European Review for Medical and Pharmacological Sciences 2021; 25: 3453-3459

Neutrophil-to-lymphocyte ratio but not monocyte-to-HDL cholesterol ratio nor platelet-to-lymphocyte ratio correlates with early stages of lower extremity arterial disease: an ultrasonographic study

L. SANTORO[1,2], P.M. FERRARO[1,3,4], A. NESCI[1,2], A. D'ALESSANDRO[1,5], N. MACEROLA[1,5], F. FORNI[1,6], R. TARTAGLIONE[1,6], R. DE VITIS[1,7], A. GASBARRINI[1,5], A. SANTOLIQUIDO[1,2]

[1]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[2]U.O.S.D. Servizio di Angiologia e Diagnostica Vascolare non Invasiva, Rome, Italy
[3]Terapia Conservativa della Malattia Renale Cronica, U.O.C. Nefrologia, Dipartimento di Scienze Mediche e Chirurgiche, Rome, Italy
[4]Dipartimento Universitario di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy
[5]Dipartimento di Scienze Mediche e Chirurgiche, Rome, Italy
[6]Istituto di Biochimica e Biochimica Clinica, Rome, Italy
[7]Istituto di Clinica Ortopedica, Rome, Italy

Abstract. – OBJECTIVE: The role of inflammatory markers as neutrophil-to-lymphocyte ratio (NLR), monocyte-to-high-density lipoprotein-cholesterol ratio (MHR), and platelet-to-lymphocyte ratio (PLR) in cardiovascular diseases has been widely investigated in recent years. In the context of lower extremity arterial disease (LEAD), this association has been mainly studied in the advanced stages. The aim of our study was to investigate the role of these inflammatory markers in all stages of LEAD, including early ones, using ultrasonography as diagnostic tool, together with ankle-brachial index (ABI) determination.

PATIENTS AND METHODS: In this cross-sectional observational study, we enrolled 240 patients undergoing ultrasonographic evaluation of the lower limb arteries and ABI determination because of symptoms suggestive of LEAD or presence of known cardiovascular risk factors.

RESULTS: In our study population, we found that ultrasonographic categories of LEAD were associated with NLR, but not with MHR and PLR.

CONCLUSIONS: These results confirm that a specific pattern of inflammation can be found in all stages of LEAD, including early ones.

Key Words:
Lower extremity arterial disease, Ultrasonographic score, Neutrophil-to-lymphocyte ratio, Monocyte-to-high-density lipoprotein-cholesterol ratio, Platelet-to-lymphocyte ratio, Ankle-brachial index.

Introduction

Lower extremity arterial disease (LEAD) represents a manifestation of systemic atherosclerosis, affecting and limiting blood circulation in lower limbs arteries[1]. It is associated with poor prognosis and high rate of mortality and morbidity especially in the advanced stages[2,3]. On the other hand, patients with early stages of disease are often asymptomatic or complain non-specific discomfort, remaining frequently misdiagnosed, with pathogenetic mechanisms being less investigated[4]. The gold standard for LEAD diagnosis is actually represented by the evaluation of the ankle-brachial index (ABI), even if this tool could present important limitations, especially in early stages of disease. Consequently, color coded-duplex ultrasonography is currently suggested to complete the examination and to characterize early atherosclerotic lesions[5,6].

In recent years, several studies have enlightened the critical role of systemic inflammation in the development and evolution of atherosclerosis[7-9]. To this purpose, several biomarkers, as the neutrophil-to-lymphocyte ratio (NLR), the monocyte-to-high-density lipoprotein-cholesterol ratio (MHR) and the platelet-to-lymphocyte ratio

Corresponding Author: Luca Santoro, MD; e-mail: luca.santoro@policlinicogemelli.it

(PLR), have been focused[10-12]. Numerous observations have related these biomarkers to cardiovascular (CV) disease, involving heart, kidney and carotid[13-15]; in the context of LEAD, the role of these parameters has only been investigated in advanced stages, such as in patients with critical limb ischemia or using ABI as test for disease diagnosis[16-20].

To our knowledge, there is no data about the association of these biomarkers with all stages of LEAD, in particular early ones. The aim of our study was to evaluate the correlation between MHR, NLR and PLR with all stages of LEAD, assessed by a recent semiquantitative ultrasonographic score together with ABI[21].

Patients and Methods

Patients

Two hundred and forty patients undergoing ultrasonographic evaluation of the lower limb arteries and ABI determination were enrolled in this cross-sectional observational study. Exclusion criteria was age <18 years.

Inclusion criteria were symptoms suggestive of LEAD or presence of known CV risk factors. Those included in the statistical model were age, gender, diabetes mellitus status, arterial hypertension status, dyslipidemia status, body mass index (BMI) and cigarette smoking modeled as number (packs/year). The presence of diabetes mellitus status, arterial hypertension and dyslipidemia were diagnosed based on relative guidelines[22-24]. All patients were also asked to complete a form with items where they recorded life habits.

Written informed consent was obtained from all the participants, before entry into the study. The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Catholic University of Rome (Ethic Committee Reference Number: l4725/2014).

Physical and Laboratory Examinations

Thorough examination including weight, height and blood pressure, was performed for each patient; BMI was calculated as weight (kg) divided by height (m^2).

After overnight fasting, blood samples were taken from each patient, for assessment of full blood count, glucose, creatinine, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides.

NLR was calculated as the ratio of absolute neutrophil ($\times 10^9$/L) to lymphocyte blood counts ($\times 10^9$/L); MHR was calculated by monocyte count ($\times 10^9$/L)/HDL-C (mg/dL); finally, PLR was calculated as the ratio of platelet ($\times 10^9$/L) to lymphocyte counts ($\times 10^9$/L).

Ultrasound Lower Limb Evaluation

Ultrasonographic examination was performed as previously described[21]. Briefly, the femoropopliteal and run-off segments were continuously scanned from the subinguinal region to the paramalleolar region with axial and sagittal scans. All segments were examined for their parietal characteristics, especially the presence of vessel wall calcifications and/or atherosclerotic plaques; in addition, flow-velocity measurements using spectral Doppler imaging and color Doppler imaging were obtained. Arteries were grouped into femoropopliteal or proximal (common, superficial and deep femoral arteries, popliteal artery) and infrageniculate or distal (tibiofibular trunk, anterior and posterior tibial arteries, fibular artery) districts.

Ultrasonographic Lower Limbs Atherosclerosis (ULLA) score was calculated to assess disease severity as previously described[21].

Ankle-Brachial Index Evaluation

The ABI was calculated from the highest ankle systolic pressure to the highest brachial systolic pressure ratio for each leg, in accordance with actual guidelines[25].

ABI values from 1.00 to 1.40 were considered normal, whereas values less than or equal to 0.90 were considered abnormal; values ranging from 0.91 to 0.99 suggested a "borderline" ABI and values >1.40 indicated non compressible arteries. After comparing the two legs, the lowest measured ABI value was chosen for the analysis. Moreover, a semi quantitative measure of the ABI has been also performed and classified in four grades: *grade 0* (ABI 0.91-1.40) were considered normal, *grade 1* (ABI 0.41-0.90) indicated mild-moderate LEAD, *grade 2* (ABI $\leq$ 0.40) indicated severe LEAD, *grade 3* (ABI > 1.40) indicated non compressible arteries.

Statistical Analysis

Continuous variables were summarized as means and standard deviations, categorical variables as frequencies and percentages. Normality of distribution of continuous variables was assessed by means of QQ-plot and histogram

inspection. Ratio parameters were right-skewed and were log-transformed in regression models. Nine patients were excluded from the analyses because of an ABI value of 3.

The association between each ratio parameter and the severity of LEAD was analyzed by linear regression models with each (log-transformed) ratio parameter as the dependent variable and ULLA and ABI scores as the independent variables; ULLA score was treated as a continuous variable, whereas ABI score was dichotomized (0 *vs.* 1-2) as too few patients were in score 2 to analyze ABI score as a continuous variable.

All analyses were performed with Stata Version 15.1 (StataCorp, TX, USA). A two-tailed p-value <0.05 was considered as statistically significant.

Results

Characteristics of the study sample are reported in Table I. The association between inflammatory markers and ultrasonographic findings is presented in Table II and Figure 1. The adjusted association between log-NLR with ULLA score was statistically significant ($p < 0.05$): a 1 unit increase in ULLA score was associated with a 0.06 (95% confidence interval 0.01, 0.11) unit increase in log-NLR. Conversely, the adjusted association between log-MHR and log-PLR with ULLA score was not statistically significant (p = ns, for both comparisons). When analyzing ABI instead of ULLA score (Table III), we found a direct association for log-NLR ($p < 0.05$), an inverse association for log-MHR ($p = 0.001$), and no association for log-PLR (p = ns).

Table I. Characteristics of the study population.

Factor	Value
N	240
Age (years), mean (SD)	69.6 (9.8) (n = 240)
BMI, mean (SD)	27.4 (4.5) (n = 240)
Sex	
Female	136 (56.7%)
Male	104 (43.3%)
High blood pressure	168 (70.0%)
Dyslipidemia	148 (61.7%)
Diabetes	74 (30.8%)
Packs of cigarettes (×300), median (IQR)	6.1 (0.0, 21.9) (n = 239)
ULLA score	
0	32 (13.3%)
1	59 (24.6%)
2	71 (29.6%)
3	19 (7.9%)
4	47 (19.6%)
5	12 (5.0%)
ABI	
0	179 (74.6%)
1	56 (23.3%)
2	1 (0.4%)
Missing	4 (1.7%)
MHR, median (IQR)	0.1 (0.1, 0.2) (n = 189)
NLR, median (IQR)	2.0 (1.5, 2.8) (n = 239)
PLR, median (IQR)	0.1 (0.1, 0.1) (n = 137)

Number of non-missing measurements for continuous variables are reported in parentheses. SD: standard deviation; BMI: body mass index; IQR: interquartile range; ULLA: ultrasonographic lower limbs atherosclerosis; ABI: ankle-brachial index. MHR: monocyte-to-high-density lipoprotein-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Discussion

LEAD represents a major CV disease with an increasing prevalence worldwide; it is associated

Table II. Association between inflammatory markers and ULLA score.

	MHR		NLR		PLR	
	Beta (95% CI)	*p*-value trend	Beta (95% CI)	*p*-value trend	Beta (95% CI)	*p*-value trend
0	0.00 (Ref.)	0.054	0.00 (Ref.)	0.023	0.00 (Ref.)	0.44
1	-0.09 (-0.32, 0.15)		-0.18 (-0.38, 0.02)		0.12 (-0.10, 0.35)	
2	-0.16 (-0.40, 0.08)		-0.05 (-0.26, 0.15)		0.12 (-0.11, 0.34)	
3	0.00 (-0.33, 0.33)		-0.12 (-0.40, 0.16)		0.17 (-0.16, 0.49)	
4	-0.35 (-0.64, -0.06)		0.19 (-0.05, 0.42)		0.15 (-0.15, 0.44)	
5	-0.19 (-0.57, 0.18)		0.01 (-0.32, 0.34)		0.13 (-0.27, 0.53)	

Betas can be interpreted as adjusted differences in log-transformed units of the ratio parameter for each ULLA category compared with the reference category. Models adjusted for age, sex, BMI, smoking status, high blood pressure, dyslipidemia, diabetes. ULLA: ultrasonographic lower limbs atherosclerosis; MHR: monocyte-to-high-density lipoprotein-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CI: confidence interval; BMI: body mass index.

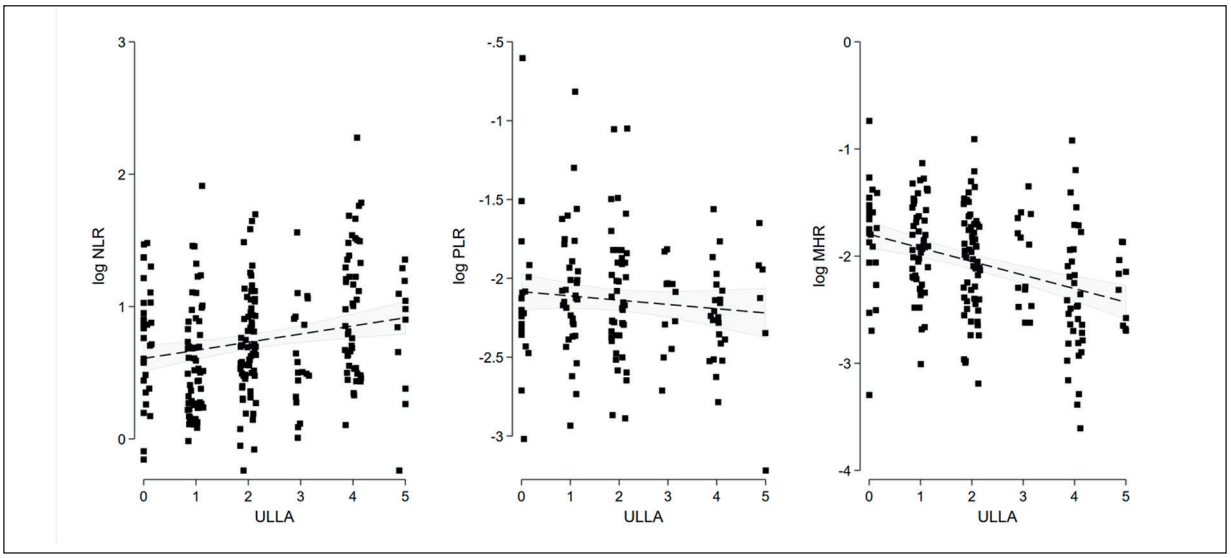

Figure 1. Scatterplot of log-transformed MHR (left), NLR (center) and PLR (right) across values of ULLA score. MHR: monocyte-to-high-density lipoprotein-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; ULLA: ultrasonographic lower limbs atherosclerosis.

with a high rate of all-cause and CV mortality[2,3]. Nevertheless, compared to other target organs of atherosclerosis, like heart or brain, pathophysiological mechanisms leading to development and progression of LEAD remain poorly understood and investigated, especially in the early stages of the disease[26,27].

Consequently, identifying which markers can ensure better risk stratification and proper selection of treatment approaches is an absolute need. In this context, three novel inflammatory biomarkers, namely NLR, MHR and PLR, have been widely studied in patients affected by LEAD, but mainly in cohorts of symptomatic subject with altered ABI or undergoing surgical or endovascular treatments[16-19]. To date, there is no data about the correlation between these inflammatory biomarkers and early stages of LEAD.

The rationale of our study was to correlate NLR, MHR and PLR to all stages of the disease as assessed by ultrasonography through ULLA score: this represents a semiquantitative score which facilitates the categorization of atherosclerotic lesions of the lower limbs in all stages of LEAD[21]. We have already demonstrated that these ultrasonographic categories correlate with traditional CV risk profiles, more strictly than ABI[28].

The role of NLR as a useful marker in order to identify and stratify CV risk has already been deeply investigated. In fact, it has been associated with occurrence of myocardial infarction, severity of coronary artery disease and left ventricular ejection fraction impairment[13,29,30]. In LEAD, its prognostic role has been established only in advanced stages, as a marker for mortality in

Table III. Association between inflammatory markers and ABI.

	MHR		NLR		PLR	
	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
0	0.00 (Ref.)	0.00 (Ref.)	0.14 (0.00, 0.29)	0.048	0.00 (Ref.)	0.25
1-2	-0.27 (-0.42, -0.11)	0.001	0.09 (−0.07, 0.25)			

ABI: ankle-brachial index; MHR: monocyte-to-high-density lipoprotein-cholesterol ratio; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; CI: confidence interval; BMI: body mass index. Betas can be interpreted as adjusted differences in log-transformed units of the ratio parameter for ABI >0 compared with the reference category. Models adjusted for age, sex, BMI, smoking status, high blood pressure, dyslipidemia, diabetes.

patients with critical limb ischemia undergoing endovascular or surgical interventions[17,18].

Our results confirm a statistically significant association between NLR and ABI, consistent with previous findings already enlightening the role of NLR as a marker of the inflammatory pattern in patients with severe disease. These data suggest a kind of "dose effect" between atherosclerotic burden, inflammation and symptoms[31]. Interestingly, our study also describes a strong association between the NLR values and early stages of LEAD; in fact, when analyzing ULLA score instead of ABI, the association remains statistically significant, meaning that neutrophils play a crucial role in all the stages of disease, not only in the advanced ones.

Conversely, our results demonstrate that MHR is not associated with severity of LEAD, when evaluated with ULLA score; surprisingly, MHR is inversely associated with LEAD when evaluated with ABI. The rationale of MHR as an inflammatory marker in atherosclerosis is related to the protective and antioxidant role of both circulating monocytes and HDL cholesterol[32,33]. Once again, in the context of LEAD, the role of MHR has been investigated only in patients with critical limb ischemia or ABI diagnostic criteria of LEAD, moreover, finding controversial results[16-20]. As already suggested by other Authors, we can hypothesize that some subsets of monocytes (CD14++/CD16+), instead of the total count, seem to have a crucial role in progression of CV diseases[34,35].

Finally, we also evaluated PLR as another systemic inflammatory marker recently pointed out for its prognostic value in CV diseases. As regards LEAD, it has already emerged as a risk factor independently associated with lower ABI, with a positive correlation with clinical manifestations as foot ulcers in type II diabetic patients and with the risk of vessel restenosis after procedure in patients undergoing angioplasty and stenting for critical limb ischemia[16,19,36,37]. Rather, PLR seems to be a more reliable marker than NLR, in particular in the advanced stages of disease. Our findings apparently are in contrast with these reports, showing no association with LEAD, when PLR is analyzed in correlation both with ABI and ULLA score. A plausible reason could be that, compared to NLR, this parameter reflects activation of platelets, being these cells involved only in advanced stages of LEAD; consistently, our results reflect a cohort of asymptomatic patients in earlier stages of LEAD.

Conclusions

To date, progresses have been made in the overall comprehension, prevention and management of CV pathological condition, mainly regarding coronary artery disease and cerebrovascular disease. In the context of LEAD, the attempt to identify simple biomarkers to stratify patients with a symptomatic or asymptomatic stage of disease has led to controversial results.

Our research, conducted by using an ultrasonographic score, enlightened a close association between a specific inflammatory pattern and LEAD severity. In particular, the novelty of our study is represented by the association between NLR with early stages of LEAD. This paves the way to more deeply analyses focused on inflammatory targets in all stages of LEAD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Informed Consent

Written informed consent was obtained from all the participants, before entry into the study.

Ethical Committee

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Catholic University of Rome (Ethic Committee Reference Number: 14725/2014).

References

1) Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, Lookstein R, Misra S, Mureebe L, Olin JW, Patel RAG, Regensteiner JG, Schanzer A, Shishehbor MH, Stewart KJ, Treat-Jacobson D, Walsh ME. AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary. Vasc Med 2017; 21: 1465-1508.

2) Unkart JT, Allison MA, Araneta MRG, Ix JH, Matsushita K, Criqui MH. Burden of peripheral artery disease on mortality and incident cardiovascular events. Am J Epidemiol 2020; 189: 951-962.

3) Melillo E, Micheletti L, Nuti M, Dell'omo G, Berchiolli R, Adami D, Farina A, Panigada G, Meini S. Long-term clinical outcomes in critical limb ischemia--a retrospective study of 181 patients. Eur Rev Med Pharmacol Sci 2016; 20: 502-508.
4) Hiatt WR, Armstrong EJ, Larson CJ, Brass EP. Pathogenesis of the limb manifestations and exercise limitations in peripheral artery disease. Circ Res 2015; 116: 1527-1539.
5) Davies JH, Kenkre J, Williams EM. Current utility of the ankle-brachial index (ABI) in general practice: implications for its use in cardiovascular disease screening. BMC Fam Pract 2014; 15: 69.
6) Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, Chraim A, Canning C, Dimakakos E, Gottsäter A, Heiss C, Mazzolai L, Madaric J, Olinic DM, Pécsvárady Z, Poredoš P, Quéré I, Roztocil K, Stanek A, Vasic D, Visonà A, Wautrecht J-C, Bulvas M, Colgan M-P, Dorigo W, Houston G, Kahan T, Lawall H, Lindstedt I, Mahe G, Martini R, Pernod G, Przywara S, Righini M, Schlager O, Terlecki P. ESVM Guideline on peripheral arterial disease. Vasa 2019; 48: 1-79.
7) Hansson GK, Jonasson L. The discovery of cellular immunity in the atherosclerotic plaque. Arterioscler Thromb Vasc Biol 2009; 29: 1714-1717.
8) Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105: 1135-1143.
9) Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352: 1685-1695.
10) Ganjali S, Gotto AM, Ruscica M, Atkin SL, Butler AE, Banach M, Sahebkar A. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. J Cell Physiol 2018; 233: 9237-9246.
11) Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther 2016; 14: 573-577.
12) Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, Aras D. Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. Angiology 2016; 67: 89-95.
13) Arbel Y, Finkelstein A, Halkin A, Birati EY, Revivo M, Zuzut M, Shevach A, Berliner S, Herz I, Keren G, Banai S. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis 2012; 225: 456-460.
14) Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, Zhang RY, Shen WF, Lu L, Wang XQ. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima-media thickness in patients with type 2 diabetes. Front Endocrinol (Lausanne) 2019; 4; 191.
15) Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology 2019; 70: 802-818.
16) Selvaggio S, Abate A, galetta GB, Musso C, Di Guardo M, Di Guardo C, Vicari ESD, Romano M, Luca S, Signorelli SS. Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-HDL cholesterol ratio as markers of peripheral artery disease in elderly patients. Int J Mol Med 2020; 46: 1210-1216.
17) Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, Eller P, Pilger E, Brodmann M. Neutrophil-to-lymphocyte ratio and its association with critical limb ischemia in PAOD patients. PLoS One 2013; 8: e56745.
18) Paquissi FC. The role of inflammation in cardiovascular diseases: the predictive value of neutrophil–lymphocyte ratio as a marker in peripheral arterial disease. Ther Clin Risk Manag 2016; 27: 851-860.
19) Liu N, Sheng J, Pan T, Wang Y. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with lower extremity vascular lesions in Chinese patients with type 2 diabetes. Clin Lab 2019; 1: 65.
20) Zhou Y, Wang L, Jia L, Lu B, Gu G, Bai L, Cui W. The monocyte to high-density lipoprotein cholesterol ratio in the prediction for atherosclerosis: a retrospective study in adult Chinese participants. Lipids 2021; 56: 69-80.
21) Santoro L, Ferraro PM, Flex A, Nesci A, De Matteis G, Di Giorgio A, Zaccone V, Gambaro G, Gasbarrini A, Santoliquido A. New semiquantitative ultrasonographic score for peripheral arterial disease assessment and its association with cardiovascular risk factors. Hypertens Res 2016; 39: 868-873.
22) Handelsman Y, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, Blonde L, Bray GA, Jay Cohen A, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda OP, Garber AJ, Timothy Garvey W, Henry RR, Hirsch IB, Horton ES, Hurley DL, Jellinger PS, Jovanovic L, Lebovitz HE, LeRoith D, Levy P, McGill JB, Mechanick JI, Mestman JH, Moghissi ES, Orzeck EA, Pessah-Pollack R, Rosenblit PD, Vinik AI, Wyne K, Zangeneh F. American association of clinical endocrinologists and American college of endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract 2015; 21: 413-437.
23) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Burnier M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Tsioufis C, Van De Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Ferrari R, Hasdai D, Hoes AW, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Gillebert TC, Rosei EA, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere

M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Ž, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Vlachopoulos C, Volpe M, Wood DA. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013; 28: 2159-2219.

24) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-3421.

25) Tendera M, Aboyans V, Bartelink M, Baumgartner I, Clement D, Collet J, Cremonesi A, De Carlo M, Erbel R, Fowkes F, Heras M, Kownator S, Minar E, Ostergren J, Poldermans D, Riambau V, Roffi M, Rother J, Sievert H, van Sambeek M, Zeller T, Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu B, Reiner Z, Sechtem U, Sirnes P, Torbicki A, Vahanian A, Windecker S, Agewall S, Blinc A, Bulvas M, Cosentino F, De Backer T, Gottsater A, Gulba D, Guzik T, Jonsson B, Kesmarky G, Kitsiou A, Kuczmik W, Larsen M, Madaric J, Mas J, McMurray J, Micari A, Mosseri M, Muller C, Naylor R, Norrving B, Oto O, Pasierski T, Plouin P, Ribichini F, Ricco J, Ruilope L, Schmid J, Schwehr U, Sol B, Sprynger M, Tiefenbacher C, Tsioufis C, Van Damme H. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Eur Heart J 2018; 39: 763-816.

26) Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001; 286: 1317-1324.

27) Flore R, Ponziani FR, Tinelli G, Arena V, Fonnesu C, Nesci A, Santoro L, Tondi P, Santoliquido A. New modalities of ultrasound-based intima-media thickness, arterial stiffness and non-coronary vascular calcifications detection to assess cardiovascular risk. Eur Rev Med Pharmacol Sci 2015; 19: 1430-1441.

28) Santoro L, Flex A, Nesci A, Ferraro PM, De Matteis G, Di Giorgio A, Giupponi B, Saviano L, Gambaro G, Franceschi F, Gasbarrini A, Landolfi R, Santoliquido A. Association between peripheral arterial disease and cardiovascular risk factors: Role of ultrasonography versus ankle-brachial index. Eur Rev Med Pharmacol Sci 2018; 22: 3160-3165.

29) Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil lymphocyte ratio and cardiovascular disease risk: a systematic review and meta-analysis. Biomed Res Int 2018; 11: 2703518.

30) Doğdu O, Akpek M, Yarlıoğlueş M, Kalay N, Ardıç I, Elçik D, Senarslan O, Kaya MG. Relationship between hematologic parameters and left ventricular systolic dysfunction in stable patients with multi-vessel coronary artery disease. Türk Kardiyol Dern Ars 2012; 40: 706-713.

31) Bath J, Smith JB, Kruse RL, Vogel TR. Neutrophil-lymphocyte ratio predicts disease severity and outcome after lower extremity procedures. J Vasc Surg 2020; 72: 622-631.

32) Jomard A, Osto E. High density lipoproteins: metabolism, function, and therapeutic potential. Front Cardiovasc Med 2020; 31: 7-39.

33. Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RA, McCormick SPA, Remaley AT, Sviridov D, Chin-Dusting J. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol 2008; 28: 2071-2077.

34) Wildgruber M, Czubba M, Aschenbrenner T, Wendorff H, Hapfelmeier A, Glinzer A, Schiemann M, Zimmermann A, Eckstein HH, Berger H, Wohlgemuth WA, Meier R, Libby P, Zernecke A. Increased intermediate CD14++CD16++ monocyte subset levels associate with restenosis after peripheral percutaneous transluminal angioplasty. Atherosclerosis 2016; 253: 128-134.

35) Cappellari R, D'Anna M, Bonora BM, Rigato M, Cignarella A, Avogaro A, Fadini GP. Shift of monocyte subsets along their continuum predicts cardiovascular outcomes. Atherosclerosis 2017; 266: 95-102.

36) Lee S, Hoberstorfer T, Wadowski PP, Kopp CW, Panzer S, Gremmel T. Platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios predict target vessel restenosis after infrainguinal angioplasty with stent implantation. J Clin Med 2020; 9: 1729.

37) Mineoka Y, Ishii M, Hashimoto Y, Yamashita A, Nakamura N, Fukui M. Platelet to lymphocyte ratio correlates with diabetic foot risk and foot ulcer in patients with type 2 diabetes. Endocr J 2019; 66: 905-913.