UDC 616.133
DOI: 10.21668/health.risk/2022.3.13.eng

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Research article

FORECASTING RISK ANALYSIS OF DETECTION FOR CAROTID ARTERY STENOSIS BASED ON SERUM LEVELS GRADING OF LIPOPROTEIN (A)

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Aim of the study: to assess the relationship between Lp(a) serum levels grading and carotid artery stenosis (CAS).

The Duplex Registry database was used for this study. CAS was verified by duplex scanning in the presence of an atherosclerotic plaque (AP), stenosing the lumen of the carotid artery (CA) by 20 % or more. Patients who underwent a blood test for Lp(a) and the results were entered into the registry database were selected for this study. The immunoturbidimetric method was used to determine the serum level of Lp(a) (mg/dl).

Data from 51 patients (66.6 % men) were included in the final analysis: median age 49.0 [46.0; 59], total cholesterol (TC) 5.93 [5.13; 6.56], Lp(a) 26.5 [14.2; 76.0]. Spearman rank correlation analysis showed the presence of significant relationships ($p < 0.05$) between Lp(a) and age ($r = 0.3$), gender ($r = 0.3$), the presence of AP in the right ICA ($r = 0.5$), HDL ($r = 0.3$). OR and 95 % CI were calculated to determine the effect of Lp(a) grades on the probability of CAS detection: Lp(a) < 30 mg/dl OR 0.36 [0.11; 1.14] $p = 0.04$; Lp(a) > 30 mg/dl OR 1.42 [0.44; 4.58] $p = 0.27$. The prevalence of CAS in the group with Lp(a) level < 30 mg/dl was 33.3 %, 30–50 mg/dl – 50 %, 50–100 mg/dl – 40 %, > 100 mg/dl – 37.5 %. The model of multiple regression analysis for Lp(a) with TC in relation to the right ICA stenosis predicting showed $R = 0.51$, $F = 8.4$, $p = 0.0007$. The statistics of 3M model of the logistic regression function for CAS predicting based on the Lp(a) and TC data showed: $-2 \cdot \log(\text{likelihood}) = 57.16$, Chi-square = 8.17 (cc = 2), $p = 0.016$.

The present study confirmed the relationship between the Lp(a) level and the CAS detection and the presence of an additive effect of total cholesterol on this. The reference role of Lp(a) gradation at the level of 30 mg/dl was determined as significant in relation to predicting CAS detection.

Keywords: *lipoprotein(a), grading, risk analysis, carotid atherosclerosis, stenosis, duplex scanning, prediction.*

Despite the fact that the role of lipid factors in the formation and development of atherosclerosis is well known, the scientific medical community continues to actively pay attention to the study of lipoprotein (a) (Lp(a)) [1, 2]. A high level of Lp(a) is an independent risk factor for the early development of atherosclerosis and related cardiovascular diseases, which is initiated through mechanisms associated with its proatherogenic, proinflammatory, and prothrombotic properties. Lp(a) is a predominantly genetic determinant of cardiovascular risk that is inherited [3]. Therefore, medical scientific associations call for close attention to this risk factor, its stratification and analysis in clinical practice [3–6].

The National Lipid Association guidelines for clinical practice recommend measuring Lp(a) to identify patients with very high Lp(a) levels who have a family history of premature cardiovascular disease or elevated Lp(a) levels [6]. The genetic predisposition to elevated levels of Lp(a) [7] and its correlation with the early development of carotid atherosclerosis [8] was convincingly confirmed in studies performed back in the 90s of the last century. A significant relationship was noted between the joint influence of an elevated level of total cholesterol and Lp(a) in the early manifestation of CVD [9]. At the same time, subsequent studies questioned the role of Lp(a) in the development of early carotid atherosclerosis in young patients

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[10]. A possible role in this could be played by the stratification of the value of Lp(a), which was defined as the limit of the norm.

Despite the fact that the previously noted Lp(a) level > 50 mg/dl was considered a reference [11, 12], other studies have noted that the gradation of the Lp(a) level, starting from 30 mg/dl, has the greatest importance [13].

Aim of the study: to assess the relationship between Lp(a) levels and carotid atherosclerosis, verified on the basis of duplex scanning of the carotid arteries within the local registry.

Materials and methods. Duplex Registry database was used for this study. Detailed methodology for this registry was described earlier in previous publications [14, 15]. Carotid atherosclerosis was verified on the basis of duplex scanning data in the presence of an atherosclerotic plaque that stenosed the lumen of the carotid artery by 20 % or more. Duplex scanning was performed on Vivid 7 (GE) devices according to the standard technique using multi-frequency linear sensors (L9 / L12, 9–12 MHz). Both common carotid arteries and their bifurcations, internal and external carotid arteries were studied in order to determine the section where the atherosclerotic plaque had the largest size. The percentage of stenosis was determined in the zone of maximum narrowing of the arterial lumen in % by the diameter and area of the vessel lumen according to the ECST criteria in accordance with the guidelines for DS performing[1] [16, 17]. The formalized minimum value of stenosis associated with atherosclerotic plaque, which can be correctly expressed as a percentage in accordance with these protocols and recommendations, was taken as 20 % when describing the results of duplex scanning.

For inclusion in the present study, patients were selected who underwent a blood test for Lp(a) and its results were entered into the registry database. The Lp(a) level was determined by the immunoturbodimetric method using a Beckman Coulter 5800 biochemical analyzer.

The referral of patients for this study by a cardiologist and / or lipidologist of the clinic was initially based on strict indications: an early family or own cardiovascular history in combination with confirmed hyperlipidemia, which made it possible to suspect a hereditary predisposition to this pathology.

Statistical analysis. Statistical data processing was performed using the Statistica 10.0 software package (StatSoft). Group data are presented as mean and standard deviation, median, 25 % and 75 % percentile, or as absolute numbers and percentages. Spearman correlation analysis was used to determine the presence of significant relationships between the studied characteristics. The chi-square test was applied to compare groups on a qualitative sign. The extended Mantel – Haenszel chi-square for a linear trend with a p-value for one degree of freedom was used as a model for the analysis of interlevel interactions depending on the gradation of a qualitative sign[2]. Odds ratio (OR) and 95 % confidence interval (95 % CI) were calculated to determine the effect of different gradations of Lp(a) on the probability of detecting carotid atherosclerosis. Multiple regression analysis for a quantitative sign was applied to build models that included Lp(a) in relation to predicting the degree of ICA stenosis. Logistic regression analysis using a Quasi-Newtonian method of estimation was applied to construct a model of the predictive function for the detection of stenosing carotid atherosclerosis based on Lp(a) and TC data (3M function model). ROC-analysis (Receiver Operator Characteristic) with ROC-curve construction and area under curve estimation (Area Under Curve) was applied to evaluate the CAS prediction classifier as a diagnostic test based on the obtained classification logistic function formula. Differences were considered statistically significant at $p < 0.05$.

Results. Data from 51 patients were included in the final analysis. The mean age of the patients was 50.2 + 6.5 years; 2/3 of them

[1] At'kov O.Yu., Gorokhova S.G., Balakhonova T.V. Ul'trazvukovoe issledovanie serdtsa i sosudov [Ultrasound examination of the heart and blood vessels]. In: O.Yu. At'kov ed. Moscow, Eksmo, 2009, 400 p. (in Russian).

[2] Rosner B. Fundamentals of Biostatistics, 5th ed. Belmont, CA, Duxbury Press, 2000, 606 p.

belonged to the male sex (n = 34). Arterial hypertension was registered in 37 % of patients (n = 19), in 4 of them the diagnosis of coronary artery disease was also verified (one of them had a history of MI). Carotid atherosclerosis (according to the AP criterion > 20 %) was detected in 19 patients (37.3 %) from the study group (n = 51).

The distribution of patients in the study group by Lp(a) level is shown in Figure 1. Detailed descriptive clinical, laboratory and ultrasound characteristics of the patients included in this study are presented in Table 1.

Spearman rank correlation analysis showed the presence of significant relationships (p < 0.05) between the following signs. Age correlated with IMT (r = 0.3), the presence of AP in the bifurcation of the CA, ICA and RSA (r = 0.3), with CAS gradation (r = 0.45), lipid-lowering therapy (LLT) (r = -0.12), Lp(a) (r = 0.3). AP of the right ICA showed correlations with age (r = 0.34), sex (r = -0.12), total cholesterol level in dynamics (TC2) (r = -0.13), LDL level in dynamics (LDL2) (r = -0.12), Lp(a) level (r = 0.5); while AP of the left ICA - with age (r = 0.33), sex (r = -0.12), TC2 (r = -0.15), LDL2 (r = -0.16). The gradation of CAS severity correlated with age (r = 0.45), sex (r = -0.13), TC2 (r = -0.13), LDL2 (r = -0.14), LLT (r = -0.08). Lp(a) correlated with age (r = 0.3), sex (r = 0.3), presence of AP in the right ICA (r = 0.5), HDL (r = 0.3) and HDL2 (r = 0.4).

The extended Mantel – Haenszel chi-square for linear trend was applied as a model for the analysis of interlevel interactions depending on the gradation of serum levels of Lp(a) and carotid atherosclerosis. The data obtained are presented in Table 2.

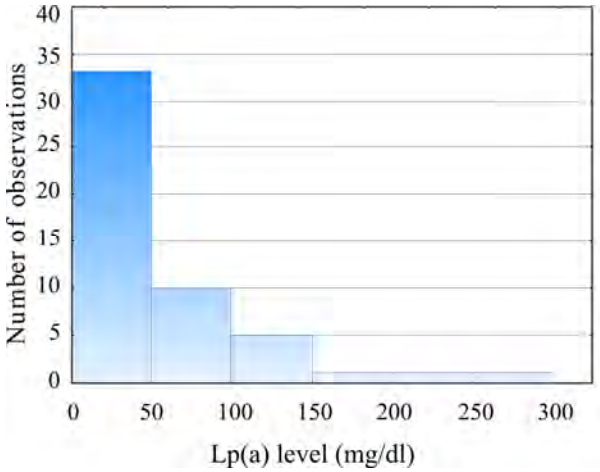

Figure 1. Distribution of patients in the study group by Lp(a) level

Table 1

Clinical, laboratory and ultrasound characteristics of patients included in this study

Sign	Mean ± SD	Med. [Q_{25}; Q_{75} %]	Min; Max
Age (years)	50.2 ± 6.5	49.0 [46.0; 59.0]	37.0; 60.0
TC (mmol/l)	5.93 ± 0.2	5.93 [5.13; 6.56]	3.5; 10.1
HDL (mmol/L)	1.55 ± 0.47	1.47 [1.18; 1.95]	0.84; 2.52
TG (mmol/l)	1.58 ± 0.9	1.42 [0.91; 1.84]	0.56; 4.79
LDL (mmol/l)	3.65 ± 1.03	3.53 [3.02; 4.17]	1.7; 7.22
Lp(a) (mg/dl)	52.8 ± 61.4	26.5 [14.2; 76.0]	0.1; 298.4
IMT right OCA (mm)	1.04 ± 0.2	1.0 [0.9; 1.2]	0.7; 1.5
IMT left OCA (mm)	1.06 ± 0.2	1.0 [0.9; 1.2]	0.7; 1.5
IMT bifurcation of the right CCA (mm)	1.35 ± 0.2	1.4 [1.2; 1.7]	0.9; 1.7
IMT of bifurcation of the left CCA (mm)	1.39 ± 0.3	1.4 [1.2; 1.6]	0.7; 2.1
IMT RSA (mm)	1.46 ± 0.2	1.5 [1.3; 1.6]	0.7; 1.9
AP bifurcation of the right CCA > 20 % (%) (7/51)	4.16 ± 11.5	0.0 [0.0; 0.0]	0.0; 59.0
AP bifurcation of the left CCA > 20 % (%) (7/51)	4.37 ± 11.8	0.0 [0.0; 0.0]	0.0; 48.0
AP right ICA > 20 % (%) (3/51)	1.56 ± 6.4	0.0 [0.0; 0.0]	0.0; 30.0
AP left ICA > 20 % (%) (3/51)	1.96 ± 8.2	0.0 [0.0; 0.0]	0.0; 46.0
AP RSA > 20 % (%) (11/51)	5.74 ± 11.2	0.0 [0.0; 0.0]	0.0; 45.0

N o t e : TC – total cholesterol, HDL – high-density lipoprotein, TG – triglycerides, LDL – low-density lipoprotein, Lp(a) – lipoprotein(a), IMT – intima-media thickness, CCA – common carotid artery, AP – atherosclerotic plaque, ICA – internal carotid artery, RSA – right subclavian artery, CAS – carotid atherosclerosis.

Table 2

Analysis of CAS associations and Lp(a) level gradations in comparison with the normal level (extended Mantel – Haenszel chi-square for a linear trend)

Gradation of levels	Lp(a) value for level	Cases	Controls	Total	Intergroup ratio	Odds ratio	Interlevel comparisons
0	< 30	9	18	27	0.5	1.0	0 vs 0
1	30–50	3	3	6	1	2.0	1 vs 0
2	50–100	4	6	10	0.67	1.3	2 vs 0
3	> 100	3	5	8	0.6	1.2	3 vs 0
Total		19	32	51			

Table 3

Analysis of multiple regression analysis models with Lp(a) and lipid factors in relation to predicting the degree of right ICA stenosis

Model	R	R2	Adjusted R2	F	B	*p*-level
LP(a)	0.50	0.25	0.23	16.7		0.0001
					0.504895	0.0001
LP(a) + TC	0.51	0.26	0.23	8.4		0.0007
	Lp(a)				0.495155	0.0002
	TC				-0.101269	0.42
LP(a) + LDL	0.52	0.27	0.24	8.5		0.0007
	Lp(a)				0.502232	0.0004
	LDL				-0.086074	0.51
Lp(a) + TC + TC2 + LDL + LDL2	0.66	0.44	0.35	4.7		0.002
	Lp(a)				0.617684	0.0002
	TC				-0.380122	0.33
	TC2				-0.145181	0.77
	LDL				0.281620	0.47
	LDL2				-0.014816	0.97

Table 4

Predicting CAS detection depending on Lp(a)

Lp(a) level	Odds ratio	95 % CI	*p*-level
< 30 mg/dl	0.36	[0.11; 1.14]	0.04
> 30 mg/dl	1.42	[0.44; 4.58]	0.27
> 50 mg/dl	1.11	[0.32; 3.70]	0.48

Given the strong correlation found between Lp(a) and the presence of right ICA stenosis, multiple regression analysis was applied to build models that included Lp(a) in predicting the degree of ICA stenosis, with stepwise inclusion of lipid factors in the models. The results of multiple regression analysis are presented in Table 3.

Odds ratio (OR) and 95 % confidence interval (95 % CI) were calculated to determine the effect of different gradations of Lp(a) on the probability of detecting carotid atherosclerosis. Models with different gradations of Lp(a) were analyzed: less than 30 mg/dl, more than 30 mg/dl and more than 50 mg/dl (see Table 4). Lp(a) level less than 30 mg/dl significantly reduced the probability of CAS detection. Lp(a) of more than 30 mg/dl in this model increased the chances of detecting CAS by 1.4 times, but did not reach the level of statistical significance. The use of Lp(a) level more than 50 mg/dl as a reference did not improve the statistics of the model. Thus, the data obtained support the use of 30 mg/dl as the reference level of Lp(a).

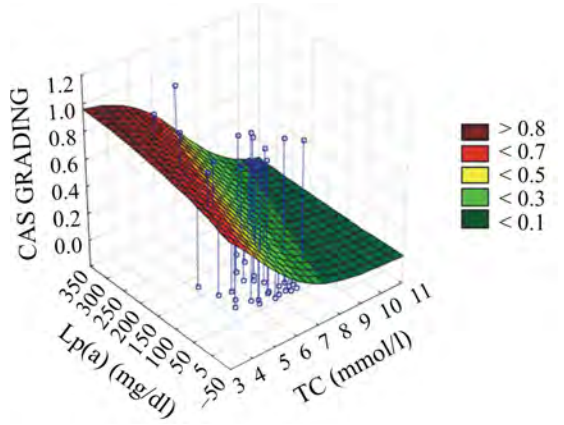

Figure 2. 3D model of the CAS prediction function based on the Lp(a) and TC data

Taking into account the fact that in previous studies a significant relationship was noted between the combined effect of elevated levels of TC and Lp(a) in relation to the development of atherosclerosis [9], TC and Lp(a) were included in the logistic regression model. Logistic regression analysis using the Quasi-Newtonian method of estimation was applied to build a 3D model of the CAS prediction function based on Lp(a) and TC data (Figure 2). As a result of the analysis, the following formula for the classification of logistic function was obtained:

$$\text{Presence of } \mathbf{CAS} = \exp(3.4922341454018 + (-0.7584332031152) \cdot \mathbf{TC} + (0.00571548810893) \cdot \mathbf{Lp(a)}) / (1 + \exp(3.4922341454018 + (-0.7584332031152) \cdot \mathbf{TC} + (0.00571548810893) \cdot \mathbf{Lp(a)})$$

Model statistics: -2·log (likelihood) for this model = 57.16 (only with intercept = 65.34), Chi-squared = 8.17 (cc = 2), $p = 0.016$. Model evaluation parameters are presented in Table 5.

ROC-analysis (Receiver Operator Characteristic) with the construction of the ROC-curve and the estimation of the Area Under Curve indicator (AUC) was applied to evaluate the CAS prediction classifier as a diagnostic test, using the obtained formula of the logistic function classification based on Lp(a) and TC data. An AUC value of 0.7 was obtained in this assay (Figure 3).

Discussion. It is worth discussing the interesting aspects and limitations of the present study. While in a previous Finnish study the role of Lp(a) in the development of early carotid atherosclerosis in young patients was questioned [10], their associations were confirmed in the present study. Although previously reported Lp(a) > 50 mg/dl was considered the reference level [11, 12], most recent studies have noted that Lp(a) levels starting at 30 mg/dl are of greatest importance [18], which was also confirmed in our study. However, the median Lp(a) value in our study group was recorded at a higher level (26.5 [14.2; 76.0]), compared with other recent studies on Lp(a) in patients with isolated stenosing carotid atherosclerosis (N.A. Tmoyan et al. – 20 [8; 55]; J.E. Jun et al. – 14 [3; 35]) [18, 19]. This may be due to differences in the clinical characteristics of the patients included in the studies. N.A. Tmoyan et al. determined that in their study the average age of patients was 60 ± 14 years (60 [47; 74]), men – 53 %, the prevalence of hypertension (AH) – 57 % [17]. In our study, the average age of patients was 50.2 + 6.5 years (49 [46; 59]), men – 66 %, prevalence of AH – 37 %. The present study was

Table 5

Estimation parameters of the logistic regression model of the CAS based on LP(a) and TC data (OR for the model 2.7)

	Estimate	Standard Error	Odds ratio	95 % CI	Wald criterion	p-level
Intercept	-3.49224	1.964310			3.160730	0.07
Lp(a)	-0.00572	0.005164	0.99	[0.98; 1.00]	1.224867	0.26
TC	0.75843	0.338744	2.13	[1.09; 4.14]	5.012934	0.02

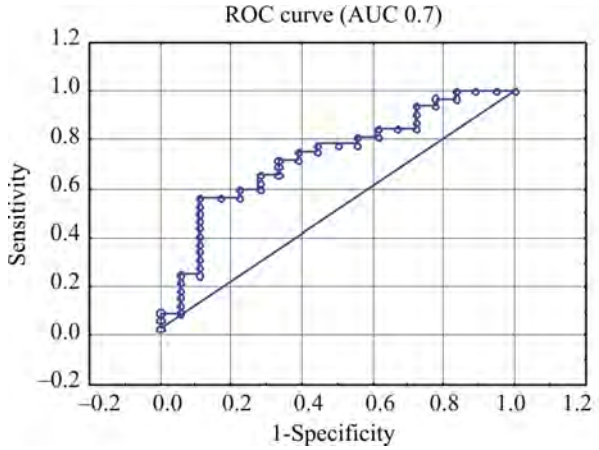

Figure 3. ROC analysis results

closer in clinical characteristics to the work of N. Nasr et al. [20], in which the average age of patients was 44.3 ± 8.6 years, male gender was 60.7 %, and the prevalence of AH was 28 %. But the mean Lp(a) level in the Nasr N et al study was also lower than in our study (35.0 + 38.0 vs 52.8 + 61.4). This may also be explained by the purposeful prescription of Lp(a) analysis by the doctor in the present study if the patient is suspected of having a hereditary (family) predisposition to this pathology (early family or own cardiovascular history in combination with confirmed hyperlipidemia), which is regulated by existing clinical guidelines [3, 4, 6, 21]. At the same time, an analysis of the data of patients included in this study showed a similar distribution of their Lp(a) levels, as in the classic Copenhagen study (Figure 1) [22].

More attention should be paid to early screening for hereditary forms of hyperlipidemia (including hyperLp(a)emia) not only among adults, but also among adolescents, which is reflected in current clinical guidelines [21], which note that the target level of LDL for children older than 10 years is < 3.5 mmol/l (this is of particular importance with a very high level of LDL, elevated levels of Lp (a) and / or a family history of premature development of coronary artery disease or other cardiovascular diseases).

The additive effect of high Lp(a) levels in combination with other lipid factors on the early development of atherosclerosis and the association of Lp(a) with the degree of carotid stenosis has been noted in previous studies [9, 19, 23] and confirmed in the present study. A clear clinical example from the cohort of this study is a 47-year-old patient without history of arterial hypertension and tobacco smoking, who was diagnosed with vertebral-subclavian steal syndrome due to 94 % stenosis of the right subclavian artery, eliminated by percutaneous transluminal angioplasty with stenting. The initial indicators of his lipid profile were follows: TC – 7.17 mmol/l, HDL – 1.02 mmol/l, LDL – 5.22 mmol/l, TG – 2.03 mmol/l, Lp (a) – 48.5 mg/dl [24].

Interesting parallels can be drawn with the study by van Buuren F et al., who analyzed the prevalence of carotid atherosclerosis depending on Lp(a) levels [25]. In the group with Lp(a) values < 2 mg/dl, the prevalence of CAS was 2.8 %, in the group with Lp(a) 23–29 mg/dl – 6.1 %, 30–60 mg/dl – 8.3 %, 60–91 mg/dl – 7.9 %, 91–110 mg/dl – 6.0 %, and > 110 mg/dl – 10.9 %. In our study, the prevalence of CAS in the group with Lp(a) values < 30 mg/dl was 33.3 %, 30–50 mg/dl – 50 %, 50–100 mg/dl – 40 %, > 100 mg/dl – 37.5 %.

It is worth paying attention to the features of the Lp(a) diagnostics by turbidimetry. The immunoturbidimetric method is a high-precision diagnostic technique designed to measure protein concentration by changing the intensity of light scattering of the test solution (serum) when a light flux passes through it[3]. The method is based on determining the concentration of the studied protein during the formation of an antigen-antibody complex with it, which leads to an increase in the turbidity of the solution. The construction of a calibration plot using several concentrations of the calibrator (from three to five) is performed to avoid inaccuracies of obtained results. This

[3] Dolgov V.V., Shevchenko O.P., Sharyshev A.A., Bondar' V.A. Turbidimetriya v laboratornoi praktike [Turbidimetry in laboratory practice]. Moscow, Reafarm, 2007, 175 p. (in Russian).

may be related to obtaining different results when examining the same blood serum using different diagnostic systems. Current commercial immunological assays for measuring Lp(a) concentrations are calibrated differently and their errors vary significantly over the clinically relevant concentration range in a nonlinear manner. This was the purpose of the study by H. Scharnagl et al. [26] to compare different commercial immunochemical analyzers to determine more reliable Lp(a) quantification methods for clinical practice. The investigators determined serum Lp(a) concentrations using six major commercial analyzers, presenting Lp(a) results in mg/dL (Denka Seiken, Abbott Quantia, Beckman, Diasys 21FS, Siemens N Latex) or nmol/L (Roche TinaQuant, Diasys 21FS). All analyzes were performed using the five-point calibration method on calibrators provided by the manufacturers. The study showed that compared to the established reference sample, the results of various analyzers differed from the target values (43.3 mg/dl or 96.6 nmol/l): from -8 % (Siemens N Latex) to +22 % (Abbott Quantia). Dividing the samples into five groups with increasing Lp(a) concentrations and plotting the differences showed that the differences between the analyzes depended on the Lp(a) concentration. Some analyzers overestimated the Lp(a) value at high serum concentrations compared to the Denka Seiken analyzer. Lp(a) levels in our study were determined using a Beckman analyzer, which was not compromised in research performed by H. Scharnagl et al. [26]. However, when conducting future studies on Lp(a), their authors should take into account this fact. Further international studies are needed to standardize the interpretation of Lp(a) analysis results to address these issues.

In conclusion, we would like to note the limitations of this study, which are typical for observational registries and all studies based on the analysis of electronic medical databases [27]. The main limitation of this study is the small sample size and a small percentage of patients with confirmed carotid atherosclerosis, which could affect the results of the statistical analysis. The regression coefficients for Lp(a) and lipid factors in the presented regression models have the opposite sign, which is reversed when the data are logarithmically transformed when performing logistic regression analysis. This can be explained by the different distribution type of signs on the one hand (the Poisson distribution for Lp(a); the Gaussian distribution for TC and LDL); and on the other hand, a more significant negative predictive value for normal Lp(a) level (less than 30 mg/dl) in relation to the probability of CAS detecting. However, it should be noted that this combination of predictors did not weaken the obtained models and led to an increase in the R correlation coefficients in the multiple regression models from 0.5 to 0.66 while maintaining a high level of significance ($p = 0.002$), as well as an increase in the chances of CAS detecting in building a logistic regression model with Lp(a) and total cholesterol (OR = 2.76, $p = 0.016$).

Conclusions. The present study confirmed the relationship between Lp(a) levels and stenosing carotid atherosclerosis and its additive effect in combination with other lipid factors on the development of carotid atherosclerosis. The Lp(a) gradation at the level of 30 mg/dl was defined as a reference in relation to predicting carotid atherosclerosis detection. Despite the fact that Lp(a) is an established risk factor for the development of cardiovascular diseases (CVD), unexplored questions remain regarding its use in real clinical practice [28]. There is a need for reliable methods for the quantitative determination of Lp(a) in clinical laboratory practice [26], which should be aimed at harmonization in the interpretation of its results in laboratory studies. More attention should be paid to early screening for hereditary forms of hyperlipidemia (including hyperLp(a)emia) not only among adults, but also among adolescents, which is reflected in current clinical guidelines [3, 4, 6, 21].

Funding. The study did not have any sponsorship.

Conflict of interests. The authors declare no conflict of interest.

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Received: 23.05.2022
Approved: 25.08.2022
Accepted for publication: 21.09.2022