TC		TG		HDL		LDL	
	r	P	r	P	r	P	r	P
Cystatin C	-0.257	0.001	-0.089	0.239	-0.128	0.089	-0.272	0.000
MHR	-0.082	0.277	0.201	0.007	-0.501	0.000	-0.110	0.145

3.3 Multifactorial Logistic Regression Analysis

In this study, the indicators with $P < 0.05$ listed in Table 1 were utilized as independent variables; however, monocyte count and HDL were excluded due to collinearity with the monocyte count, HDL, and MHR. The presence of LEAD in patients with EH was designated as the dependent variable (where assignment was yes = 1 and no = 0). Multifactorial logistic regression analysis revealed that MHR and cystatin C are significant risk factors for LEAD in patients diagnosed with EH.(Table 3)

Table 3: Multifactorial Logistic Regression Analysis of LEAD Occurrence in EH Patients

variate	β	SE	Waldχ^2	*P*	OR	95%*CI*
MHR	2.320	0.871	7.097	0.008	10.172	1.846-56.046
Cystatin C	2.933	0.602	23.709	0.000	18.778	5.767-61.14

3.4 Predictive value of MHR, cystatin C and their combination for the development of LEAD in patients with EH

In patients with EH, the areas under the ROC curve for MHR, cystatin C, and their combination regarding the occurrence of LEAD were 0.714 (95% CI: 0.639–0.788), 0.809 (95% CI: 0.745–0.873), and 0.834 (95% CI: 0.775–0.894), respectively. The optimal cutoff values are 0.398, 1.275, and 0.562, with corresponding sensitivities of 0.841, 0.693, and 0.682, and specificities of 0.467, 0.800, and 0.878, respectively. MHR, cystatin C, and their combination demonstrate a certain predictive value for the occurrence of LEAD in patients with EH. Notably, the sensitivity of combined detection is lower than that of MHR, while its specificity is the highest. (Fig 1. Table 4)

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Table 4: Predictive value of MHR, cystatin C and their combination for the development of LEAD in patients with EH

variate	AUC	95%*CI*	cutoff values	*P*	sensitivity(%)	specificity(%)
MHR	0.714	0.639~0.788	0.398	0.000	84.1	46.7
Cystatin C	0.809	0.745~0.873	1.275	0.000	69.3	80.0
Combination	0.834	0.775~0.894	0.562	0.000	68.2	87.8

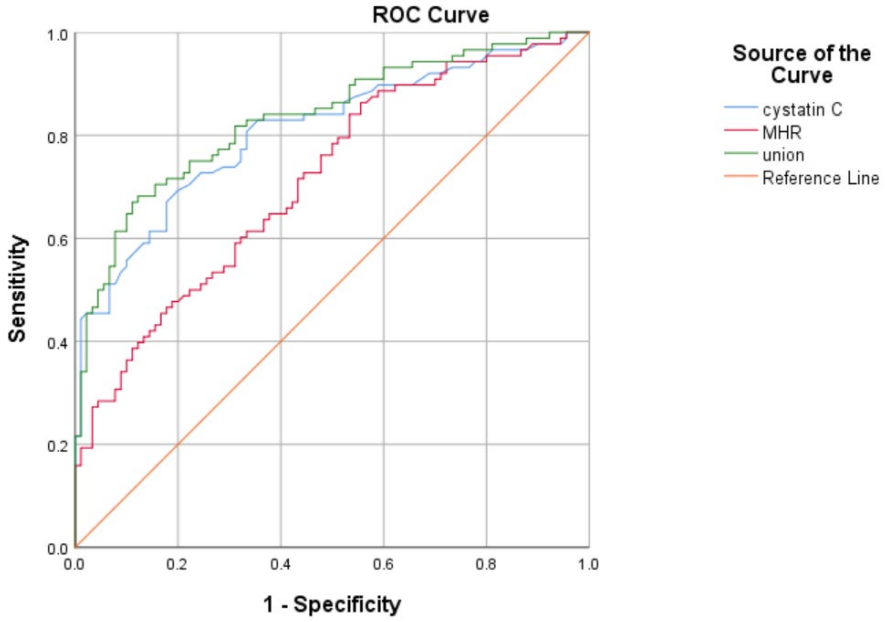

Figure 1: ROC curves of MHR, cystatin C and their combination for the diagnosis of LEAD in patients with EH

4. Discussion

LEAD refers to a disease characterized by atherosclerosis in the lower limbs, which leads to arterial stenosis or even occlusion, resulting in chronic or acute ischemic symptoms in the tissues of the lower limbs. This condition primarily occurs in patients with hypertension. When blood pressure increases, the force exerted by the blood on the vessel walls rises, causing the arterial endothelial cells to retract and disrupting the continuity of the endothelium. This disruption results in mechanical damage and functional abnormalities of the vascular endothelium. Patients with hypertension often exhibit lipid metabolism disorders, characterized by elevated levels of TC and TG, which can accumulate at sites of endothelial damage and ultimately contribute to the development of atherosclerosis. Furthermore, following vascular endothelial injury, there is an increase in the expression of adhesion factors, which promotes the adhesion of monocytes to the blood vessel wall, thereby triggering a vascular inflammatory response. Concurrently, an imbalance in the secretion of vasodilator factors (such as nitric oxide and prostaglandin E1) and vasoconstrictor factors (such as endothelin and angiotensin II) leads to vasomotor dysfunction, further exacerbating the occurrence and progression of atherosclerosis. Additionally, hypertensive patients frequently exhibit heightened sympathetic nervous system activity, overactivation of the renin-angiotensin system, and insulin resistance. These factors can result in oxidative stress damage, endoplasmic reticulum stress, collagen fiber deposition, vascular smooth muscle cell proliferation, and fibrinolysis. The resulting systemic imbalance and other pathological changes contribute to the advancement of atherosclerosis [10].

Most patients with EH combined with LEAD exhibit no obvious symptoms in the early stages.

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When symptoms such as intermittent claudication, pale skin, and abnormal sensations manifest, the condition often progresses rapidly. Once ulceration or necrosis occurs in the lower limbs, the likelihood of amputation increases significantly [11]. Due to the absence of clear symptoms in the initial stages, many patients miss the opportunity for early diagnosis and treatment. Therefore, it is essential to identify cost-effective and easily accessible screening indicators to facilitate early detection of LEAD in patients with EH.

Cystatin C is a cysteine protease inhibitor with a molecular weight of 13.3 kDa, and it is abundantly present in body fluids and tissue cells. As a non-glycosylated protein, its production rate remains remarkably stable [12]. The mechanism of action of cystatin C in atherosclerosis can be outlined as follows: (1) Cystatin C and its degradation products can chemoattract neutrophils, participate in inflammatory reactions, and induce atherosclerosis; (2) Cystatin C can damage vascular endothelial cells, influence the expression of nitric oxide, promote platelet adhesion, and increase the risk of atherosclerosis; (3) it can reduce the activity of cathepsins, prevent the breakdown of proteases, and contribute to the reconstruction of the blood vessel wall matrix. When the blood vessel wall is damaged, the balance between cystatin C and protease is disrupted, which compromises arterial integrity, leads to an increase in blood pressure, and ultimately induces atherosclerosis. This study found that the cystatin C level in the combined group was significantly higher than that in the control group, with a statistically significant difference ($P < 0.05$). Additionally, Zhang Jincao et al. [13] reported that cystatin C is closely associated with atherosclerotic plaques, and the results of this study corroborate their findings.This study found that the leukocyte levels in the combined group were significantly higher than those in the control group, with a statistically significant difference ($P < 0.05$). Spearman rank correlation analysis revealed a positive correlation between cystatin C and WBC. Leem AY et al. [14] have identified cystatin C as a marker of chronic inflammation in the body, indicating that its levels are directly proportional to WBC during the inflammatory response. This study aligns with those findings. Furthermore, it was observed that the levels of urea nitrogen and creatinine in the combined group were also higher than in the control group, with statistically significant differences ($P < 0.05$). Spearman rank correlation analysis indicated a positive correlation between cystatin C and both urea nitrogen and creatinine. However, urea nitrogen and creatinine levels are unstable and can be influenced by factors such as age, race, gender, and body composition, making them unsuitable for early evaluation of LEAD in patients with EH. Cystatin C, on the other hand, can freely pass through the glomerular filtration membrane under physiological pH conditions and is subsequently degraded or reabsorbed in the proximal convoluted tubule, which makes it a reliable indicator of glomerular filtration rate [15-16].The concentration of cystatin C is primarily influenced by glomerular filtration rate and is not significantly affected by variables such as gender, age, diet, hemolysis, and bilirubin levels. Therefore, cystatin C is a valuable factor for the early evaluation of LEAD in patients with EH [17].

Atherosclerosis involves multiple reactions, including oxidative stress, lipid regulation, inflammatory responses, and endothelial dysfunction [18]. At the molecular level, the accumulation of inflammatory cells, the formation of foam cells, and the apoptosis and degradation of smooth muscle cells and extracellular matrix are crucial to the development of arterial plaques. Monocytes migrate continuously, initially differentiating into macrophages and subsequently transforming into macrophage-derived foam cells. Hypertension positively regulates this transformation process, ultimately contributing to the onset of atherosclerosis [19]. HDL combats atherosclerosis through several mechanisms: (1) it inhibits the migration and differentiation of monocytes [20]; (2) it oxidizes LDL, which accelerates the formation of macrophage-derived foam cells and promotes their binding to scavenger receptors, thereby facilitating the progression of atherosclerosis. Additionally, HDL and paraoxonase work together to inhibit the oxidation of LDL [21]. Due to the opposing effects of monocytes and HDL, the MHR has recently been utilized as a systemic inflammation indicator to assess atherosclerosis in clinical practice [22-23].This study found that the MHR of the combined group was significantly higher than that of the control group, with a statistically significant difference ($P < 0.05$). Additionally, research conducted by Ding Yan et al. [24] indicated that MHR increases with the severity of lower limb arterial stenosis, identifying high MHR as a risk factor for the development of lower limb arterial stenosis, which aligns with the findings of this study. Similarly, the study by Tu Zhenxing et al. [25] demonstrated a positive correlation between MHR and the severity score of lower limb arterial conditions, further supporting the results presented here.This study found that Spearman rank correlation analysis indicated a positive correlation between cystatin C and MHR. Additionally, multifactorial logistic regression analysis identified MHR and cystatin C as risk factors for the occurrence of LEAD in patients with EH. ROC curve analysis revealed that the sensitivity was lower when MHR and cystatin C were used in combination, while the specificity was highest in this

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combined approach. The occurrence and progression of EH and LEAD are both associated with inflammatory responses, and both MHR and cystatin C serve as inflammatory markers. This study selected these two indicators to evaluate the diagnostic value for LEAD in EH patients through ROC curve analysis. The results demonstrate that MHR, cystatin C, and their combined use possess predictive value for the occurrence of LEAD in patients with EH. However, the sensitivity is low when these markers are used in combination, leading to a relatively high rate of missed diagnoses in clinical settings. This may be attributed to the severity of coronary heart disease affecting sensitivity. In future studies, we will further assess sensitivity by increasing the sample size and categorizing patients with coronary heart disease based on the Gensini score. The high specificity observed in the combined use indicates a strong exclusion value for screening LEAD. Compared to traditional predictors such as interleukin 8, interleukin 6, and tumor necrosis factor, MHR and cystatin C are straightforward to implement, cost-effective, readily available, and reproducible, making them particularly advantageous for community and primary healthcare settings.

Age is an independent risk factor for atherosclerosis, with chronic inflammatory responses serving as the key mechanism that mediates the relationship between age and the formation of atherosclerosis [26]. Research conducted by Alba Fernández-Sanlé et al. [27] indicates that age plays a particularly significant role in the occurrence and progression of EH. Specifically, for each additional year of age, the prevalence of EH increases by 4%. As individuals age, blood vessels undergo structural changes; smooth muscle cells in these vessels proliferate and migrate in substantial numbers, enhancing their ability to secrete extracellular matrix. This process results in decreased vascular elasticity, dilation of blood vessel lumens, and vascular remodeling, ultimately contributing to atherosclerosis [28-29]. This study found that the average age of the combined group was significantly higher than that of the control group, with a statistically significant difference ($P < 0.05$). Consistent with findings by Zhang Cuntai et al. [30], the incidence of atherosclerosis also rises with advancing age. Consequently, increasing age is an unavoidable risk factor for patients with EH to develop lower extremity artery disease (LEAD). Therefore, it is essential for elderly patients to manage their health proactively and control other modifiable risk factors.

RBC membranes contain a substantial amount of free cholesterol, participate in plasma lipid metabolism, and are involved in the reverse transport of cholesterol, which plays a crucial role in the formation and progression of atherosclerosis [31]. The primary function of Hb is to ensure an adequate supply of oxygen to body tissues. Low Hb levels can result in tissue hypoxia and altered blood flow patterns, potentially contributing to the development of atherosclerosis [32]. This study demonstrated that the RBC and Hb levels in the combined group were significantly lower than those in the control group, with the differences being statistically significant ($P < 0.05$). Delbosc et al. [33] observed in a rabbit aortic atherosclerosis model that RBC can infiltrate the arterial wall during the atherosclerotic plaque stage and be phagocytosed by smooth muscle cells, leading to a reduction in RBC, which aligns with the findings of this study. Furthermore, research by Hong et al. [34] indicated that Hb levels were negatively correlated with the absolute necrotic core volume of atherosclerotic plaques in patients with coronary heart disease, suggesting that lower Hb levels are associated with a greater plaque burden.Low Hb levels may significantly contribute to the pathophysiological processes involved in the occurrence and progression of atherosclerosis, a finding that aligns with the results of this study.Consequently, for patients with EH and LEAD, it is crucial to closely monitor RBC and Hb levels. In future studies, it is recommended to increase the sample size and simultaneously monitor relevant data, including reticulocyte count, erythropoietin levels, folic acid, vitamin B12, and iron, to eliminate potential confounding factors. This approach will further elucidate the occurrence of lower limb symptoms in hypertensive patients, particularly in relation to specific ranges of RBC and Hb in cases of arterial disease.

This study found that the TC level in the combined group was lower than that in the control group, with a statistically significant difference ($P < 0.05$). Additionally, the levels of TG, HDL, and LDL in the combined group were lower than those in the control group; however, these differences were not statistically significant ($P > 0.05$). According to the "Chinese Expert Recommendations for the Diagnosis and Treatment of Atherosclerotic Diseases of the Lower Limbs (2007)" [9], dyslipidemia, characterized by increased serum TC,LDL,and TG levels, decreased HDL levels, is associated with the onset of LEAD. The results of this study are inconsistent with the findings presented in the aforementioned recommendations. A possible explanation for this discrepancy is that the majority of the study subjects were elderly patients with poor compliance and challenges in managing blood lipid levels. Such patients typically require long-term, combined use of multiple lipid-lowering medications. This study did not categorize participants based on the types of lipid-lowering drugs used, which may account for the lack of positive results in certain blood lipid indicators during inter-group comparisons.

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Future studies that increase the sample size and classify participants according to the types of lipid-lowering medications are likely to yield more insightful conclusions.

5. Limitations

This study has several limitations: (1) It is a small-sample, single-center cohort study, and the findings require further validation through multi-center, large-sample studies; (2) Patients included in this study were only tested once, which may introduce errors in the calculation of the MHR. Future research should measure MHR multiple times and compute an average for statistical analysis; (3) The progression of EH combined with LEAD is a long-term process, and this study captures only a single time point in the disease's development. While the MHR has been calculated, subsequent studies should conduct regular follow-ups of the included patients to monitor MHR over time; (4) The dietary habits in this region are characterized by high salt intake and relatively low protein consumption. Future studies should categorize participants based on different dietary patterns and further explore the relationship between MHR, cystatin C, and the combination of EH with LEAD at various time points.

6. Conclusion

In summary, this study proposes for the first time that MHR and cystatin C are independent risk factors for the occurrence of LEAD in patients with EH. These two factors are positively correlated and exhibit significant predictive value for the onset of LEAD in this patient population. Additionally, this research establishes, for the first time, the relationship between MHR, cystatin C, and the combination of EH with LEAD. Consequently, it is recommended that in EH patients with elevated levels of both MHR and cystatin C, a color Doppler ultrasound examination of the blood vessels in both lower limbs be conducted promptly. This approach facilitates the early detection and active treatment of LEAD, thereby enhancing the patient's long-term prognosis and quality of life while reducing the economic burden on patients, their families, and society.

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