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Assessment of Lipoprotein (a) Levels in Patients with Atherosclerotic Cardiovascular Disease: Single Center Experience from Türkiye

Aterosklerotik Kardiyovasküler Hastalığı Olan Hastalarda Lipoprotein (a) Düzeylerinin Değerlendirilmesi: Türkiye'den Tek Merkez Deneyimi

ABSTRACT

Objective: This study aims to evaluate the role of elevated lipoprotein (a) [Lp(a)] levels as a potential contributor to residual risk in individuals with atherosclerotic cardiovascular disease (ASCVD). Considering that approximately 90% of Lp(a) levels are genetically determined and can vary regionally, we assessed Lp(a) levels in a cohort of ASCVD patients from the Turkish population, where data is currently limited.

Methods: We conducted a retrospective analysis of data and Lp(a) measurements collected from individuals diagnosed with ASCVD at a single center.

Results: The analysis included Lp(a) levels of 1193 consecutive individuals. The mean Lp(a) level was 28.2 mg/dL, with a median of 16 mg/dL and an interquartile range (IQR) from the 2^{5th} to the 75th percentile, 7 mg/dL to 39 mg/dL. The highest recorded Lp(a) level was 326 mg/dL. Among the cases, 18.7% exhibited Lp(a) levels ≥ 50 mg/dL, 10.8% had levels ≥ 70 mg/dL, and 5.8% had levels ≥ 90 mg/dL. The mean levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) were 132 ± 47 mg/dL and 212 ± 54 mg/dL, respectively. Lp(a) levels were significantly higher in females compared to males. Furthermore, the proportion of females with Lp(a) levels ≥ 90 mg/dL was higher than in males (11.4% vs. 1.4%; $P < 0.01$). Additionally, a modest but significant correlation was observed between Lp(a) levels and TC ($r = 0.075$, $P = 0.01$) as well as LDL-C ($r = 0.106$, $P < 0.01$).

Conclusion: This study revealed that Lp(a) concentrations were higher in women and statin users among ASCVD patients and identified a weak but significant correlation between Lp(a) levels and both TC and LDL-C.

Keywords: Atherosclerotic cardiovascular disease, lipoprotein (a), Turkish population

ÖZET

Amaç: Bu çalışma, aterosklerotik kardiyovasküler hastalığı (ASKVH) olan bireylerde rezidüel riske potansiyel bir katkıda bulunan yüksek lipoprotein (a) [Lp(a)] seviyelerinin rolünü araştırmayı amaçlamaktadır. Lp(a) seviyelerinin yaklaşık %90'ının genetik olarak belirlendiğini ve coğrafi bölgeler arasında farklılık gösterebileceğini kabul ederek, şu anda verilerin yetersiz olduğu Türk toplumu içerisinden bir grubun, Lp(a) seviyelerini değerlendirmeye odaklandık.

Yöntem: Tek merkezde, ASKVH tanısı almış ve Lp(a) ölçümü yapılmış hastaların verileri retrospektif olarak toplanmıştır.

Bulgular: Toplam ardışık 1193 hastanın Lp(a) ölçümleri analiz edilmiştir. Ortalama Lp(a) düzeyi 28,2 mg/dL idi (medyan 16 mg/dL; 25.-75. persantil 7 mg/dL ve 39 mg/dL). En yüksek Lp(a) düzeyi 326 mg/dL idi. Tüm vakaların %18,7'sinde Lp(a) düzeyi ≥ 50 mg/dL, %10,8'inde Lp(a) düzeyi ≥70 mg/dL ve %5,8'inde Lp(a) düzeyi ≥ 90 mg/dL idi. Ortalama düşük yoğunluklu lipoprotein kolesterol (LDL-K) ve toplam kolesterol (TK) düzeyleri sırasıyla 132 ± 47 mg/dL ve 212 ± 54 mg/dL idi. Kadınlarda Lp(a) düzeyi daha yüksek saptandı. Ayrıca, Lp(a) düzeyleri ≥ 90 mg/dL olan kadınların oranı erkeklerden daha yüksekti (%11,4'e karşı %1,4; $P < 0,01$). Lp(a) seviyeleri ile TK ($r = 0,075$, $P = 0,01$) ve LDL-K ($r = 0,106$, $P < 0,01$) arasında ılımlı ancak anlamlı bir korelasyon vardı.

Sonuç: Bu çalışma, ASCVD hastaları arasında Lp(a) konsantrasyonlarının kadınlarda ve statin kullananlarda daha yüksek olduğunu ve Lp(a) seviyesi ile TC ve LDL-C arasında zayıf ancak anlamlı bir korelasyon olduğunu ortaya koymuştur.

Anahtar Kelimeler: Aterosklerotik kardiyovasküler hastalığı, lipoprotein (a), Türk popülasyonu

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Dr. Kåre Berg[1] pioneered the study of lipoprotein (a) [Lp(a)] in 1963. Since then, our knowledge on this lipid subtype increased progressively. Lp(a) functions as a lipid transporter, similar to low-density lipoprotein cholesterol (LDL-C). This molecule consists of an apolipoprotein (apo) B, containing an LDL-like particle strongly linked to the plasminogen-like glycoprotein apo (a).[2] The genetic impact on plasma Lp(a) levels is primarily determined by the *LPA* gene. Recent studies have highlighted the association between increased Lp(a) concentrations, changes in the *LPA* gene, and the development of atherosclerotic cardiovascular disease and calcific aortic valve disease (CAVD).[3]

International guidelines from the global medical community recommend a once-in-a-lifetime assessment of Lp(a) concentrations, considering levels exceeding 50 mg/dL (or ≥ 100 nmol/L) as a risk factor for ASCVD.[4-7] Significant ethnic variations in Lp(a) levels play a crucial role in the observed disparities,[2,3,6,7] and there is a lack of data on Lp(a) levels for the Turkish population. Thus, this single-center study aims to address this gap by examining Lp(a) levels and their implications in a cohort suffering from ASCVD.

Materials and Methods

This observational and cross-sectional analysis involved 1,381 consecutive patients with ASCVD who underwent Lp(a) measurements at a single tertiary center. The study population included patients visiting the outpatient clinic of our center between 2018 and 2022. A total of 1,381 patients were enrolled in the study. Excluded patients consisted of 20 patients under 18 years of age, 35 with severe kidney and liver failure, 18 with infectious or inflammatory diseases, and 21 with diagnosed or suspected cancer. This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Approval number: HNEAAH-KAEK/KK/2023/4, Date: 09.01.2023). Percutaneous or surgical coronary, peripheral, or carotid arterial revascularization is recognized as diagnostic of ASCVD according to current guidelines. Additionally, the presence of at least one coronary lesion with greater than 50% stenosis on coronary angiography, and at least one arterial lesion with greater than 50% stenosis on peripheral arterial or carotid artery imaging are also considered diagnostic criteria.[5,6] Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) equation. A glomerular filtration rate less than 30 ml/min/1.73 m^2 or the need for dialysis indicated severe renal failure. Significant liver dysfunction was identified by abnormal liver enzyme levels and hepatomegaly. Systemic diseases such as active rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, ankylosing spondylitis, scleroderma, and Sjögren's disease were classified as active inflammatory diseases. Blood samples were consistently collected from the antecubital region during outpatient clinic visits. Biochemical analyses, including measurements of fasting lipid levels such as high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG), were conducted using the Roche Cobas Integra 800 device (Roche Diagnostics Limited, Switzerland) during the index examination. Lp(a) levels were quantified by nephelometry using an apo (a) isoform-dependent assay (BN-II-System, Siemens HD) and reported in mg/dL.

Statistical Analysis

To provide a comprehensive overview of the study population, descriptive statistics were used to summarize demographic, clinical, and laboratory parameters. Continuous variables were reported as mean ± standard deviation, while nonparametric values were expressed as median [25th-75th percentile]. Descriptive statistics were presented through percentages and frequencies. Statistical comparisons between various groups were performed using either the Mann-Whitney U test or the Student's t-test for continuous variables. Exploration of potential correlations between Lp(a) concentrations and other study parameters was conducted using the Pearson or Spearman's rank correlation test. Statistical significance was accepted at $P < 0.05$. All analyses were meticulously performed with the Statistical Package for Social Sciences software (SPSS 22.0 for Windows, SPSS Inc., Chicago, IL, USA).

Results

Our study included Lp(a) measurements from a consecutive cohort of 1,193 patients, as detailed in Table 1. Among these individuals, 77.4% (923) were male with a mean age of 53.6 ± 8.5 years. Notably, approximately half of the participants were identified as hypertensive, while one-third were diagnosed with diabetes mellitus, which had a higher prevalence in females. Coronary artery disease was the predominant form of ASCVD, with 80.7% of cases requiring percutaneous coronary intervention, 5.7% undergoing coronary artery bypass grafting, and 13.8% receiving medical treatment. Peripheral artery disease accounted for 5.9% and stroke for 1.5% of ASCVD diagnoses, with about 6% of patients exhibiting coexisting forms of ASCVDs.

The average concentrations of LDL-C and TC were 132 ± 47 mg/dL and 212 ± 54 mg/dL, respectively. Total cholesterol, LDL-C, and HDL-C levels were significantly higher in females, whereas estimated glomerular filtration rate (eGFR) was significantly lower in females.

The average Lp(a) level was 28.2 mg/dL, with a median of 16 mg/dL and a 25th-75th percentile range of 7-39 mg/dL. The maximum Lp(a) level reached 326 mg/dL. Noteworthy percentages of patients exhibited elevated Lp(a) levels, with 18.7% ≥ 50 mg/dL, 10.8% ≥ 70 mg/dL, and 5.8% ≥ 90 mg/dL (Figure 1). Lipoprotein (a) levels were significantly higher in females compared to males (mean 35.3 mg/dL vs. 26.1 mg/dL; median 21.5 mg/dL, 25-75th percentile 8-52 mg/dL vs. median 16 mg/dL, 25-75th percentile 7-36 mg/dL) ($P < 0.01$) (Table 1). In males, the prevalence of Lp(a) levels < 30 mg/dL was significantly higher (70.8% vs.

ABBREVIATIONS

ASCVD	Atherosclerotic cardiovascular disease
CAVD	Calcific aortic valve disease
HDL-C	High-density lipoprotein cholesterol
HERITAGE	HEalth, RIsk factors, exercise Training And GEnetics
LDL-C	Low density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
MESA	Multi-Ethnic Study of Atherosclerosis
TC	Total cholesterol
TG	Triglycerides

Table 1. Demographic, clinical, and laboratory characteristics of the study population

Variables	All (n = 1193)	Male (n = 923)	Female (n = 270)	*P*
Age, (years)	53.6 ± 8.5	59.6 ± 10.1	63.6 ± 10.7	<0.01
Hypertension, n (%)	596 (49.9)	425 (46)	171 (63)	<0.01
Diabetes Mellitus, n (%)	363 (30.4)	255 (27)	108 (40)	<0.01
Active Smoker, n (%)	420 (35.2)	373 (40)	47 (17)	<0.01
ASCVD Diagnosis				
Medical Therapy, n (%) Percutaneous Coronary Intervention, n (%)	165 (13.8) 963 (80.7)	90 (9.7) 799 (86)	75 (28) 164 (60)	<0.01 <0.01
Coronary Artery Bypass Graphing Surgery Stroke, n (%)	65 (5.7) 18 (1.5)	45 (5) 12 (1)	20 (7) 6 (2)	0.11 0.26
Peripheral Arterial Disease, n (%)	56 (5.9)	44 (5)	11 (4)	0.63
Multiple Territories, n (%)	70 (6)	57 (6)	13 (5)	0.46
Statin Use, n (%)**				
No Statin, n (%)	319 (27)	230 (25)	89 (33)	<0.01
Low-Moderate Intensity Statin, n (%)	482 (40)	370 (40)	112 (41)	0.68
High İntensity Statin, n (%)	320 (23)	264 (28)	56 (20)	0.01
Laboratory Parameters				
Total Cholesterol, mg/dL	212 ± 54	209 ± 52	224 ± 57	<0.01
LDL-C, mg/dL	132 ± 47	130 ± 46	139 ± 51	<0.01
HDL-C, mg/dL	43 ± 11	41 ± 10	49 ± 13	<0.01
Non-HDL-C, mg/dL	170 ± 53	169 ± 52	175 ± 55	0.11
Lipoprotein (a), mg/dL	16 [7-39]	16 [7-36]	21.5 [8-52]	<0.01
eGFR, mL/min/1.73 m^2	84 ± 19	85 ± 19	80 ± 21	<0.01

ASCVD, Atherosclerotic Cardiovascular Diseases; eGFR, Estimated Glomerular Filtration Rate; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein.
*Parametric variables are depicted as mean ± standard deviation, and nonparametric variables as median [25th-75th percentile].
**Data of statin use status could not be reached in 72 cases.

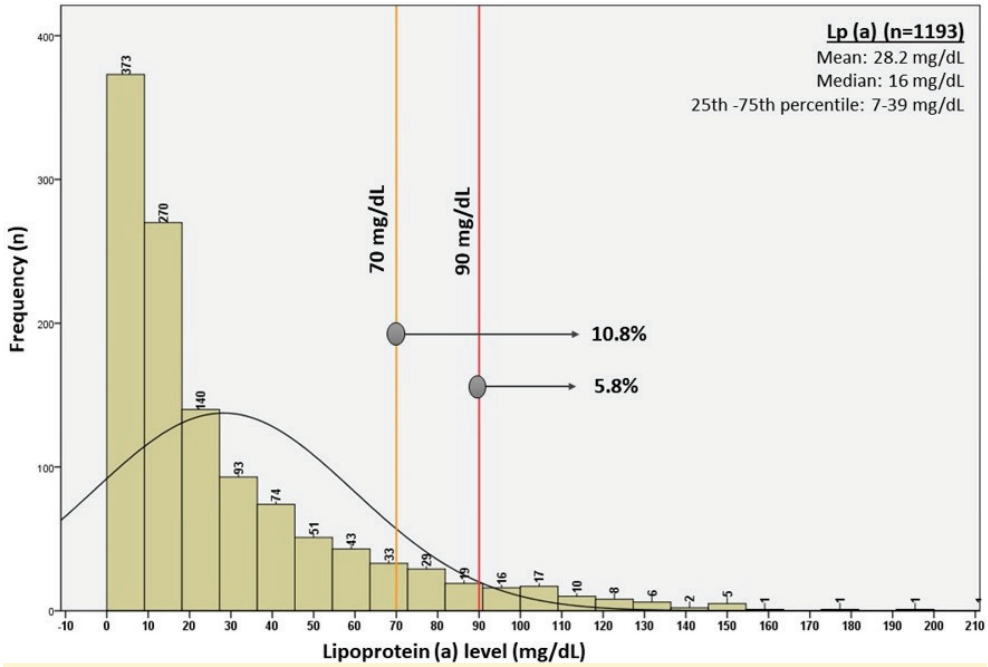

Figure 1. Scatter plot depicting the distribution of patients based on Lp(a) levels.

Table 2. Comparison of Lp(a) level categories in male and female patients

Lipoprotein(a) Category	Total (n = 1193)	Male (n = 923)	Female (n = 270)	*P*
<30 mg/dL, n (%)	820 (68.7)	654 (70.8)	166 (61.5)	<0.01
30-49.9 mg/dL, n (%)	151 (12.6)	117 (12.7)	34 (12.6)	0.97
50-69.9 mg/dL, n (%)	93 (7.8)	72 (7.8)	21 (7.8)	0.99
70-89.9 mg/dL, n (%)	59 (4.9)	41 (4.4)	18 (6.7)	0.14
≥90 mg/dL, n (%)	70 (5.9)	39 (1.4)	31 (11.4)	<0.01

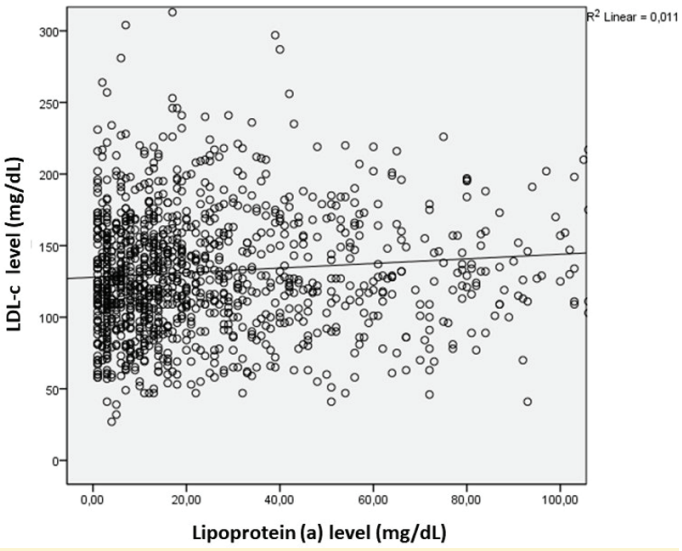

Figure 2. Graph illustrating the correlation between Lp(a) and LDL-C levels (*r* = 0.106, *P* < 0.01).

61.5%, *P* < 0.01). Adversely, the frequency of females with Lp(a) levels ≥ 90 mg/dL was significantly higher compared to males (11.4% vs. 1.4%; *P* < 0.01) (Table 2).

Information on statin use was available for 1,121 cases. Fewer females were on statin therapy compared to men (62% vs. 69%; *P* < 0.01), and the frequency of females receiving high-intensity statin therapy was significantly lower (20% vs. 28%; *P* = 0.01) (Table 1). Lipoprotein (a) levels were significantly higher in statin users (median 20 mg/dL, 25-75th percentile 8-46 mg/dL vs. median 13 mg/dL, 25-75th percentile 5-27 mg/dL; *P* < 0.01). However, there was no significant difference between high-intensity and moderate/low intensity statin therapies (median 19 mg/dL, 25-75th percentile 7-42 mg/dL vs. median 20 mg/dL, 25-75th percentile 9-48 mg/dL; *P* = 0.20).

In univariate correlation analysis, a weak but significant correlation was found between Lp(a) levels and TC (*r* = 0.075, *P* = 0.01) and LDL-C (*r* = 0.106, *P* < 0.01) (Figure 2). The correlation of Lp(a) levels with age (*r* = 0.044, *P* = 0.131); HDL-C (*r* = 0.048, *P* = 106), non-HDL-C (*r* = 0.038, *P* = 0.204), and eGFR (*r* = 0.03, *P* = 0.923) were not significant.

Discussion

High Lp(a) concentrations have been associated with various diseases such as ASCVD, CAVD, arrhythmia, stroke, peripheral artery disease, and heart failure.[2,8-14] The exact physiological importance of Lp(a) and its role in the development of atherosclerosis remain unclear. However, the role of Lp(a) in cardiovascular diseases has attracted considerable attention, especially since the development of Lp(a)-lowering agents. In this study, mean Lp(a) levels were reported in a relatively younger Turkish population diagnosed with ASCVD. The proportion of the population with an Lp(a) level (≥ 100 nmol/L [≥ 50 mg/dL]) recommended by guidelines for risk management was 18.7%. Additionally, a weak but statistically significant association was observed between Lp(a) and other lipid markers.

The global consensus on Lp(a) assessment is consistent across major international guidelines, which advocate for testing individuals at least once in their lifetime. The 2019 European and the 2021 Canadian dyslipidemia guidelines recommend obtaining Lp(a) values for all adults, highlighting increased Lp(a) concentrations as a significant risk enhancer.[4,5] Similarly, the 2020 Endocrine Society Lipid Management Guideline and the 2019 American College of Cardiology Primary Prevention Guidelines emphasize Lp(a) as a critical factor, particularly for those with borderline risk and a strong history of early ASCVD.[6,7] The recommended method for measuring Lp(a) is an isoform-dependent assay reported in nanomoles per liter (nmol/L), with concentrations exceeding 100 nmol/L (≥ 50 mg/dL) identified as a risk factor for ASCVD.[4-7]

A comparative analysis with diverse ethnic groups was conducted. In the Multi-Ethnic Study of Atherosclerosis (MESA) data, Guan and colleagues observed varying median Lp(a) concentrations among Blacks (35.1 mg/dL), Whites (12.9 mg/dL), Hispanics (13.1 mg/dL), and Chinese (12.9 mg/dL) (15). Patel et al.[16] reported median Lp(a) levels from the UK Biobank cohort, with differences among White (19 nmol/L), Chinese (16 nmol/L), Black (75 nmol/L), and another Chinese cohort (16 nmol/L). Pare et al.[17] provided insights from the case-control International Study of Heart Disease (INTERHEART) study, encompassing diverse ethnicities with varying median Lp(a) concentrations related to coronary artery disease. In our investigation, the median Lp(a) level was 16 mg/dL, situating it between the higher levels observed in the Black cohort from MESA and lower levels compared to Latin American, Arab, and South Asian patients in the INTERHEART study's cardiovascular cohort. Furthermore, in the MESA study, the proportion of patients with Lp(a) levels ≥ 50 mg/dL varied between 9.7% and 33% across populations, while in the UK Biobank cohort, it was shown to be 12.2% when Lp(a) levels ≥ 70 mg/dL were considered a risk value. According to the INTERHART study results, the rates of patients with Lp(a) levels

> 50 mg/dL were lowest among Chinese at 3% and highest among Africans at 27%. In our study, the proportion of patients with Lp(a) levels ≥ 50 mg/dL, which is the risk-modifying level recommended by current guidelines, was 18.7%.

In a study by Onat et al.[18] involving high-risk Turkish individuals from the TEKHARF cohort, the average Lp(a) level was 11 mg/dL. Another study by Örem et al.,[19] comparing Turkish cohorts with and without coronary artery disease, reported median Lp(a) values of 16 mg/dL and 24 mg/dL, respectively. The mean Lp(a) value from the Turkish Heart Study, which included individuals from regions with different dietary characteristics, was 12.9 mg/dL, showing no statistical differences between regions.[20] The Turkish Adult Risk Factor Survey (TEKHARF) and Turkish Heart studies analyzed the general population, whereas the Örem et al.[19] study focused solely on coronary artery disease patients. In this study, only patients with ASCVD were included. The variations in findings across the studies mentioned above can be attributed to factors such as small population sizes, population diversity, and selection biases. Additionally, in the TEKHARF and Turkish Heart studies involving the general population, the proportions of patients with Lp(a) levels considered risk factors were 22% and < 10%, respectively. Given that these studies are relatively dated, Lp(a) levels > 30 mg/dL were considered pathological. As noted earlier, the proportion of patients with risk-modifying Lp(a) levels was 18.7% in our study.

Within a study focusing on individuals with ASCVD, an average Lp(a) level of 18.0 mg/dL was identified, highlighting the complex relationship between high Lp(a) concentrations and consistently elevated median LDL-C levels.[21] This association underscores the potential impact of Lp(a) on lipid profiles. Conversely, findings from the Turkish Heart Study[20] deviate from this trend, revealing no significant correlation between Lp(a) levels and plasma TC or LDL-C. In our study, a nuanced perspective emerges as we observe a weak yet statistically significant positive correlation between Lp(a) concentrations and both TC and LDL-C. These variations in correlation patterns, compared to two previously mentioned studies, prompt consideration of potential contributing factors such as differences in risk status and treatment regimens among the diverse patient populations investigated. This underscores the importance of recognizing the complex nature of Lp(a) dynamics within the setting of ASCVD.

While heredity is a significant cause of variability in Lp(a) levels, the influence of sex and age remains unclear.[2,3,10,14] According to current guidelines, the risk-modifying level of Lp(a) is comparable for both sexes.[4-7] In the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) cohorts, female patients exhibited higher mean Lp(a) concentrations than males.[21] Contrarily, the Turkish Heart Study reported no significant impact of sex on Lp(a) levels, while contrasting observations emerged from the TEKHARF population, where Lp(a) levels were higher in women.[18,20] In our study, characterized by a sizable and high-risk cohort, we observed a significant departure from the Turkish Heart Study's findings. Specifically, our analysis revealed that mean Lp(a) levels were notably higher in women, highlighting the complexity of sex-related influences on Lp(a) dynamics and emphasizing the need for a comprehensive understanding that considers the unique characteristics of different study populations. Additionally, we found higher Lp(a) levels in statin users compared to non-users, consistent with previous studies that implicated Lp(a) elevation following statin therapy.[22,23] However, no difference was found between high-intensity statin therapy and moderate/low-intensity statin therapies.

Study Limitations

Several limitations must be acknowledged for this investigation. Firstly, this research adopts a retrospective design within a single-center framework and is potentially susceptible to selection bias. Despite this inherent limitation, a concerted effort was made to mitigate potential biases by selecting consecutive patients. It is important to note that the single-center nature of this study introduces challenges in generalizing findings to the entire national population. However, it is noteworthy that our center, as a referral hospital located in a cosmopolitan province, attracts individuals from diverse corners of the country, offering a partial alleviation to the representativeness challenge. We could not access data on statin use for 6% of the study population, which might have affected the analysis on Lp(a) levels in statin users. Additionally, Lp(a) was measured in mg/dL, which is another significant limitation of the study. Nonetheless, the study's results should be interpreted with an awareness of these inherent limitations.

Conclusion

This study revealed that among individuals with ASCVD admitted to a tertiary center in Türkiye, Lp(a) concentrations were higher in women and statin users. There was also a weak but significant correlation between Lp(a) level and TC and LDL-C, whereas the correlation between age, HDL-C, non-HDL-C, and eGFR were not significant. Given the absence of current Turkish data on this topic, it provided crucial information about the current distribution of Lp(a). The unveiling of these findings is anticipated to serve as a catalyst for future investigations, paving the way for targeted therapeutic approaches in the management of ASCVD patients.

Ethics Committee Approval: Ethics committee approval was obtained from Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Approval number: HNEAAH-KAEK/KK/2023/4, Date: 09.01.2023).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients and no personnel information was used.

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