

# Lipoprotein(a) and Other Risk Factors in Dyslipidemic Patients with and without Heart Failure.

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## Keywords

lipoprotein(a), heart failure, risk stratification, prevention, hyperlipidemia

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## Abstract

### Introduction

We aimed to assess the differences between patients with or without HF regarding lipid profile including Lp(a) as well as comorbidities and pharmacotherapy.

### Material and methods

We included 510 consecutive patients from the PMMHRI-Lp(a) Registry.

### Results

HF was diagnosed in 59 patients (11.57%). Higher Lp(a) levels were observed in HF group, but it was not statistically significant. The multivariable analysis revealed four significant HF, including higher category of Lp(a) (OR 2.00, 95%CI:1.19-3.35, p=0.009).

### Conclusions

Lp(a) may play a more significant role than other lipid parameters in HF patients, warranting further investigation and emphasizing the need to measure Lp(a) in these patients.

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# **Lipoprotein(a) and Other Risk Factors in Dyslipidemic Patients with and without Heart Failure**

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**Introduction:** Lipid disorders are prevalent among individuals with heart failure (HF), and among patients with lipid disorders, we also observe individuals with heart failure. However, current evidence suggests that in the absence of other specific indications, such as e.g., cardiovascular disease (CVD) the routine administration of statins in HF patients is not recommended. Nevertheless, it is worth emphasizing statin therapy does not pose harm to patients who continue its use following the onset of HF (1,2).

Lipoprotein(a) [Lp(a)], recognized as an independent cardiovascular risk factor for atherosclerotic CVD (ASCVD) (3,4), has also been investigated in the context of HF risk. Wu B *et al.* demonstrated that in an unadjusted model, a 10 mg/dL increase in baseline Lp(a) levels was associated with an 85% higher risk of developing HF with reduced ejection fraction (HFrEF). Even after adjusting for various covariates, this association remained significant, with a 10 mg/dL increase in baseline Lp(a) correlating with a 17% higher risk of incident HFrEF, reflected by an odds ratio (OR) of 1.17 (95% confidence interval [CI]: 1.05, 1.46) (5). A meta-analysis by Singh S *et al.* was aimed to clarify the association of Lp(a) and HF. From an initial pool of 360 studies, seven were selected for Mendelian randomization (MR) analysis. The MR meta-analysis revealed that elevated Lp(a) levels significantly increased the HF risk (OR 1.064,

95% CI: 1.043-1.086,  $I^2=97.59\%$ ,  $p<0.001$ ). Leave-one-out sensitivity analysis confirmed the robustness of this association, with ORs ranging from 1.051 to 1.111 (6). These results highlight the importance of monitoring lipid profiles, including Lp(a) levels, in patients with HF to better understand and manage their cardiovascular risk.

Thus, we aimed to assess the differences between patients with or without heart failure regarding lipid profile including lipoprotein(a) as well as comorbidities and pharmacotherapy.

**Methods:** We included 510 consecutive patients from the departments of cardiology and endocrinology, as well as outpatient metabolic and lipid disorder clinics – as a part of the PMMHRI-Lp(a) Registry (NCT06610669), which design and details were presented elsewhere (7). Medical history was retrospectively extracted from the electronic health records (EHRs). For the purposes of our study, we collected data regarding lipid profile with Lp(a), demographic data, comorbidities, and concomitant medication. We ranged Lp(a) levels based on the following categories:  $<30$  mg/dL ( $<75$  nmol/L),  $30-50$  mg/dl ( $75-125$  nmol/L),  $>50-180$  mg/dl ( $>125-450$  nmol/L) and  $>180$  mg/dl ( $>450$  nmol/L). Statistical analysis was conducted utilizing Statistica v.13 software (TIBCO Software Inc., Palo Alto, CA, USA). Continuous variables were expressed as mean  $\pm$ SD or median (25th-75th percentile), while categorical variables were presented as proportions. Group comparisons employed Student's t-test for independent variables and the Mann-Whitney U test or  $\chi^2$  test with Yates's correction, as applicable. A significance level of  $p<0.05$  was adopted for all calculations to denote statistical significance. Analysis of the relationship between dependent and independent variables was performed with the use of logistic regression with a backward stepwise method.

**Results:** Among our population HF was diagnosed in 59 patients (11.57%). Patients with HF (mean:  $65\pm 12$ , median:  $66(58-73)$ ) were significantly older compared to those without (mean:  $46\pm 21$ , median:  $50(33-62)$ ) ( $p<0.001$ ). No significant differences were observed in weight, height, systolic and diastolic blood pressure, and heart rate between the two groups (**Table 1**). In patients with HF the following diseases were more prevalent: chronic coronary syndromes (CCS) ( $67.8$  vs.  $9.53\%$ ,  $p<0.001$ ), myocardial infarction ( $50.85$  vs.  $3.99\%$ ,  $p<0.001$ ), stroke ( $10.17$  vs.  $3.10\%$ ,  $p=0.009$ ), hypertension ( $83.05$  vs.  $37.11\%$ ,  $p<0.001$ ), diabetes mellitus ( $33.90$  vs.  $18.89\%$ ,  $p=0.007$ ), left bundle branch block ( $6.78$  vs.  $0.89\%$ ,  $p=0.001$ ), arrhythmias ( $31.58$  vs.  $9.82\%$ ,  $p<0.001$ ), and chronic kidney disease ( $18.64$  vs.  $2.22\%$ ,  $p<0.001$ ). Former and current smokers were significantly more prevalent in the HF group ( $21.05$  vs.  $9.45\%$  and  $40.35$  vs.

7.21%, respectively; all p-values < 0.001), while never smokers were more common in the non-HF group (38.60 vs 83.33%) (**Table 1**).

Significant differences were also observed in various blood parameters: patients with HF had lower red blood cell count ( $p=0.002$ ), hemoglobin (HGB) ( $p=0.042$ ), platelet count (PLT) ( $p<0.001$ ) and estimated glomerular filtration rate (eGFR). Patients with HF had higher levels of urea ( $p=0.012$ ), creatinine ( $p<0.001$ ), indicative of impaired kidney function. Among lipid profile parameters, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), non-HDL cholesterol, were significantly lower in the HF group ( $p<0.001$ ;  $p<0.001$ ;  $p=0.006$  and  $p<0.001$ , respectively), while there were no statistically significant differences regarding triglycerides (TG) (**Table 1**). Higher levels of lipoprotein(a) [Lp(a)] were observed in the HF group, but it was not statistically significant (**Figure 1**). There was also no statistically significant association between Lp(a) categories and heart failure. The correlation analysis between Lp(a) and coronary artery disease (CAD) revealed a very weak positive correlation ( $r = 0.0253$ ). This suggests that there was minimal linear relationship between Lp(a) levels and the presence of CAD in this dataset. The applied pharmacotherapy, including statins, ezetimibe (as a part of lipid lowering combination therapy), proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, anticoagulants, diuretics, calcium channel blockers were significantly more prevalent in the HF group (**Table 1**).

The multivariable analysis using logistic regression with a backward stepwise method revealed four significant predictors of heart failure, including CCS (OR 19.13, 95%CI: 7.23-50.45,  $p<0.001$ ), PLT, which was inversely associated with HF risk (OR 0.99, 95%CI: 0.98-1.00,  $p=0.025$ ), history of smoking (OR 1.87, 95%CI: 1.11-3.16,  $p=0.019$ ), and higher category of Lp(a) level, which was significantly associated with a higher HF risk (OR 2.00, 95%CI: 1.19-3.35,  $p=0.009$ ). Alternative model that included Lp(a) level as a continuous variable, instead of categorization of Lp(a), showed even higher level of significance.

**Discussion:** While hypercholesterolemia is a significant risk factor for coronary artery disease (CAD) (8), we may assume, that among patients with lipid disturbances there will be those with HF, a prevalent and severe medical condition, frequently resulting from CAD. However, it is paradoxical that individuals with advanced HF may exhibit low cholesterol levels, which correlates with a worse prognosis (9). Familial hypercholesterolemia (FH) and elevated non-fasting triglycerides have been linked to an increased risk of heart failure (HF) (10). Conversely,

low HDL and LDL-C levels might be strongly correlated with poor outcomes in severe or end-stage HF, regardless of the underlying cause (however in some analysis it might be a reverse causality) (11). Additionally, low serum TC levels are independently associated with poor prognosis in end-stage HF patients, increasing mortality in both ischemic and non-ischemic HF (12). In our analysis of lipid profile parameters - TC, HDL-C, and non-HDL-C were significantly reduced in the heart failure (HF) group, which is consistent with the previously described the HF lipid-paradox (9). In opposite, no statistically significant differences were observed for LDL-C and TG levels. However, none of the traditional lipid profile parameters was statistically significant in the multivariable analysis. On the other hand, we observe only numerical differences in Lp(a) levels in patients with or without HF (higher in the former group) and showed that higher category of Lp(a) level was strongly associated with a higher HF risk in multivariable analysis. Other studies also showed the role of elevated Lp(a) in HF. Yan *et al* conducted an observational study with 309 patients, of whom 10.03% were lost to follow-up during a median follow-up period of 186 days. Multivariate Cox regression analysis confirmed that elevated Lp(a) levels independently predicted recurrent HF, even after adjusting for confounders (HR: 2.720, 95%CI: 1.730-4.277,  $p < 0.0001$ ). Kaplan-Meier analysis showed that higher Lp(a) levels were associated with a greater incidence of recurrent heart failure (HF) (log-rank  $p < 0.0001$ ) (13). Another prospective observational study which recruited 362 HFrEF patients showed that elevated Lp(a) levels remained independently associated with higher cardiovascular mortality (HR 1.22, 95%CI: 1.04-1.64,  $p = 0.02$ ) and composite endpoint (HR 1.38, 95 CI: 1.16-2.01,  $p = 0.006$ ) after adjusting for covariates (14). The above-mentioned meta-analysis of Singh *et al.* also showed that elevated Lp(a) levels significantly increased the risk of heart failure (HF) (OR 1.064, 95% CI: 1.043-1.086,  $P < 0.001$ ). The underlying mechanisms, whether increased inflammation and thrombotic risk, direct effects on heart muscle contraction or increased risk of ischemic cardiac disease, still require further investigation (6). Another explanation for the link between Lp(a) and HF is significantly influenced by its impact on CAD and calcific aortic valve stenosis (CAVS). A large case-control study with 143,087 participants confirmed that Lp(a) genetic variants are associated with HF risk. Specifically, each 50 nmol/l (~20 mg/dl) increase in Lp(a) concentration corresponded to a 5% higher risk of developing HF (15).

*In conclusions*, HF patients typically exhibit advanced age, modified blood parameters indicative of possible renal and metabolic dysfunction, and unfavorable lipid profiles. The level or category of Lp(a) may play a more significant role than other lipid parameters in HF patients,

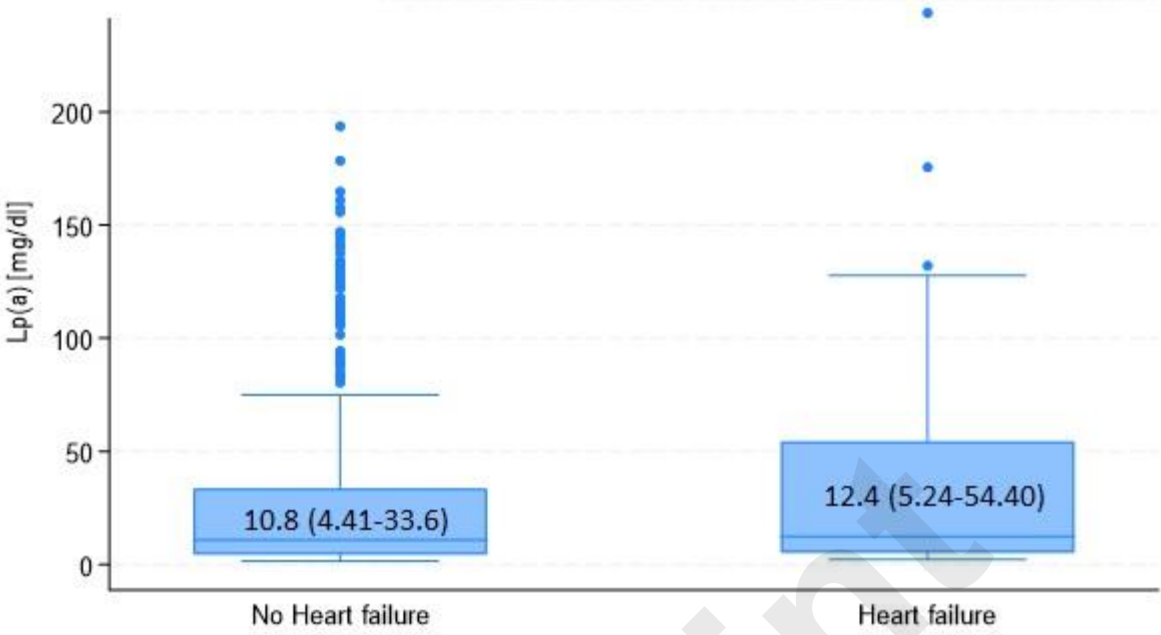
warranting further investigation and emphasizing the need to measure Lp(a) in these patients. Our findings underscore the multifactorial nature of HF and highlight the importance of managing CCS, platelet count, smoking habits, and Lp(a) levels in mitigating HF risk.

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**Figure 1.** Lack of difference in Lp(a) levels between patients with or without HF.



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**Table 1.** Comparison between patients with and without heart failure.

	<b>Heart Failure (n=59)</b>	<b>No HF (n=451)</b>	<b>p</b>
Age (years)	66 (58-73)	50 (33-62)	<0.001
Female sex (%)	35.59	55.88	0.003
Height (cm)	168 (163-176)	168 (162-177)	0.745
Weight (kg)	82 (75-97)	82 (69-96)	0.376
BMI (kg/m <sup>2</sup> )	29.69 (26.47-33.68)	28.19 (24.84-31.96)	0.116
Systolic BP (mmHg)	128 (117-140)	131 (120-144)	0.324
Diastolic BP (mmHg)	78 (70-90)	81 (75-90)	0.175
Heart rate (bpm)	70 (67-81)	74 (65-80)	0.965
History of smoking (%)	21.05	9.45	<0.001
Current smoking (%)	40.35	7.21	<0.001
Never smoking (%)	38.60	83.33	<0.001
<b>Laboratory tests</b>			
TC (mg/dl)	142 (114-197)	193 (151-237)	<0.001
LDL-C (mg/dl)	81 (65-110)	121 (88-156)	<0.001
HDL-C (mg/dl)	44 (35-60)	52 (42-62)	0.006
TG (mg/dl)	123 (90-161)	121 (82-174)	0.816
Non-HDL-C (mg/dl)	91 (75-135)	138 (103-178)	<0.001
Lp(a) (mg/dl)	12.4 (5.24-54.40)	10.8 (4.41-33.6)	0.296
ALAT (IU/l)	21 (16-26)	24 (17-35)	0.108
AspAT (IU/l)	27 (23-30)	26 (22-33)	0.737
Creatinine (mg/dl)	0.92 (0.8-1.1)	0.79 (0.68-0.92)	<0.001
eGFR (ml/min/1,73 m <sup>2</sup> )	72.4 (60.2-87.8)	88.7 (74.5-103.8)	<0.001
Urea (mg/dl)	34.9 (28.5-45.4)	30.7 (25-37)	0.012
WBC (K/ $\mu$ l)	6.65 (5.54-7.77)	6.87-5.72-8.49)	0.171
RBC (mln/ $\mu$ l)	4.32 (3.99-4.79)	4.66 (4.39-4.98)	0.002
HGB (g/dl)	13.5 (12.45-14.5)	13.9 (13-14.9)	0.042
PLT (K/ $\mu$ l)	194 (151-228)	237 (199-285)	<0.001
TSH (mIU/l)	1.45 (1.16-2.30)	1.78 (1.16-2.70)	0.572
HBA1c (mmol/mol)	40.5 (39-45)	37 (32-43)	0.131
D-Dimer (ng FEU/ml)	303 (201-562)	460 (294-790)	0.168
<b>Comorbidities</b>			
Hyperlipidemia (%)	58.11	41.89	0.208
Myocardial infarction (%)	50.85	3.99	<0.001
Chronic coronary syndrome (%)	67.80	9.53	<0.001
Stroke (%)	10.17	3.10	0.009
Hypertension (%)	83.05	37.11	<0.001
Diabetes mellitus (%)	33.90	18.89	0.007
LBBB (%)	6.78	0.89	0.001
Arrhythmias (%)	31.58	9.82	<0.001
Chronic Kidney Disease (%)	18.64	2.22	<0.001
<b>Pharmacotherapy</b>			
Statins (%)	86.21	51.97	<0.001
Ezetimibe (%)	43.10	18.64	<0.001
PCSK9i (%)	10.53	4.24	0.045
Fibrate (%)	6.90	5.65	0.707
Beta-bloker (%)	77.59	35.21	<0.001
ACEI (%)	77.59	33.62	<0.001



Anticoagulants (%)	41.38	4.52	<0.001
Diuretics (%)	43.10	14.10	<0.001
CCB (%)	37.93	20.28	0.030

**Abbreviations:** BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; TG – triglyceride; Lp(a) – lipoprotein(a); ALAT – alanine aminotransferase, AspAT - Aspartate aminotransferase; eGFR – estimated glomerular filtration rate; WBC, white blood cells; RBC, red blood cells; HGB, hemoglobin; PLT, platelet counts; TSH, thyroid stimulating hormone; HbA1c – hemoglobin A1c; LBBB, Left Bundle Branch Block; PCSK9i, proprotein convertase subtilisin/kexin 9 inhibitors, ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers.

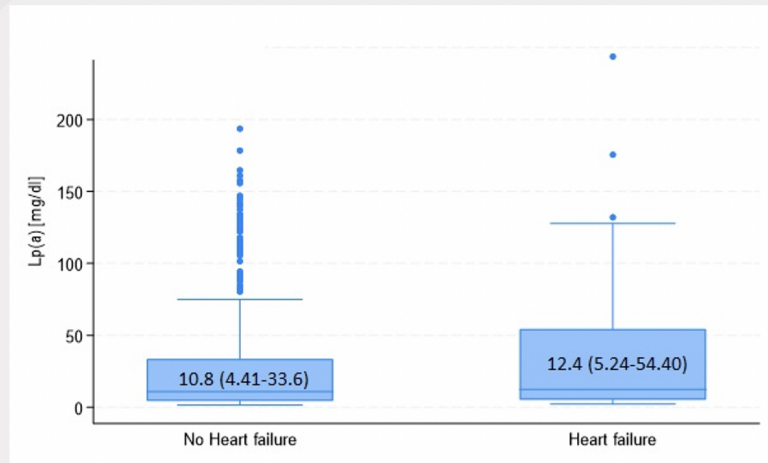
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**Table.** Logistic regression with a backward stepwise method model for heart failure.

	Odds ratio (95%CI)	p
<b>Chronic coronary syndromes</b>	19.13 (7.23-50.45)	<0.001
<b>Platelet count</b>	0.99 (0.98-1.00)	0.025
<b>Smoking history</b>	1.87 (1.11-3.16)	0.019
<b>Lp(a) category</b>	2.00 (1.19-3.35)	0.009

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